Multi-Institutional Randomized Phase II Trial of Gefitinib for Previously Treated Patients With Advanced Non–Small-Cell Lung Cancer

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Purpose: **To evaluate the efficacy and tolerability of two doses of gefitinib (Iressa [ZD1839]; AstraZeneca, Wilmington, DE), a novel epidermal growth factor receptor tyrosine kinase inhibitor, in patients with pretreated advanced non–small-cell lung cancer (NSCLC).**

Patients and Methods: **This was a randomized, double-blind, parallel-group, multicenter phase II trial. Two hundred ten patients with advanced NSCLC who were previously treated with one or two chemotherapy regimens (at least one containing platinum) were randomized to receive either 250-mg or 500-mg oral doses of gefitinib once daily.**

Results: **Efficacy was similar for the 250- and 500-mg/d groups. Objective tumor response rates were 18.4% (95% confidence interval [CI], 11.5 to 27.3) and 19.0% (95% CI, 12.1 to 27.9); among evaluable patients, symptom improvement rates were 40.3% (95% CI, 28.5 to 53.0) and 37.0% (95% CI, 26.0 to 49.1); median progression-free survival times were 2.7 and 2.8 months; and median overall survival times were 7.6 and 8.0 months, respectively. Symptom improvements were recorded for 69.2% (250 mg/d) and 85.7% (500 mg/d) of patients with a tumor response. Adverse events (AEs) at both dose levels were generally mild (grade 1 or 2) and consisted mainly of skin reactions and diarrhea. Drug-related toxicities were more frequent in the higher-dose group. Withdrawal due to drug-related AEs was 1.9% and 9.4% for patients receiving gefitinib 250 and 500 mg/d, respectively.**

Conclusion: **Gefitinib showed clinically meaningful antitumor activity and provided symptom relief as second- and third-line treatment in these patients. At 250 mg/d, gefitinib had a favorable AE profile. Gefitinib 250 mg/d is an important, novel treatment option for patients with pretreated advanced NSCLC.**

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LUNG CANCER is the most common cause of cancer deaths in both men and women worldwide.[1] Despite advances in treatment, such as combination chemotherapy and chemoradiation, survival has improved very little over the past few decades.[2] A meta-analysis demonstrated that the median survival time for patients with advanced disease receiving cisplatin-based chemotherapy is around 6 months.[3] The 5-year survival rate for all stages is less than 15%.[4] Prognosis is particularly poor for patients who have progressive disease following chemotherapy; for non–small-cell lung cancer (NSCLC) patients receiving best supportive care (BSC) after 1 or more prior chemotherapy regimen, median survival time is just 16 weeks, with a 1-year survival rate of 16%.[5]

Recently, it has become generally accepted that systemic chemotherapy is beneficial in terms of improved survival and quality of life (QoL) in those with advanced NSCLC.[3,6] As more patients receive first-line chemotherapy, the need for effective second-line therapy is increasing. Currently, docetaxel, having demonstrated survival benefits over BSC, is the only approved treatment in the United States and the European Union for patients who have been failed by previous platinum-based chemotherapy.[7]

Patients with late-stage NSCLC are often symptomatic, with specific pulmonary problems (eg, cough, breathlessness, hemotypsis) and general symptoms (eg, fatigue, weight loss) that can

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cause extreme distress to the patient. Therefore, improvements in disease-related symptoms and QoL are the key desired outcomes of medical management.[8] Effective, palliative, low-toxicity treatments for patients with advanced NSCLC are needed.

The epidermal growth factor receptor (EGFR) is a promising target for anticancer therapy because it is expressed or highly expressed in a variety of tumors, including NSCLC.[9,10] Furthermore, high levels of EGFR expression have been associated with a poor prognosis in lung cancer patients in several studies.[11-13] EGFR-targeted cancer therapies are currently being developed; strategies include inhibition of the intracellular tyrosine kinase domain of the receptor by small molecules such as gefitinib (Iressa [ZD1839]; AstraZeneca, Wilmington, DE).[14] Gefitinib is an orally active, selective EGFR tyrosine kinase inhibitor that blocks signal transduction pathways implicated in the proliferation and survival of cancer cells.[15,16]

Four phase I studies assessed gefitinib tolerability and pharmacokinetics in pretreated patients with solid tumors, including 100 patients with heavily pretreated advanced NSCLC.[17] Evidence of major tumor regression was seen in 10 patients with NSCLC; a number of other patients had nonprogressive disease lasting for 6 months or longer; and palliation of specific symptoms was also frequently observed. In these trials, responses were seen across the dose range 150 to 800 mg/day, while the majority of dose interruptions and reductions due to toxicity were required in patients receiving more than 600 mg/d. From these data, two doses (250 and 500 mg/d) were selected for investigation in phase II and phase III trials. The 250 mg/d dose is higher than the lowest dose level at which objective tumor regression was seen, while 500 mg/d is the highest dose that was well tolerated when taken over an extended period in phase I trials.

The aims of this Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL 1) trial were to further investigate the efficacy and safety of oral gefitinib in patients with advanced NSCLC who had previously received one or two chemotherapy regimens, with at least one containing platinum. The population was prospectively stratified into Japanese and non-Japanese patients to investigate whether there were any differences between the two patient populations with respect to efficacy.

PATIENTS AND METHODS

Study Design

This randomized, double-blind, parallel group, phase II multicenter trial recruited patients at 43 centers across Europe, Australia, South Africa, and Japan. Primary objectives were to evaluate the objective tumor response rate (RR) for gefitinib doses of 250 and 500 mg/d and to further characterize the safety profile of these doses. Secondary objectives were to estimate disease-related symptom improvement rate, disease control rate (response + stable disease), progression-free survival (PFS), and overall survival (OS); to evaluate changes in QoL; and to assess any differences between Japanese and non-Japanese patients with respect to efficacy and safety.

Patient Eligibility

Eligibility criteria were histologic or cytologic confirmation of locally advanced or metastatic NSCLC; stage III or stage IV disease not curable with surgery or radiotherapy at study entry; recurrent or refractory disease following one or two previous chemotherapy regimens (at least one containing platinum); at least one bidimensionally measurable or radiographically assessable lesion; age of 18 years or older; World Health Organization performance status (PS) of 0 to 2; and life expectancy of 12 weeks or longer. Patients with stable brain metastases were eligible. Exclusion criteria were more than two previous chemotherapy regimens, systemic anticancer therapy within 21 days, or radiotherapy within 14 days before the start of treatment; unresolved chronic toxicity higher than the National Cancer Institute common toxicity criteria (NCI-CTC, version 2) grade (G) of 2 (excluding cases of alopecia); ALT or AST levels greater than 2.5 times the upper limit of reference range (ULRR; more than 5 times the ULRR in the presence of liver metastases); serum creatinine levels greater than 1.5 times the ULRR; serum bilirubin levels greater than 1.25 times the ULRR; and neutrophils less than 1.5×10^9/L or platelets less than 75×10^9/L. Patients gave informed consent, and trial document approval was obtained from the ethics committee or institutional review board at each trial center. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Treatment

Patients were randomly assigned to receive double-blind gefitinib doses at 250 or 500 mg/d. Tablets were administered once daily, except on day 1 when patients received two doses approximately 12 hours apart. Patients continued uninterrupted treatment until disease progression, intolerable toxicity, withdrawal of consent, or trial closure (4 months after the last patient was recruited). Patients without progression were permitted to continue gefitinib treatment in a further study.

One dose reduction per patient was permitted in the event of unacceptable toxicity. New blinded treatment supplies, decreasing the dose from 500 mg to 250 mg or from 250 mg to 100 mg, were dispensed. Gefitinib administration could be interrupted for a maximum of 14 days.

No systemic anticancer treatment was permitted during the trial, except for palliative radiotherapy in patients with isolated symptomatic bone metastases, and as long as trial drug administration was not interrupted for longer than 14 days.

Efficacy

We assessed objective tumor response as complete response (CR), partial response (PR), partial response in nonmeasurable disease (PRNM), stable disease (SD), or progressive disease (PD) in accordance with the Southwest Oncology Group modification of Union Internationale Contre le Cancer/WHO criteria.[18] Baseline assessments were performed within 14 days before randomization. After the start of treatment, assessments were performed every 4 weeks, then every 8 weeks following the fourth month. An independent response evaluation committee consisting of three radiologists/oncologists at each session reviewed images of patients with CR, PR, and SD; reviewers were blinded to the investigators' assessment and dose of gefitinib. Duration of response was defined as the time from the first objective assessment of CR or PR to the first instance of progression or death.

Disease Control

Disease control was defined as the best tumor response of CR, PR, or SD that was confirmed and sustained for 4 weeks or longer.

Disease-related symptom improvement was measured using the Lung Cancer Subscale (LCS), a validated subscale of the QoL instrument, the Functional Assessment of Cancer Therapy – Lung (FACT-L) questionnaire (Fig 1).[19] Patients completed a weekly diary card rating the severity of each of the following seven LCS items on a scale of 0 to 4: shortness of breath, weight loss, lack of clear thinking, coughing, loss of appetite, tightness in the chest, and difficulty breathing. On day 28, the LCS was completed as part of the entire FACT-L questionnaire. The maximum (asymptomatic) attainable score was 28. Patients with a baseline LCS score of 24 or lower were evaluable for symptom improvement. This information was used to determine symptom improvement rate, time to symptom improvement, and

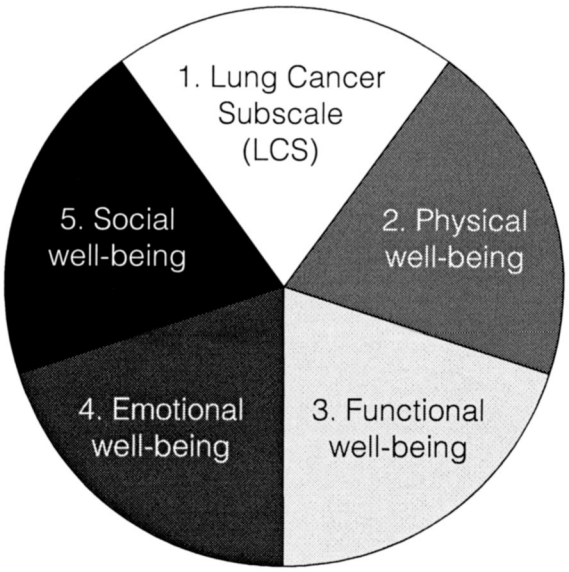

Fig 1. The five components of the Functional Assessment of Cancer Therapy - Lung (FACT-L). Component 1 is measured by the Lung Cancer Subscale itself; components 1 through 3, by the Trial Outcome Index; and components 1 through 5, by FACT-L.

duration of symptom improvement. Based on data showing that a 2-point change in LCS score is clinically meaningful for patients and is significantly associated with Eastern Cooperative Oncology Group performance status, weight loss, objective tumor response, and time to progression,[20] symptom improvement was prospectively defined as a 2-point (or greater) improvement in LCS score sustained for 4 weeks or longer, with no worsening at any interim weekly time points. Duration of symptom improvement was defined as the interval between the first visit presenting with symptom improvement and a subsequent visit at which symptoms had worsened. Missing data points were counted as no change in symptoms.

QoL Assessment

Patients completed the FACT-L questionnaire to assess QoL. The FACT-L assessment has been validated with respect to its psychometric properties and sensitivity to clinical changes.[19] FACT-L was completed at baseline and then every 28 days after the start of treatment. The questionnaire was administered before clinical assessment and before patients heard news about their disease status. The Trial Outcome Index (TOI) of FACT-L (Fig 1) measures the more physical aspects of patient QoL that are shown to be sensitive to chemotherapy.[19] TOI and FACT-L scores were derived in a similar manner to the LCS scores; the highest scores attainable for TOI and FACT-L were 84 and 136, respectively. TOI and FACT-L responses were prospectively defined as a 6-point (or greater) improvement (for 4 weeks or longer), a change that has been shown to be clinically meaningful.[20]

PFS and OS

PFS was defined as the period from the randomization date to the date when disease progression (or death) was observed. OS was defined as the period from the randomization date to the date of death. Patients alive at data cutoff were censored at the last date the patient was known to be alive.

Safety and Tolerability

All adverse events (AEs) were reported, and severity was assessed by the NCI-CTC (version 2.0) grading system. Data were collected on therapy interruptions and withdrawals due to AEs. Routine clinical and laboratory assessments were performed. ECGs and complete ophthalmic evaluations, including slitlamp examination, were performed at baseline, at 4 months, and on completion of or withdrawal from the trial.

Statistical Methods

Patients were randomized to receive oral gefitinib at doses of 250 or 500 mg/d, and were stratified by ethnicity as Japanese and non-Japanese. Randomization and allocation were performed by a centralized registration or randomization center using dynamic balancing[21] with factors for country and WHO-PS of 0 to 1 versus 2. Patients were categorized at randomization with respect to prior taxane therapy (docetaxel ± paclitaxel *v* paclitaxel alone *v* no taxane) and number of prior regimens (one *v* two).

The target sample population of 200 patients (100 in each dose group and 100 in each ethnic group) was chosen to enable the tumor lower limit for RR to be independently evaluated in the four strata defined by dose and ethnicity. Within each stratum, the goal was to have 90% power for a two-sided 5% significance test to show that the RR was greater than 5% assuming that the actual RR was 20%, which required 45 or more evaluable patients per stratum.

RRs and disease control rates were compared between strata using Fisher's exact test. Logistic regression models were used to further explore observed differences and to identify baseline factors that may independently predict for tumor response and disease control. PFS and OS were compared between strata using the log-rank test. Further analyses were conducted on these data using Cox's proportional hazard modeling.

RESULTS

Patients

A total of 210 patients were randomized within 4 months (October 2, 2000 to January 30, 2001). Of these, 208 patients were evaluable for efficacy, and 209 patients were evaluable for safety (Fig 2). The two dose groups were well balanced for most baseline demographic factors, with the exception of sex (Table 1). As planned, approximately half of the patients randomized were Japanese. There were some demographic imbalances between the Japanese and non-Japanese populations (62.7% *v* 77.8% male; 20.6% *v* 15.7% PS of 0; 8.8% *v* 16.7% PS of 2; and 76.5% *v* 50.0% adenocarcinoma, respectively).

Efficacy

The investigator assessments of the best overall tumor responses are shown in Table 2. RR was 18.4% for the 250-mg/d group, which was not statistically different from that of the 500-mg/d group (RR, 19.0%; Table 2). The independent response evaluation committee reviewed 107 of the 110 patients whom the investigator considered to have CR, PR, PRNM or SD. These included 38 of the 39 responders. There was a high concordance in tumor response evaluation between investigators and independent reviewers (73.8%; Table 3). In addition, the response evaluation committee evaluated an additional 25 patients who were assessed by the investigators as having a best response of PD. Of these 25 patients, the response evaluation committee considered 7 patients to have had a best response of SD.

Of the patients who responded, most showed rapid tumor regression, with 68% meeting the criteria for objective response by the first postbaseline assessment. The remaining patients met the criteria in the second, third, or fourth month following randomization. Furthermore, across both doses, most responders (87.2%) still had a response at the data cutoff, with a median follow-up of 6.3 months (range, 4.0–7.9 months). For patients who responded, median duration of response was more than 3 months (ranges: 250-mg/d group, 1–5 months; 500-mg/d group, 1–5.5 months). RRs were similar irrespective of whether

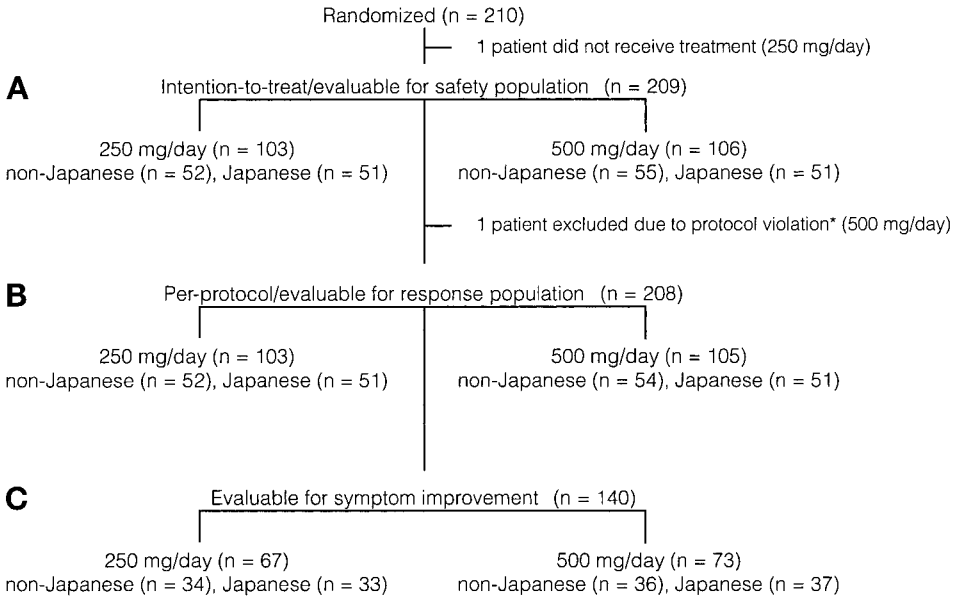

Fig 2. Number of patients included in the analysis populations. (A) Patients who received 1 or more doses of trial treatment. (B) Patients who received 14 or more days of trials treatment in each 28-day treatment period before the first tumor assessment recorded their best tumor response. (C) Patients with a Lung Cancer Subscale score of 24 or lower. Asterisk indicates that this patient's last dose of systemic anticancer therapy was received within 21 days prior to the start of trial treatment.

gefitinib was used as second-line (17.5%, 250 mg/d; 18.3%, 500 mg/d) or third-line treatment (19.6%, 250 mg/d; 20.0%, 500 mg/d). A post hoc nonrandomized analysis showed that RRs for the subgroup of patients who had previously received a platinum and a taxane were 24.0% at 250 mg/d and 28.0% at 500 mg/d. Similarly, RRs for patients previously given platinum and docetaxel were 24.0% at 250 mg/d and 26.0% at 500 mg/d. RRs for patients who had progressed on two prior chemotherapy regimens were 13.6% at 250 mg/d and 7.9% at 500 mg/d.

Table 1. Baseline Demography of the Randomized Population

	Gefitinib			
	250 mg/d		500 mg/d	
	No.	%	No.	%
No. of patients randomized	104		106	
Age				
Median	61.0		60.0	
Range	28 to 85		37 to 78	
Sex (male:female)	78:26	75:25	70:36	66:34
Performance status				
0	18	17.3	20	18.9
1	73	70.2	72	67.9
2	13	12.5	14	13.2
Disease stage at study entry				
IIIA	4	3.8	2	1.9
IIIB	19	18.3	16	15.1
IV	81	77.9	88	83.0
Tumor histology				
Adenocarcinoma*	67	64.4	71	67.0
Squamous	25	24.0	18	17.0
Large-cell	9	8.7	9	8.5
Undifferentiated	3	2.9	8	7.5
Previous cancer treatment				
Failed 1 previous chemotherapy regimen	104	100.0	106	100.0
Failed 2 previous chemotherapy regimens	46	44.2	46	43.4
Radiotherapy	52	50.0	48	45.3
Surgery	32	30.8	25	23.6
Immuno/hormonal therapy	4	3.8	9	8.5
Symptomatic at entry	67	64.4	73	68.9

*Bronchioalveolar carcinomas were included in this group. Three patients in each dose group had adenosquamous histology.

Table 2. Best Overall Objective Response

	Gefitinib			
	250 mg/d		500 mg/d	
	No.	%	No.	%
No. of patients evaluable	103		105	
Complete response	0	0	1	1.0
Partial response	18	17.5	19	18.1
Partial response in nonmeasurable disease	1	1.0	0	0.0
Stable disease	37	35.9	34	32.4
Progressive disease	42	40.8	44	41.9
Unknown*	5	4.9	7	6.7
Response rate				
%	18.4		19.0	
95% CI	11.5 to 27.3		12.1 to 27.9	
Disease control rate				
%	54.4		51.4	
95% CI	44.3 to 64.2		41.5 to 61.3	

Abbreviation: CI, confidence interval.

*No conclusion was reached about the best overall tumor response (eg, because of missing scans or relevant x-ray films).

As expected, the mean number of days under treatment was higher for responders than for nonresponders (150 *v* 68 days, respectively); however, the number of days under treatment, as compared with the number of days under the trial was 95% versus 96% in both groups.

Disease Control

The disease control rate was 54.4% for the 250-mg/d group, which was not statistically different from that of the 500-mg/d group, 51.4% ($P = .68$; Table 2). Median duration of disease control for patients who responded or had stable disease was 3.2 and 4.6 months, respectively. Disease control was similar for second-line (59.6%, 250 mg/d; 50.0%, 500 mg/d) and third-line treatment (47.8%, 250 mg/d; 53.3%, 500 mg/d). SD rate was 35.9% at 250 mg/d and 32.4% at 500 mg/d.

Disease-Related Symptom Improvement

Evaluable baseline questionnaires were received from 80 and 81 patients from the 250- and 500-mg/d groups, respectively. Of these, 67 and 73 patients, respectively, were evaluable for symptom improvement. Median baseline scores for LCS were 18.0 (ranges: 250 mg/d, 4–24; 500 mg/d, 2–24) for each dose group, indicating that this was a symptomatic population. The symptom improvement rate was 40.3% (95% confidence interval [CI], 28.5 to 53.0) for the 250-mg/d group and 37.0% (95% CI, 26.0 to 49.1) for the 500-mg/d group. Most patients with a tumor response who were evaluable for symptom improvement also showed an improvement in their disease-related symptoms, and more than 50% of the patients with SD also had symptom improvement (Fig 3).

The median of the maximum change in LCS score for the patients with symptom improvement was 7.0 points (range, 3–17 points) during the first interval of improvement (time between the first visit response of improved, to the subsequent response of worsened). Importantly, median time to symptom improvement was only 8 days (the time of first postbaseline assessment) for both doses. Median duration of symptom improvement was 5.1 month (range, 1.1–5.6+ months) at 500 mg/d. At 250 mg/d, the median duration of symptom improvement was not calculable because patients were still responding at the time of data cutoff; symptom improvement lasted for at least 3 months in 75% of patients and for 6 months in 65% of patients. Median time to

Table 3. Tumor Response Evaluation by Investigators and Independent Response Evaluation Committee

	Investigator Evaluation	
REC Evaluation	PR (n = 38)	SD (n = 69)
PR (n = 34)	31	3
SD (n = 53)	5	48
PD (n = 18)	1	17
UK (n = 2)	1	1

NOTE. Complete response and partial response in nonmeasurable disease are indicated by PR for the purpose of calculating concordance rates.

Abbreviations: REC, response evaluation committee; PR, partial response; SD, stable disease; PD, progressive disease; UK, unknown due to missing slides or scans.

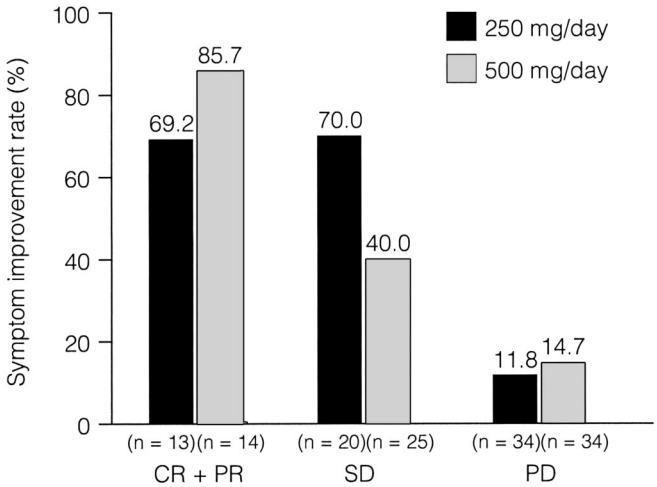

Fig 3. Symptom improvement benefits by tumor response. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

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