Gefitinib (ZD1839) Monotherapy as a Salvage Regimen for Previously Treated Advanced Non-Small Cell Lung Cancer

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ABSTRACT

Purpose: **A worldwide compassionate-use program has enabled >42,000 patients with advanced non-small cell lung cancer (NSCLC) to receive gefitinib treatment. Here we report the outcome of gefitinib therapy in patients who enrolled in the "Iressa" Expanded Access Program at the Samsung Medical Center.**

Experimental Design: **Patients with advanced or metastatic NSCLC who had progressed after prior systemic chemotherapy and for whom no other treatment option was available were eligible to receive gefitinib treatment as part of the Expanded Access Program. A post hoc assessment of potential prognostic factors for response and survival was performed by multivariate analysis.**

Results: **All 111 evaluable patients had stage IV disease; most patients had a baseline performance status of 2 [$n = 52$ (47%)] or 3 [$n = 18$ (16%)] and had received ≥2 prior chemotherapy regimens (56%). The objective response rate was 26%, the disease control rate (measured over ≥8 weeks) was 40%, and the 1-year survival rate was 44%. Adenocarcinoma histology was associated with better response and disease control rates, and a performance status of 0–2 was also associated with a better disease control rate. Both of these factors, as well as female gender, were significantly associated with longer survival. Gefitinib was well tolerated; the most common adverse event was grade 1 skin rash.**

Conclusions: **Gefitinib demonstrated significant antitumor activity and a favorable tolerability profile in this series of NSCLC patients with poor prognosis.**

INTRODUCTION

Non-small-cell lung cancer (NSCLC) has, since the start of the new millennium, been the leading cause of cancer-related mortality in Korea as well as in western countries (1). Approximately one-third of patients present with disseminated disease at the time of diagnosis (2). Standard 1st-line treatment of advanced NSCLC is platinum-based chemotherapy. However, despite advances in treatment, such as the development of new chemotherapy regimens, there is evidence that a therapeutic plateau has been reached (3). Furthermore, treatment options are limited for patients who relapse after 1st- or 2nd-line chemotherapy. A retrospective analysis of patients with advanced NSCLC receiving 3rd- and 4th-line chemotherapy showed that response rates decreased with each successive chemotherapy regimen, as follows: 1st line, 20.9%; 2nd line, 16.3%; 3rd line, 2.3%; and 4th line, 0% (4). There is therefore an urgent need for effective and well-tolerated therapies for these patients.

Novel biological agents have been developed to specifically target signal transduction pathways within cancer cells, thus halting tumor growth and metastases with minimum toxicity. A prime target for such agents is the epidermal growth factor receptor (EGFR), which is highly expressed in a variety of human tumors and implicated in aberrant cell signaling pathways that mediate tumorigenic processes (5, 6).

The orally active EGFR tyrosine kinase inhibitor gefitinib ("Iressa," ZD1839) is a leading agent in this class of novel therapies (7, 8). Gefitinib has demonstrated clinically meaningful antitumor activity, symptom relief, and quality-of-life benefits, together with an acceptable tolerability profile, in Phase II studies of patients with advanced refractory NSCLC (9, 10).

Gefitinib is now approved for the treatment of advanced NSCLC in several countries, including Korea, Australia, Japan, and the United States. In a worldwide compassionate-use program, patients with advanced NSCLC and no alternative therapeutic options were able to receive gefitinib treatment. To date, >42,000 patients have received gefitinib as part of the Iressa Expanded Access Program (EAP). Here we report the outcome of gefitinib therapy in patients who enrolled in the EAP at the Samsung Medical Center.

PATIENTS AND METHODS

Patient Selection and Therapy. Gefitinib therapy was offered through the EAP to patients with pathologically confirmed advanced or metastatic NSCLC that had progressed after

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Note: Preliminary results were presented at the 10th World Conference on Lung Cancer, Vancouver, Canada, August 10–14, 2003. Iressa is a trademark of the AstraZeneca group of companies.
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systemic chemotherapy and for which no other treatment option was available. All participants gave written informed consent. Patients received 250 mg/day oral gefitinib for an indefinite period until disease progression or unacceptable toxicity.

Assessments. Baseline assessments included a complete medical history and physical examination. Hematological and biochemical testing and urinalysis were performed within 14 days of starting treatment. Electrocardiography, chest radiography, and computed tomography of the chest and upper abdomen were required ≤4 weeks before treatment.

Objective tumor response was assessed using the Response Evaluation Criteria In Solid Tumors (11). Duration of overall response was defined as the time from the date of the first objective assessment of a complete/partial response until the date on which progressive disease was objectively documented (11). Chest radiography was performed every 2-4 weeks and computed tomography every 8 weeks. Disease control was defined as a best tumor response of complete response, partial response or stable disease, confirmed and sustained for ≥4 weeks. Survival and progression-free survival were defined as the period from the start of gefitinib treatment to the date of death or disease progression, respectively, or last follow-up. Symptom improvement, including cough, dyspnea, and pain, was assessed by medical history review at doctor-patient consultations. Survival curves were constructed using the Kaplan-Meier method. Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria version 2.0. Routine clinical and laboratory assessments were performed every 2-4 weeks.

Statistical Methods. A post hoc exploratory analysis investigated factors that might predict survival, response, and disease control. Variables of interest for survival, response rates, and disease control rates were initially examined by univariate analysis and included baseline factors of gender, age, histology, performance status (PS), response to previous chemotherapy, and number of prior chemotherapy regimens. In addition, the on-treatment factors of occurrence of skin rash and response to gefitinib were investigated. The association between response rates and disease control rates and each of the variables of interest was measured using Pearson's χ^2 or Fisher's exact tests. Baseline factors found to be significant by univariate analysis were incorporated in logistic regression multivariate models to identify baseline factors that might independently predict response and disease control. Statistical significance was defined as $P < 0.05$. To examine the prognostic significance of covariates on survival, baseline factors significant in the univariate analysis were included in a forward stepwise Cox multivariate regression model. All reported *P*s are two-sided and statistical significance was defined as $P < 0.05$.

RESULTS

Patient Characteristics

Between January 2002 and June 2003, 133 patients were enroled in the EAP at the Samsung Medical Center, of whom 111 were evaluable for efficacy and toxicity. Eighteen patients died and four had rapid disease progression before receiving gefitinib. Patient demographics are presented in Table 1. The patient population had a poor prognosis; all patients had stage IV disease, and most had an Eastern Cooperative Oncology Group PS of 2 [*n* = 52 (47%)] or 3 [*n* = 18 (16%)] and had received at least 2 prior chemotherapy regimens (56%). All patients had previously received platinum-, taxane-, and/or gemcitabine-containing regimens either concurrently or separately; 102 (92%) had received platinum, 86 (78%) taxane, and 73 (66%) gemcitabine. The majority of patients (64%) had adenocarcinoma.

Table 1 Patient demography

Characteristic	*n* = 111
Gender, *n* (%)	
Male	73 (66)
Female	38 (34)
Age	
Median, years (range)	55 (25–82)
≤60 years, *n* (%)	61 (55)
>60 years, *n* (%)	50 (45)
AJCC[a] disease stage IV, *n* (%)	111 (100)
ECOG PS, *n* (%)	
0–1	41 (37)
2	52 (47)
3	18 (16)
Histology, *n* (%)	
Adenocarcinoma	71 (64)
Squamous-cell carcinoma	30 (27)
Other (non-classifiable)	10 (9)
Prior treatment, *n* (%)	
Surgery	25 (23)
Radiotherapy	56 (50)
No. prior chemotherapy regimens, *n* (%)	
1	49 (44)
2	40 (36)
≥3	22 (20)
Prior chemotherapy, *n* (%)	
Platinum	102 (92)
Taxane	86 (78)
Gemcitabine	73 (66)

[a] AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Efficacy

Response. Twenty-nine patients experienced a best response of partial response, corresponding to an objective response rate of 26% [95% confidence interval (CI), 17.8–34.2]. In addition, 15 patients had stable disease, producing an overall disease control rate (measured over ≥8 weeks) of 40% (95% CI, 30.9–49.1). More female patients, patients with adenocarcinoma, and patients with PS 0-2 experienced partial response or stable disease compared with male patients, patients with non-adenocarcinoma histology, and patients with PS 3, respectively (Table 2). However, responses were also observed in patients who were male, had PS 3, or who had tumor histology other than adenocarcinoma. In patients with PS 2, the objective response rate was 27%, and the disease control rate was 39%. The occurrence of skin rash was more frequent in patients who responded to gefitinib. As with the baseline factors, responses were also observed in patients who did not develop skin rash.

Multivariate analysis of response and disease control rates with the baseline factors of gender, age, histology, PS, and number of prior chemotherapy regimens showed that only adenocarcinoma histology was independently associated with a

Table 2 Effect of adenocarcinoma histology, PS[a], sex, and occurrence of skin rash on tumor response

	Adenocarcinoma		PS			Sex		Skin rash	
	Yes (n = 71)	No (n = 40)	0–1 (n = 41)	2 (n = 52)	3 (n = 18)	Female (n = 38)	Male (n = 73)	Yes (n = 67)	No (n = 44)
Objective tumour response									
PR, n (%)	25 (35)	4 (10)	14 (34)	14 (27)	1 (6)	16 (42)	13 (18)	26 (39)	3 (7)
P^b	0.004			0.031		0.006		<0.0001	
Disease control									
PR + SD, n (%)	36 (51)	8 (20)	22 (54)	20 (38)	2 (11)	20 (53)	24 (33)	36 (54)	8 (18)
P^b	0.001			0.009		0.043		<0.0001	

[a] PS, performance status; PR, partial response; SD, stable disease.
[b] Univariate analysis.

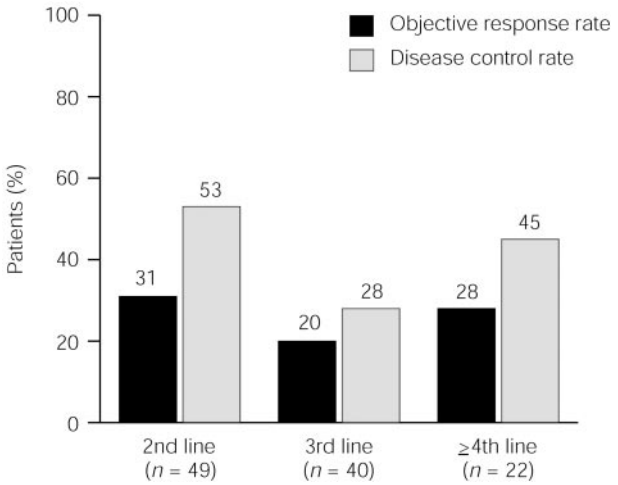

Fig. 1 Objective tumor response and disease control rates with gefitinib as 2nd-, 3rd-, and ≥4th-line therapy.

better response rate (odds ratio 4.9; 95% CI, 1.5–15.3; P = 0.006) and that adenocarcinoma histology and PS were independently associated with a better disease control rate. Patients with adenocarcinoma had a 4-fold higher disease control rate compared with non-adenocarcinoma histology (odds ratio 4.1; 95% CI, 1.7-10.2; P = 0.008). PS also significantly affected tumor response and disease control (P = 0.031 and 0.009, respectively). Tumor response was observed in 14 of 41 (34%) patients with PS 0-1, 14 of 52 (27%) patients with PS 2, and 1 of 18 (6%) patients with PS 3 (Table 2). Disease control was observed in 22 of 41 (54%) patients with PS 0-1, 20 of 52 (38%) patients with PS 2, and 2 of 18 (11%) patients with PS 3 (Table 2).

The response and disease control rates were similar whether gefitinib was used as second-, third-, or ≥4th-line treatment (Fig. 1). For patients who responded, the median duration of response was 10.4 (range 2, 13.3+) months, and the median duration of disease control for the patients who responded or had stable disease was 11.2 (range 2, 15.6+) months. In patients who had previously received a platinum agent combined with a taxane (n = 83) or gemcitabine (n = 67), response rates were 29% and 22%, respectively, and disease control rates were 40% and 39%, respectively. The overall response and disease control rates for patients who had progressed on two prior chemotherapy regimens (n = 40) were 20% and 28%, respectively.

Disease-Related Symptom Improvement. Of the 110 patients who were symptomatic at the start of therapy, 40 (36%) experienced symptom improvement. Symptom improvement rates were associated with tumor response. A higher proportion of patients with partial response or stable disease had symptom improvement (30 of 44, 68.2%) compared with those with disease progression (10 of 67, 14.9%).

Survival. Median overall and progression-free survival times were 8.8 (95% CI, 5.6–12.0) and 2.1 (95% CI, 1.9–2.2) months, respectively (Fig. 2), after a median follow-up of 9.2 (range 3.1-20.2) months. The 6-month overall and progression-free survival rates were 61.1% and 22.2%, respectively. One-year overall and progression-free survival rates were 44.4% and 16.8%, respectively. Patients who responded to gefitinib treatment, with a partial response or stable disease, had longer overall survival than non-responders, and 26 of the 29 responders are still alive.

Univariate analysis showed that gender, PS, histology, response to prior chemotherapy, response to gefitinib, and occurrence of skin rash were significant factors for overall survival. The baseline variables were incorporated into a multivariate model in which adenocarcinoma histology, female gender,

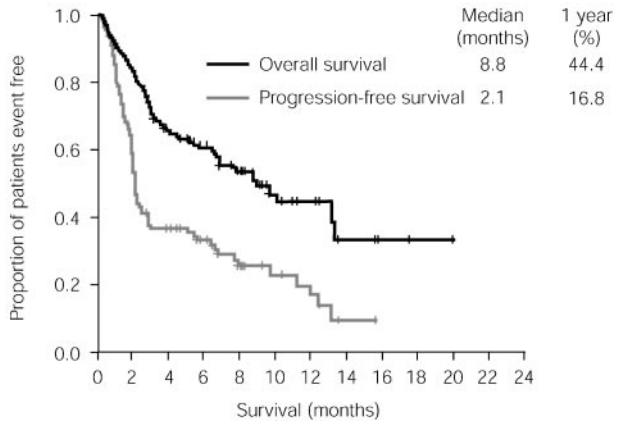

Fig. 2 Kaplan-Meier curve showing overall and progression-free survival.

and PS 0-2 (Fig. 3) were significantly associated with longer survival. Patients with adenocarcinoma histology survived twice as long (95% CI, 1.2–4.1; $P = 0.005$) as patients with non-adenocarcinoma histology. Significantly longer survival was seen in patients with PS 0-1 than in those with PS 3 (odds ratio 6.8; 95% CI, 3.1–15.4; $P < 0.0001$) or PS 2 (odds ratio 1.5; 95% CI, 0.8–3.2; $P < 0.0001$). Women had longer survival than men (odds ratio 2.1; 95% CI, 1.1–3.9; $P = 0.002$). In contrast, the number of prior chemotherapy regimens did not significantly influence survival (Fig. 4).

Eighteen patients progressed rapidly within the first month. Twenty-seven patients (20 with partial response and 7 with stable disease) are continuing on gefitinib treatment [median treatment duration 6.7 (range 3.8-15.6) months], and 18 patients have received gefitinib for >6 months.

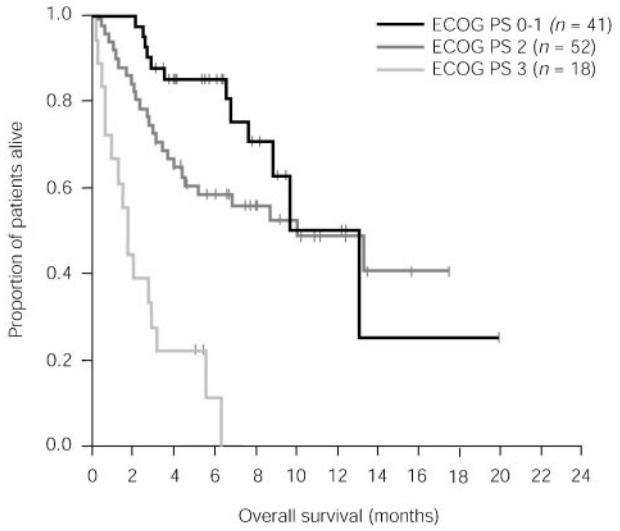

Fig. 3 Kaplan-Meier curve showing overall survival by PS. *ECOG*, Eastern Cooperative Oncology Group; *PS*, performance status.

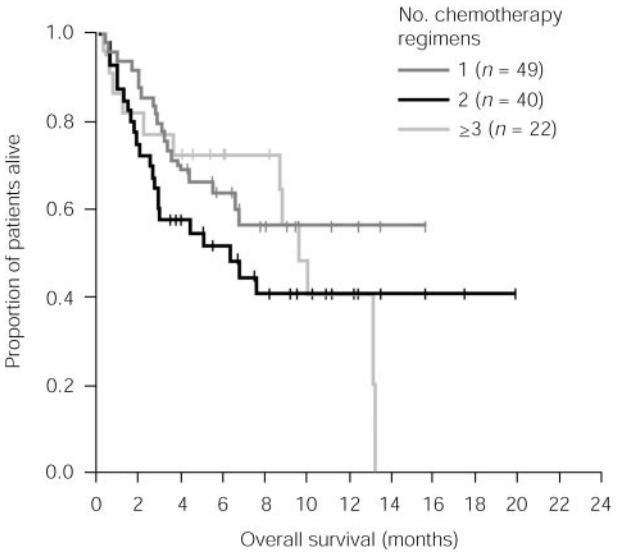

Fig. 4 Kaplan-Meier curve showing overall survival by the number of prior chemotherapy regimens received.

Table 3 Patients with drug-related adverse events during treatment and follow-up

	Grade 1	Grade 2	Grade 3
Non-hematologic, *n* (%)			
Skin rash	55 (50)	11 (10)	1 (1)
Acne	20 (18)	2 (2)	0
Pruritus	16 (14)	1 (1)	1 (1)
Diarrhea	16 (14)	2 (2)	1 (1)
Nausea/vomiting	4 (4)	0	1 (1)
Stomatitis	2 (2)	0	0
Hepatitis	2 (2)	1 (1)	1 (1)
Hematologic, *n* (%)			
Anaemia	1 (1)	1 (1)	0
Neutropenia	0	0	0
Thrombocytopenia	0	0	0

Safety

Seventy-eight (70.3%) of the 111 evaluable patients had at least one drug-related adverse event (AE); most were mild or moderate (grade 1 or 2) and reversible (Table 3). Sixty-seven patients experienced drug-related skin rash, often in association with other skin-related symptoms, including acne and pruritus. In most patients, these skin disorders resolved with antihistaminergic agents during gefitinib treatment, after a temporary treatment interruption or after treatment cessation. Another commonly reported AE was diarrhea, which could be controlled if necessary with antidiarrheal agents such as loperamide. No clinically significant deterioration in renal function was observed during the trial, even in patients who entered the trial with mild or moderate renal impairment. Hematology parameters did not show any clinically significant changes and the only drug-related hematological toxicity reported was anemia (grade 1 or 2). No cases of gefitinib-related pulmonary fibrosis or interstitial pneumonia were reported. There were no grade 4 AEs reported, and only five patients reported a grade 3 AE. Two patients required a short treatment interruption, one because of a grade 3 skin reaction and the other because of grade 3 elevated transaminases. No dose reductions were required. One patient withdrew because of drug-related toxicity of grade 1 nausea and poor compliance. There were no drug-related deaths.

DISCUSSION

In this series of patients with stage IV NSCLC who received gefitinib as part of a compassionate-use program, the objective response and disease control rates were 26% and 40%, respectively, and the overall median survival was 8.8 months. This patient population was heavily pretreated, the majority having received gefitinib as ≥3rd-line therapy and having PS 2 or 3. Thus, although this patient group had a poor prognosis, treatment with gefitinib delivered significant antitumor activity. These results strongly support the use of gefitinib as a ≥2nd-line treatment for advanced NSCLC and, furthermore, demonstrate that the clinical benefits of gefitinib are not confined to patients with a good PS. Objective responses were achieved

irrespective of whether the patients received gefitinib as a second-, third-, or ≥4th-line treatment, as in the Phase II IDEAL (Iressa Dose Evaluation in Advance Lung cancer) 1 and 2 studies of gefitinib (9, 10). This contrasts directly with the response rates obtained with standard chemotherapy regimens (4) and indicates that novel targeted agents such as gefitinib herald a promising new generation of therapy for NSCLC.

Although the total disease control rate was comparable with that obtained in the IDEAL trials (9, 10), the response rate was higher in this case series, which might suggest an ethnic difference. Data from another hospital in Korea that participated in the EAP demonstrated a response rate of 21% and a disease control rate of 61% (12). In the IDEAL 1 trial, Japanese patients had a higher response rate than non-Japanese patients. However, this was not found to be statistically significant when analyzed by a multivariate model that included all significant baseline prognostic factors, including PS and adenocarcinoma histology (9).

Potential prognostic factors such as gender, age, histology, PS, response to previous chemotherapy, and number of prior chemotherapy regimens were examined. Multivariate analysis showed that only adenocarcinoma histology was associated with a better response rate, whereas adenocarcinoma histology and PS 0-2 were associated with a better disease control rate. In addition, adenocarcinoma histology, female gender and PS 0-2 were all significantly associated with longer survival. In post hoc exploratory analyses, adenocarcinoma histology was also identified as a potential prognostic factor in the IDEAL 1 trial, and female gender was associated with response to gefitinib in both IDEAL 1 and 2 (13). It has been suggested that the association of adenocarcinoma histology with response to gefitinib may be related to the coexpression of both EGFR and high levels of human epidermal growth factor receptor 2 in this histological subtype (14). Thus, in adenocarcinoma, EGFR stimulation might be more likely to produce EGFR-human epidermal growth factor receptor 2 heterodimers, which have been shown to induce a stronger and more sustained proliferative signal than homodimers (15). Consequently, this histological subtype would be more reliant on EGFR signaling for growth and survival and more sensitive to its disruption. Further investigation is required to definitively assess the association of such clinical characteristics with response. However, existing data demonstrate that responses do occur in all groups.

As with the IDEAL results, we observed an association between symptom improvement and tumor response, with a higher proportion of responders experiencing symptom improvement. However, it should be noted that symptom improvement was not assessed by a validated questionnaire in this case series.

In this series of patients, most AEs were mild or moderate (grade 1 or 2). The most commonly reported AE was grade 1 skin rash (50% of patients), followed by grade 1 acne, pruritus, and diarrhea. There was a low incidence of grade 3 AEs and no grade 4 AEs. The favorable safety profile of gefitinib demonstrated in this case series concurs with that seen in previous studies (9, 10).

We observed that skin rash occurred more frequently in patients who responded to gefitinib. However, patients who derive clinical benefit are likely to receive treatment for longer periods than those who do not and thus have more opportunity to develop skin toxicity. Recent analysis of data from the IDEAL trials showed that the development of skin toxicity was not a reliable predictor for clinical benefit (16). Unpublished research results from our group, together with other evidence, suggest that the tumor response and skin rash observed with gefitinib and other EGFR-targeted approaches may be related to expression of the tumor suppressor gene PTEN.[2] This gene is thought to function primarily via negative regulation of the phosphatidylinositol 3-kinase pathway, resulting in down-regulation of Akt and a subsequent increase in apoptosis (17–19). We have preliminary findings demonstrating that human diploid skin fibroblasts expressing low levels of PTEN have increased Akt phosphorylation and resistance to tumor-necrosis-factor-α-induced apoptosis.[2] Bianco *et al.* (20) have also demonstrated that loss of PTEN in tumor cells and the consequent high levels of phosphatidylinositol 3-kinase and Akt activity result in resistance to gefitinib-mediated EGFR inhibition, effects that are abolished by overexpression of PTEN. Together, these data suggest that gefitinib treatment in a patient with a high expression of PTEN could result in a greater degree of apoptosis in skin fibroblasts and tumor cells, resulting in skin rash and tumor response, respectively. Albanell *et al.* (21) have shown that gefitinib treatment results in increased apoptosis in cutaneous cells. Therefore, PTEN expression in a cutaneous biopsy could be a marker for tumor response to gefitinib, although the relationship between PTEN expression in cutaneous cells and tumor response requires further investigation.

In conclusion, gefitinib demonstrated significant antitumor activity and a favorable tolerability profile in this series of patients with advanced metastatic NSCLC and a poor prognosis. These results indicate that gefitinib is a promising novel therapeutic agent for patients in whom chemotherapy has failed. In a post hoc exploratory analysis, we identified histological subtype as a baseline factor that might be associated with higher response rates. However, further investigations are required to clarify the prognostic factors for response to gefitinib. Phase III trials are now underway to prospectively evaluate gender, histology, and smoking history as prognostic factors.

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