Efficacy of Gefitinib, an Inhibitor of the Epidermal Growth Factor Receptor Tyrosine Kinase, in Symptomatic Patients With Non–Small Cell Lung Cancer

A Randomized Trial

Mark G. Kris, MD
Ronald B. Natale, MD
Roy S. Herbst, MD
Thomas J. Lynch, Jr, MD
Diane Prager, MD
Chandra P. Belani, MD
Joan H. Schiller, MD
Karen Kelly, MD
Harris Spiridonidis, MD
Alan Sandler, MD
Kathy S. Albain, MD
David Cella, PhD
Michael K. Wolf, PhD
Steven D. Averbuch, MD
Judith J. Ochs, MD
Andrea C. Kay, MD

Context More persons in the United States die from non–small cell lung cancer (NSCLC) than from breast, colorectal, and prostate cancer combined. In preclinical testing, oral gefitinib inhibited the growth of NSCLC tumors that express the epidermal growth factor receptor (EGFR), a mediator of cell signaling, and phase 1 trials have demonstrated that a fraction of patients with NSCLC progressing after chemotherapy experience both a decrease in lung cancer symptoms and radiographic tumor shrinkages with gefitinib.

Objective To assess differences in symptomatic and radiographic response among patients with NSCLC receiving 250-mg and 500-mg daily doses of gefitinib.

Design, Setting, and Patients Double-blind, randomized phase 2 trial conducted from November 2000 to April 2001 in 30 US academic and community oncology centers. Patients (N=221) had either stage IIIB or IV NSCLC for which they had received at least 2 chemotherapy regimens.

Intervention Daily oral gefitinib, either 500 mg (administered as two 250-mg gefitinib tablets) or 250 mg (administered as one 250-mg gefitinib tablet and 1 matching placebo).

Main Outcome Measures Improvement of NSCLC symptoms (2-point or greater increase in score on the summed lung cancer subscale of the Functional Assessment of Cancer Therapy-Lung [FACT-L] instrument) and tumor regression (>50% decrease in lesion size on imaging studies).

Results Of 221 patients enrolled, 216 received gefitinib as randomized. Symptoms of NSCLC improved in 43% (95% confidence interval [CI], 33%-53%) of patients receiving 250 mg of gefitinib and in 35% (95% CI, 26%-45%) of patients receiving 500 mg. These benefits were observed within 3 weeks in 75% of patients. Partial radiographic responses occurred in 12% (95% CI, 6%-20%) of individuals receiving 250 mg of gefitinib and in 9% (95% CI, 4%-16%) of those receiving 500 mg. Symptoms improved in 96% of patients with partial radiographic responses. The overall survival at 1 year was 25%. There were no significant differences between the 250-mg and 500-mg doses in rates of symptom improvement ($P=.26$), radiographic tumor regression ($P=.51$), and projected 1-year survival ($P=.54$). The 500-mg dose was associated more frequently with transient acne-like rash ($P=.04$) and diarrhea ($P=.006$).

Conclusions Gefitinib, a well-tolerated oral EGFR-tyrosine kinase inhibitor, improved disease-related symptoms and induced radiographic tumor regressions in patients with NSCLC persisting after chemotherapy.

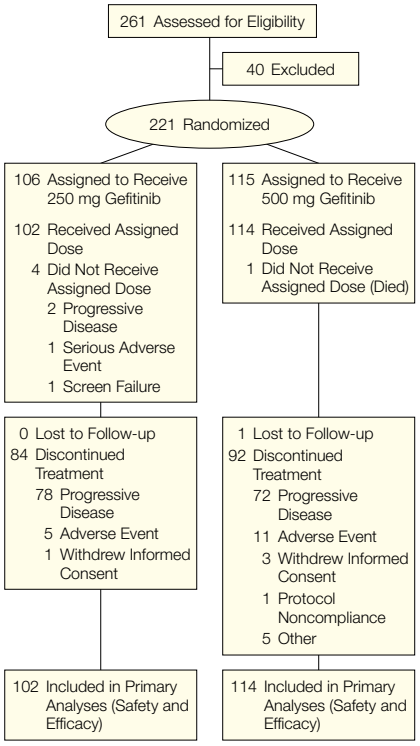
JAMA. 2003;290:2149-2158 www.jama.com

MORE PERSONS IN THE United States die from non–small cell lung cancer (NSCLC) than from breast, colorectal, and prostate cancer combined.[1] Each year, more than 60 000 persons develop stages IIIB and IV NSCLC; nearly all go on to die from metastatic spread. In addition, most individuals experience symptoms caused directly by lung cancer. These symptoms are often the first manifestations of the illness and increase in frequency and severity as the disease progresses. Cough, shortness of breath, weight loss, loss of appetite, and chest tightness impair the quality of lives already cut short by NSCLC. For patients with advanced lung cancer, physical well-being and changes in quality of life correlate with survival.[2] Espe-

Author Affiliations and Financial Disclosures are listed at the end of this article.
Corresponding Author and Reprints: Mark G. Kris,MD, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021.

©2003 American Medical Association. All rights reserved.

Figure 1. Study Flow



cially among patients with metastatic NSCLC, who are rarely cured, lessening lung cancer symptoms without adding burdensome adverse effects is an important goal of care. No anticancer therapy has been proven to be beneficial to persons seeking additional care after receiving 2 or more chemotherapy regimens.

The epidermal growth factor receptor (EGFR) mediates cancer cell growth, proliferation, invasion, and metastasis, and inhibits apoptosis.[3] When ligands bind to the receptor, the molecule is phosphorylated by constitutive tyrosine kinases, causing activation of downstream pathways.[4] Preclinically, drugs targeting these tyrosine kinases block EGFR activation and the intracellular events that follow.[5] Compounds disrupting EGFR tyrosine kinases inhibit the growth of human tumors that express EGFR and cause overexpressing tumors to regress.[5-7] These same agents reduce levels of vascular endothelial growth factor and enhance apoptosis.[8,9]

Many lines of evidence suggest that EGFR has relevance to patients with NSCLC and thus may serve as a potential therapeutic target. Expression of EGFR has been detected by immunohistochemistry testing in from 62%[8-11] to 93% of resected primary tumors,[12] and EGFR mRNA has been found in 100%.[11] The overexpression of EGFR has been variably correlated with clinical outcomes.[11,13-15]

The oral drug gefitinib (ZD1839, Iressa, AstraZeneca Pharmaceuticals, Wilmington, Del) blocks EGFR tyrosine kinases and prevents epidermal growth factor–induced proliferation in cell culture. It inhibits growth and causes regressions in human tumor xenografts with EGFR overexpression.[5] When given to patients with cancer, gefitinib inhibits EGFR activation in skin.[16] Phase 1 trials identified diarrhea as dose-limiting at daily oral gefitinib doses of 700 to 1000 mg.[17-20] A continuous gefitinib dosing schedule was developed because it was determined to be the best schedule to counter the continuous oncogenic signaling through this receptor, as seen in animal models[5] and presumed to occur in persons with cancer. An acne-like rash was also noted. Unlike conventional chemotherapy, gefitinib did not cause myelosuppression, neuropathy, or significant alopecia. In these same phase 1 studies, rapid symptom improvement and radiographic regressions were documented in patients with NSCLC who had previously received chemotherapy.[21]

In light of preclinical activity in EGFR-expressing tumors, evidence of EGFR expression in NSCLC, and antitumor effects in patients with NSCLC persisting after chemotherapy in the phase 1 trials, we initiated this phase 2 trial of gefitinib. We hypothesized that blocking EGFR tyrosine kinases with gefitinib would lead both to symptomatic benefits and objective regressions in patients with NSCLC. We further tested whether there were important differences in outcomes or adverse effects comparing 250-mg and 500-mg doses of gefitinib using a randomized, double-blind, phase 2 design.

METHODS

Patients

From November 2000 to April 2001, 221 patients were enrolled at 30 sites in the United States for the second Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL2) trial. Patients were included if they had pathological confirmation of NSCLC; stage IIIB or IV disease extent[22]; treatment with 2 or more regimens containing cisplatin or carboplatin and docetaxel, given either concurrently or as separate regimens; disease progression or unacceptable toxicity with the last chemotherapy regimen; symptomatic NSCLC as determined by a score of 24 or lower out of 28 using the lung cancer subscale of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality-of-life instrument[23,24]; measurable or evaluable indicator lesions[25]; World Health Organization performance status of 0-2; and if they had provided written informed consent. Patients were excluded if they had received chemotherapy or irradiation within 14 days; unresolved toxicity greater than grade 2 from prior chemotherapy; neutrophil count less than 1.5×10^9 cells/L, platelet count less than 75×10^9 cells/L, bilirubin level more than 1.25 times the upper limit of normal, and alanine aminotransferase or aspartate aminotransferase levels more than 2.5 times the upper limit of normal; and creatinine clearance less than 30 mL/min (0.50 mL/s).

Patients were randomized to receive either two 250-mg tablets of gefitinib (500-mg total dose) or one 250-mg gefitinib tablet and 1 matching placebo tablet (250-mg total dose) daily. These dosages were chosen, based on phase 1 study results, to maximize the potential for therapeutic activity with an ample safety margin. Responses had been observed at doses as low as 150 mg in the phase 1 studies.[21] Gefitinib and placebo (both supplied by AstraZeneca Pharmaceuticals) were dispensed on day 1 of each 28-day treatment cycle. One blinded dose reduction from 250 to 100 mg or from 500 to 250 mg was permitted.

©2003 American Medical Association. All rights reserved.

Symptom Assessments

Symptom assessments were measured using the FACT-L instrument.[23,26] This instrument was completed pretreatment and then every 28 days. Weekly, patients recorded the presence and severity of 7 symptoms using the lung cancer subscale: shortness of breath, weight loss, clarity of thinking, cough, appetite, chest tightness, and difficulty breathing. Severity was assessed using a 0-4 scale (0-1, most symptomatic; 2-3, less symptomatic; 4, asymptomatic); thus, on the 0 to 28 summed lung cancer subscale score, a score of zero denotes the worst symptoms and 28, none of the 7 symptoms. A 2-point change in the summed score has been proven to correlate with both survival and performance status.[23,24] Symptom improvement required confirmation of the 2-point increase with no interim worsening over the subsequent 4 weeks. Time to symptom improvement was measured from randomization. The duration of improvement was measured from the first visit at which a 2-point change in the summed lung cancer subscale score was observed until the visit when worsening occurred. Patients were removed from the study based on radiographic criteria or toxicity.

Radiographic Assessments

Partial radiographic responses required a greater than 50% decrease in lesion size.[25] Imaging studies were repeated 4 and 8 weeks after randomization, then every 8 weeks. As prespecified, the investigators' assessment of response was used in the analysis. Eighty-eight percent of participants had at least 1 bidimensionally measurable indicator lesion. The National Cancer Institute Common Toxicity Criteria (NCI CTC version 2.0) were used to describe and quantitate adverse effects.

Tumor specimens for immunohistochemical analysis for EGFR were requested from all patients. Of the 97 specimens received, 70 were suitable for analysis. Results of these immunohistochemical tests were presented[27] and will be reported separately. Baseline characteristics of the 70 patients with adequate samples were similar to the entire group enrolled.

Statistical Methods

Patients were stratified by World Health Organization performance status (0-1 vs 2) and number of prior chemotherapy regimens (2 vs 3 vs 4 or more). Coprimary end points were rates of symptom improvement and radiographic tumor regression. We included all patients who received any gefitinib. Sample size was chosen to independently evaluate each coprimary end point for each dose. For both rates, 100 patients per group yielded a power of 0.90 for a 1-sided .0125 significance-level test that the rate of symptom or radiographic improvement is 5% or less when the true rate is 15%.[28]

Secondary end points included overall survival by dose, frequency, and severity of adverse events, and overall quality of life using the FACT-L instrument. Quality of life analyses have been presented[29] and will be reported separately. Kaplan-Meier plots were calculated by dose using an unadjusted log-rank test. Analyses were planned to correlate the symptom improvement and radiographic response rates with each other and with survival. We used logistic regression and χ^2 tests to explore the coprimary outcomes in relation to disease and demographic factors. The data cutoff date for this analysis was August 1, 2001. Radiographic responses were updated to December 17, 2001, when the trial closed. Survival data were updated May 7, 2002. Statistical analyses were carried out using SAS version 8.1 (SAS Institute Inc, Cary, NC) and StatXact version 4 (Cytel Software Corp, Cambridge, Mass); $P<.05$ was used to determine statistical significance.

RESULTS

From November 7, 2000, to April 6, 2001, 221 patients were enrolled at 30 sites in the United States (listed at the end of this article). The flow of patients through the trial is illustrated in FIGURE 1. Five individuals who never received gefitinib were excluded after randomization. Baseline patient characteristics are summarized in TABLE 1. No significant differences were observed between the treatment groups receiving 250 mg and 500 mg of gifitinib. With their last chemotherapy regimen before starting gefitinib, 170 patients (79%) had disease progression and 38 (18%) had intolerable toxicity, mainly peripheral neuropathy. Overall, 58% of patients had received 3 or more prior chemotherapy regimens. TABLE 2 shows the severity of 7 lung cancer symptoms at baseline. Pulmonary symptoms were most common. The median number of days receiving gefitinib was 56 and 53 for the

Table 1. Pretreatment Patient Characteristics

Characteristic	No. (%) Gefitinib, 250 mg	No. (%) Gefitinib, 500 mg
No. entered	102	114
Women	42 (41)	51 (45)
Median age (range), y	61 (34-84)	62 (30-80)
Age ≥65 y	38 (37)	48 (42)
WHO performance status*		
0	18 (18)	15 (13)
1	64 (63)	75 (66)
2	19 (19)	23 (20)
Stage		
IIIB	15 (15)	9 (8)
IV	87 (85)	105 (92)
Bone metastases	26 (25)	32 (28)
Brain metastases	19 (19)	15 (13)
FACT-L symptom score, median (range)†	17 (8-24)	16 (2-27)
Histologic cell type		
Adenocarcinoma	70 (69)	73 (64)
Squamous cell carcinoma	14 (14)	18 (16)
Large cell and other	18 (18)	23 (20)
Prior chemotherapy‡		
2 Regimens	41 (40)	48 (42)
3 Regimens	31 (30)	41 (36)
≥4 Regimens	29 (28)	25 (22)

Abbreviations: FACT-L, Functional Assessment of Cancer Therapy; WHO, World Health Organization.
*One patient excluded from the 250 mg-group because of unknown status and 1 patient from the 500-mg group because of symptom progression.
†Summed score from the lung cancer subscale of the FACT-L instrument.[23,24] A score of zero denotes the worst symptoms, 28 the least severe.
‡One patient excluded from the 250-mg group because patient had received prior therapy.

©2003 American Medical Association. All rights reserved.

groups receiving 250 mg and 500 mg, respectively. The median number of days in the study was 56 for both groups. Patients completed 84% of lung cancer subscale assessments while in the study.

Table 2. Severity of Lung Cancer Symptoms at Baseline*

Symptom	No. (%) Asymptomatic (Score = 4)	Less Symptomatic (Score = 2-3)	Most Symptomatic (Score = 0-1)
Shortness of breath (n = 216)	20 (9)	98 (45)	98 (45)
Cough (n = 215)	31 (14)	90 (42)	94 (44)
Tightness in chest (n = 212)	66 (31)	110 (52)	36 (17)
Difficulty breathing (n = 213)	22 (10)	126 (59)	65 (31)
Appetite loss (n = 214)	42 (20)	113 (53)	59 (28)
Weight loss (n = 216)	97 (45)	92 (43)	27 (13)
Clear thinking (n = 215)	101 (47)	101 (47)	13 (6)

*Measured using the lung cancer subscale of the FACT-L instrument.[23,24]

Table 3. Efficacy Results

Efficacy Measure	No. (%) Gefitinib, 250 mg (n = 102)	Gefitinib, 500 mg (n = 114)	Total (N = 216)	*P* Value
Symptom Improvement*				
Symptom improvement rate [95% CI]	44 (43) [33-53]	40 (35) [26-45]	84 (39) [32-45]	.26
Duration of symptom improvement, median (range), mo†	0 (1+ to 7+)	0 (1+ to 8+)	0 (1+ to 8+)	
Symptom improvement apparent				
1 wk	24 (55)	23 (58)	47 (56)	
3 wk	32 (73)	31 (78)	63 (75)	.89
4 wk	38 (87)	33 (83)	71 (85)	
Symptom improvement rates				
By sex				
Men	23 (38)	15 (24)	38 (31)	.12
Women	21 (50)	25 (49)	46 (50)	>.99
By histologic cell type				
Adenocarcinoma	34 (49)	28 (38)	62 (43)	.24
Other	10 (31)	12 (29)	22 (30)	>.99
Radiographic Response‡				
Radiographic response rate [95% CI]	12 (12) [6-20]	10 (9) [4-16]	22 (10) [6-14]	.51
Duration of radiographic response, median (range), mo	7 (3 to 9+)	6 (3 to 8+)	7 (3 to 9+)	.28
Radiographic response rates				
By sex				
Men	2 (3)	2 (3)	4 (3)	>.99
Women	10 (24)	8 (16)	18 (19)	.43
By histologic cell type				
Adenocarcinoma	10 (14)	9 (12)	19 (13)	.81
Other	2 (6)	1 (2)	3 (4)	.58
Survival				
Survival duration, median (range), mo	7	6	6	.40
Projected 1-year survival, %	27	24	25	.54

Abbreviation: CI, confidence interval.
*Defined as ≥2-point increase in summed score on the lung cancer subscale of the Functional Assessment of Cancer Therapy–Lung instrument.[23,24]
†Zero indicates that median duration of benefit was not reached.
‡Defined as >50% decrease in tumor size on radiography.

Symptom Improvement

TABLE 3 lists outcome measures. The symptom improvement rate was 43% (95% confidence interval [CI], 33%-53%) for patients who received 250 mg of gefitinib and 35% (95% CI, 26%-45%) for those who received 500 mg ($P=.26$). Fifty-five percent of symptom improvements in patients receiving 250 mg and 58% of symptom improvements in patients receiving 500 mg were apparent after 1 week of treatment. For those patients with symptom improvement, the median durations of benefit were not reached (range, 1+ to 7+ months for patients receiving 250 mg and 1+ to 8+ months for those receiving 500 mg). For all participants, the best median symptom score improved by 25%, from a baseline of 16 (out of 28) to 22 after treatment with gefitinib ($P<.001$). For all but 1 study week, the mean change in the summed lung cancer subscale score for all patients was 2 or more, the predefined level for significant symptom improvement (FIGURE 2). The greatest mean improvement in summed lung cancer subscale scores (4.8) occurred in the patients with partial radiographic responses. Mean changes were 2.6 for individuals with stable disease and 1.0 for those with progression. The change in mean summed lung cancer subscale scores for patients with disease progression did not improve by the prespecified 2-point cutoff defining improvement.

Radiographic Response

The response rate (all partial) was 12% (95% CI, 6%-20%) for the group receiving 250 mg of gefitinib and 9% (95% CI, 4%-16%) for the group receiving 500 mg ($P=.51$). The P value for the test that the true rate is greater than 5% was .005 for the group receiving 250 mg and .06 for the group receiving 500 mg. The median duration of radiographic response was 7 (range, 3 to 9+) months for patients receiving 250 mg and 6 (range, 3 to 8+) months for patients receiving 500 mg. Symptoms improved in 96% of patients with partial responses, 73% of those with no partial response but no progression (stable disease), and 17%

©2003 American Medical Association. All rights reserved.

of those with disease progression ($P<.001$). Rates of symptom improvement were improved comparing the patients with partial response and those with stable disease ($P=.02$). FIGURE 3 displays correlations between symptom improvement and radiographic response.

Symptom improvement and radiographic responses were observed in all patient subgroups. Symptom improvement was more common with adenocarcinoma than with other histologic types (43% vs 30%, $P=.06$). Response rates were 13% for adenocarcinoma vs 4% for other types ($P=.046$). The incidence of adenocarcinoma was 79% in women and 58% in men. A multivariable comparison (which included sex, histologic subtype, performance status, age, number of prior regimens, and months from initial diagnosis) demonstrated only female sex to be predictive of response both for symptom improvement (50% vs 31% for women vs men, respectively; $P=.006$) and radiographic regression (19% vs 3%, $P=.001$). Eighteen of 22 partial responses (82%) occurred in women.

Partial response rates did not differ significantly whether patients had received 2 (8%), 3 (10%), or 4 or more (15%) prior chemotherapy regimens ($P=.38$), and rates of symptom improvement were similar based on the number of prior regimens ($P=.38$). Radiographic response rates did not differ among patients with performance status of 0, 1, or 2 (12%, 9%, and 14%, respectively; $P=.53$). Rates of symptom improvement also were unaffected by performance status ($P=.53$).

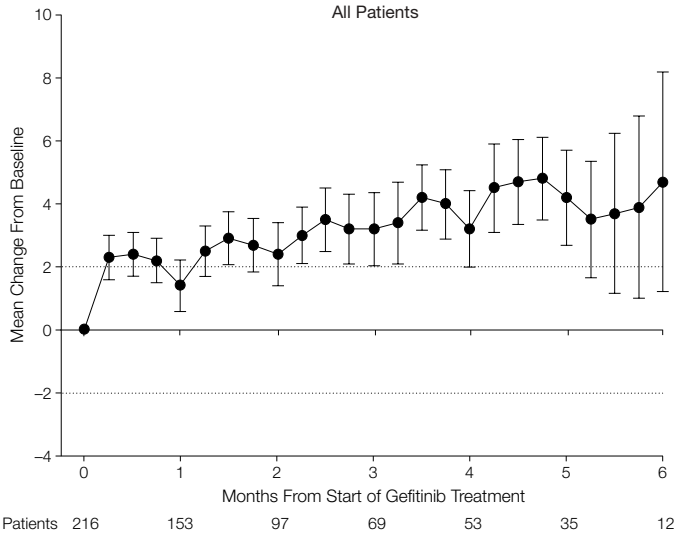
Survival

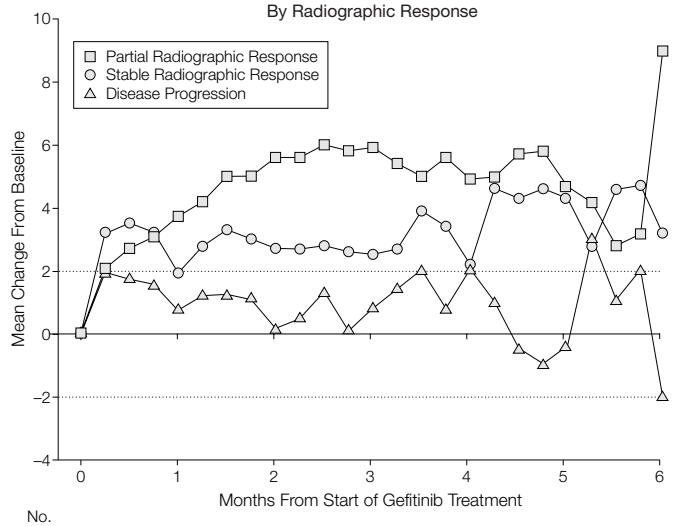
The projected median survival was 7 months for patients receiving 250 mg of gefitinib and 6 months for those receiving 500 mg ($P=.40$). The estimated 1-year survival was 27% for patients receiving 250 mg and 24% for those receiving 500 mg ($P=.54$). FIGURE 4 displays the overall survival by dose. Using a landmark analysis to examine the survival of only patients who lived at least 2 months (the time needed to assess radiographic response), median survival differences were observed among partial responders (13 months), patients with no partial response but no progression (ie, stable disease) (9 months), and those with progression (5 months) ($P<.001$). Also using the landmark method, patients with symptom improvement had a median survival of 13 months vs 5 months for those without symptom benefit ($P<.001$).

Adverse Effects

TABLE 4 presents deaths, discontinuations, withdrawals, and gefitinib-related diarrhea and skin toxicities. Skin toxicity, described variably as rash, acne, dry skin, or pruritus, was observed in 62% of patients receiving 250

Figure 2. Mean Change From Baseline in the Summed Score of the Lung Cancer Subscale of the Functional Assessment of Cancer Therapy–Lung





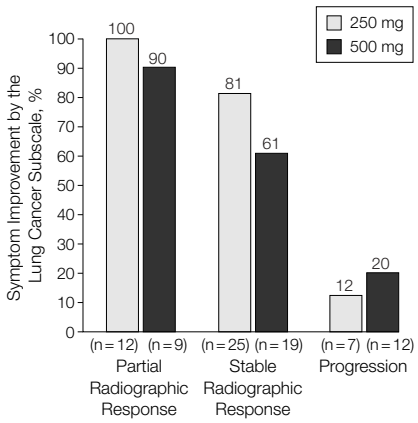
No.							
Partial Radiographic Response	22	18	19	17	20	14	4
Stable Radiographic Response	62	52	50	48	30	19	7
Disease Progression	113	77	27	4	3	2	1

Dotted lines indicate 2-point changes in median scores. The protocol-specified improvements or decrements have been shown to be clinically significant in prior trials.[25,27] Error bars indicate 95% confidence intervals.

©2003 American Medical Association. All rights reserved.

mg of gefitinib vs 75% of those receiving 500 mg ($P=.04$). The rash appeared on the face, neck, and trunk, and commonly faded or improved despite continuing therapy. It occurred during the first treatment cycle in 82% of patients. Although all 22 patients with partial responses had some skin toxicity, 65% of those who did not have a partial response also experienced this adverse effect. Skin toxicity was documented in 86% (72/84) of patients with symptom improvement and in 58% (76/132) of those whose symptoms did not improve (observed difference, 28%; 95% CI, 17%-39%).

Figure 3. Correlation Between the Symptom Improvement Rate and the Best Radiographic Response Rate Following Gefitinib Administration



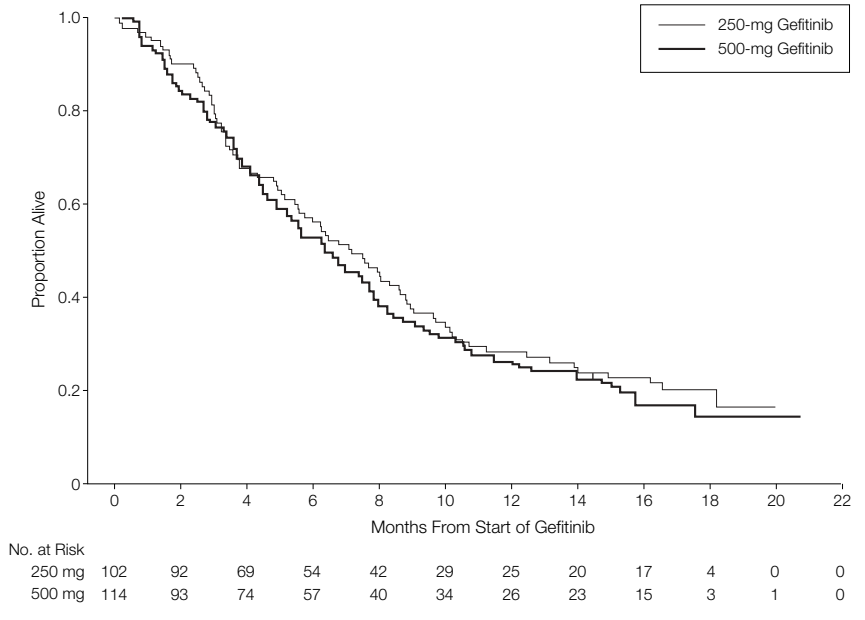
Measure of association (Goodman and Kruskal gamma coefficient) for 250-mg dose, 0.95; for 500-mg dose, 0.78; $P<.001$ for both.

Diarrhea was noted in 57% of patients receiving 250 mg of gefitinib and in 75% of those receiving 500 mg ($P=.006$). No routine prophylactic antidiarrheal medication was given. Only 1 patient receiving 250 mg had diarrhea greater than grade 2 (up to 6 daily bowel movements) compared with 6 patients in the group receiving 500 mg. Two individuals receiving 500 mg withdrew because of diarrhea. In 76% of patients, diarrhea was observed during the first treatment cycle. Symptoms were generally controllable with loperamide taken after each bowel movement. Approximately one third took an antidiarrheal medication. Diarrhea was documented in 82% (69/84) of patients with symptom improvement and in 56% (74/132) whose symptoms did not improve (observed difference, 26%; 95% CI, 14%-38%).

Nineteen percent of patients reported grade 1 or 2 eye toxicities such as redness or itchiness. All were self-limited and in no case led to study withdrawal. Treatment-related vomiting or nausea (grade 1 or 2 only) was observed in 15% and 10% of patients, respectively. There were no cases of investigator-identified interstitial lung disease following gefitinib administration (observed rate, 0%; 95% CI, 0%-1.7%). Pulmonary events (collected as pneumonia, aspiration pneumonia, lung disorder, respiratory distress syndrome) were noted in 13 patients (6 of grade 3 or 4) receiving 250 mg of gefitinib and in 14 patients (8 of grade 3 or 4) receiving 500 mg. None of the pulmonary events were considered drug-related by the investigators. One patient had grade 3 thrombocytopenia and 3 had reversible grade 3 elevations of alananine aminotransferase and aspartate aminotransferase levels that were deemed drug-related. No grade 3 or 4 neutropenia, anemia, or neuropathy occurred.

Only 1 possible treatment-related death was recorded. This patient experienced cavitation of his primary tumor, developed massive hemoptysis, and died on day 11. Only 1 patient receiving 250 mg of gefitinib and 5 patients receiving 500 mg experienced a drug-related adverse event leading to study withdrawal. Dose reductions for toxicity occurred in 1 patient receiving 250 mg and 10 receiving 500 mg. Grade 3 or 4 drug-related adverse events were observed in 7 patients receiving 250 mg and 20 patients receiving 500 mg. Thirty-day all-cause mortality was 3.8% for patients receiving 250 mg and 8.8% for those receiving 500 mg. Sixty-day all-cause mortality was 8.8% for patients receiving 250 mg and 18% for those receiving 500 mg.

Figure 4. Overall Survival for all Patients, Comparing Patients Receiving 250-mg and 500-mg Doses of Gefitinib



COMMENT

This trial demonstrated that oral gefitinib given once daily caused rapid symptom improvement and tumor regressions in patients with NSCLC. Until now, only chemotherapy, surgery, and radiotherapy have demonstrated the ability to cause lung tumors to re-

©2003 American Medical Association. All rights reserved.

gress. Once these modalities have been exhausted, only supportive care measures remain. Gefitinib, which was designed to achieve its anticancer effects through a different mechanism, can help fill this therapeutic void.

There is no comparable prospective series treating a cohort of symptomatic patients who had received both cisplatin or carboplatin and docetaxel. In a retrospective review of 43 individuals treated with various chemotherapies, the response rate for a third regimen was 2%.[30] One study randomized individuals who had received 1 or more chemotherapy regimen(s) to either docetaxel or supportive care alone. The response rate with docetaxel was 6%. Those who did not receive chemotherapy had a median survival of 5 months.[31] In another "second-line" trial conducted in the United States, radiographic tumor regressions were induced in 7% of patients receiving docetaxel vs in 1% of those receiving vinorelbine or ifosfamide.[32] The 10% response rate with gefitinib, achieved without myelosuppression or neurotoxicity, and with virtually no hair loss, is provocative in comparison. The results of this trial are consistent with the gefitinib phase 1 experience in patients with NSCLC.[21] The recent international phase 2 trial (IDEAL1) also compared 250-mg and 500-mg gefitinib doses, but in patients pretreated with 1 or 2 prior chemotherapy regimens who were not required to have symptoms at trial entry. For the 250-mg dose, they reported an 18% radiographic response rate.[33] Similar efficacy has been observed with the EGFR tyrosine kinase inhibitor erlotinib (OSI-774, Tarceva, OSI Pharmaceuticals, Melville, NY).[34] In our study, approximately 15% of patients with the "best response" of progression had some symptomatic improvement by study criteria. This likely reflects either a placebo effect or the resolution of adverse effects of the prior chemotherapy regimens.

Adverse effects of gefitinib were generally mild, manageable, noncumulative, and reversible with the cessation of the drug and sometimes even with continued use. Among individuals receiving 250 mg, some degree of skin toxicity occurred in 62% and of diarrhea in 57%. For the 250-mg dose, toxicity caused just 1 patient to stop taking gefitinib and 1 to reduce the dosage. Interstitial lung disease has been associated with use of gefitinib in Japan and reported to occur in 1% to 2% of patients.[35] This is a recognized but uncommon adverse effect of cytotoxic drugs[36] and also has been described following treatment with the tyrosine kinase inhibitor imatinib (STI571, Gleevec, Novartis Pharmaceuticals, Basel, Switzerland).[37] With no case of interstitial lung disease reported in this trial, the 95% confidence limit for the true incidence of this complication after gefitinib administration ranges from 0% to 1.7%, lower than that observed with many chemotherapeutic agents.[36]

There were no significant differences in the incidence of symptomatic or radiographic improvement between the 250-mg and 500-mg doses of gefitinib. The incidence and severity of both rash and diarrhea, however, were higher among patients receiving 500 mg. Consistent with the proposed mechanism of action of gefitinib, once plasma levels adequate to block tyrosine kinases such as EGFR have been achieved, additional dose escalations are unlikely to improve response and will increase toxicity. That is likely what we observed in this study. We recommend the 250-mg dose. The IDEAL1 trial reached the same conclusion.[33]

Can the amount of EGFR protein in tumors predict response to gefitinib? The answer appears to be no. In a combined analysis of tumor EGFR expression levels determined by immunohistochemistry in 157 analyzable specimens submitted from patients enrolled in the IDEAL1 trial and in this study, there were no consistent associations between levels of EGFR expression and radiographic or symptomatic improvements.[27] In clinical trials of the EGFR inhibitors cetuximab and erlotinib, response also did not correlate with the degree of EGFR expression measured by immunohistochemistry.[34,38]

Of all clinical characteristics, only female sex and adenocarcinoma histological type showed a correlation with response, both in our study and in the international study.[33] Patients in Japan also had higher rates of radiographic re-

Table 4. Gefitinib-Related Adverse Effects

Adverse Effect	No. (%) Gefitinib, 250 mg (n = 102)	No. (%) Gefitinib, 500 mg (n = 114)	*P* Value
Possible treatment-related death	0	1 (1)*	.36
Withdrawal due to drug-related event	1 (1)	5 (4)	.13
Dose reduction for toxicity	1 (1)	10 (9)	.009
Any grade 3/4 drug-related event	7 (7)	20 (18)	.02
Rash, pruritus, dry skin, or acne, grade†			
Any	63 (62)	85 (75)	.04
1	50 (49)	48 (42)	
2	13 (13)	22 (19)	
3	0	5 (4)	
4	0	0	
Diarrhea, grade†			
Any	58 (57)	85 (75)	.006
1 (increase of <4 stools/d)	48 (47)	59 (52)	
2 (increase of 4-6 stools/d)	9 (9)	20 (18)	
3 (increase of ≥7 stools/d)	1 (1)	6 (5)	
4	0	0	

*This patient died on study day 11 from massive hemoptysis developing from a primary lung lesion that cavitated on therapy. The investigator listed this death as definitely cancer related and possibly related to the study drug.
†Grades listed are the maximum at any time in the trial, and are determined using the Common Toxicity Criteria of the National Cancer Institute.

©2003 American Medical Association. All rights reserved.

sponse than those enrolled from other countries.[33] Investigators from Memorial Sloan-Kettering Cancer Center also have reported that in a multivariable analysis of 140 patients that included 6 people treated as part if this trial, individuals who have never smoked cigarettes and those with any bronchioloalveolar histologic features in their tumor specimens are more likely to respond to gefitinib.[39] Although female sex has been associated with longer survival in patients with advanced NSCLC, it has not been found to be a predictor of radiographic response with chemotherapy.[40] It is likely that the consistently higher sensitivity to gefitinib in women, Japanese patients, persons with adenocarcinoma histological type (especially bronchioloalveolar), and those who have never smoked cigarettes has a biological basis. Understanding these observations may help reveal the mechanisms that underlie response to gefitinib. At this time, we do not recommend using any pretreatment characteristics to routinely select patients to receive gefitinib. Although we observed higher rates of response in women, radiographic regressions were nonetheless documented in men and symptoms were improved in 31%. For now, the only way to predict which patients will benefit from gefitinib is to administer the drug and observe its effects, which are quickly apparent. In this trial, symptom improvement was documented in 75% of responding patients within 3 weeks and in 85% by 4 weeks.

Why do these results not appear as striking as those from other "targeted" approaches? The pathobiology of growth-factor signaling in lung cancer may be fundamentally different from that in other tumors, in which blockade of growth-factor receptors has proved to be of benefit. In breast cancer, persons who respond to trastuzumab (Herceptin, Genentech Inc, San Francisco, Calif) uniformly have high expression of HER2 protein caused by *HER2* gene amplification. In lung cancer, even high-level EGFR protein expression is not commonly linked to gene amplification.[10] Growth-factor–mediated proliferation in NSCLC also is different from that observed in gastrointestinal stromal tumors, in which specific mutations of either the *c-KIT* or *PDGFRA* genes cause ligand-independent activation of receptor proteins that drive tumor growth.[41-44] No similar controlling mutations of EGFR have been reported in NSCLC. The targeted therapy imatinib inhibits several tyrosine kinases, including those expressed by c-KIT and PDGFRA.[45] Imatinib causes dramatic regressions in gastrointestinal stromal tumors regardless of whether the controlling mutations are in the *PDGFRA* or *c-KIT* genes, because it effectively blocks both tyrosine kinases and the resulting oncogenic signals emanating from either receptor. Similarly, gefitinib may inhibit other tyrosine kinases in addition to EGFR. If this occurred in patients with lung cancer, oncogenic signaling in tumors in the fraction of patients who derive substantial benefit from gefitinib could be driven at least in part by activation of other tyrosine kinases in addition to or instead of EGFR.

Preclinical studies have demonstrated the uncoupling of the effects of EGFR tyrosine kinase inhibition and tumor growth.[46,47] This observation may be relevant in NSCLC. Since multiple genetic lesions are necessary to initiate lung cancers, many cell-signaling pathways may be aberrant and provide multiple mechanisms to maintain tumors and permit "signaling redundancy." For example, *Kristen-ras* mutations,[4] *PTEN* promoter hypermethylation,[48] *PI3-Ká* amplification,[49] and *p53* mutations[50] are all downstream of EGFR and occur in lung tumors. Any or all of these aberrations may be present in patients whose tumors fail to respond to gefitinib. We may be able to help individuals with gefitinib-resistant tumors by determining which downstream factor works in concert with EGFR and then designing a combination therapy inhibiting both EGFR and the downstream aberration as well. Characterization of the presence or absence of these additional lesions in a given patient's tumor also could lead to more discriminate use of gefitinib.

The strength of downstream oncogenic signaling can be determined by which member of the HER family dimerizes with EGFR.[4] Identifying the presence of other HER family members in tumors and their degree of dimerization with EGFR may help identify persons with lung cancer more likely to be sensitive to gefitinib. Investigations also have revealed that amino acid substitutions in the ATP binding pocket in regions sequentially distant but conformally important to the imatinib binding site have been identified in both clinically and laboratory induced mutations of the Abelson tyrosine kinase in chronic myelogenous leukemia.[51] These substitutions confer resistance to imatinib. This mechanism may have relevance to understanding gefitinib resistance and provides yet another direction for research.

The results of this trial proved our study hypothesis. Blocking EGFR tyrosine kinase with gefitinib leads to symptom improvement and radiographic regressions in patients with NSCLC. These findings support the use of gefitinib for the treatment of patients with NSCLC who have received cisplatin or carboplatin and docetaxel, and other agents. The magnitude and duration of benefits, coupled with the safety of gefitinib, justifies its use in patients previously treated with chemotherapy. These results further demonstrate that a therapy that disrupts biological pathways specific for cancer cells can improve the outcome of patients with advanced NSCLC.

Author Affiliations: Thoracic Oncology Service, Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan-Kettering Cancer Center and the Weill Medical College of Cornell University, New York, NY (Dr Kris); Cedars-Sinai Comprehensive Cancer Center, Los Angeles, Calif (Dr Natale); University of Texas M. D. Anderson Cancer Center, Houston (Dr Herbst); Massachusetts General Hospital Cancer Center, Boston (Dr Lynch); UCLA Medical Center, Los Angeles, Calif (Dr Prager); University of Pittsburgh Cancer Institute, Pittsburgh, Pa (Dr Belani); University of Wisconsin Hospital, Madison (Dr Schiller); University of Colorado Health Sciences Center, Denver (Dr Kelly); Hematology Oncology Consultants Inc, Columbus, Ohio (Dr Spiridonidis); Vanderbilt University, Nashville, Tenn (Dr Sandler); Loyola University Medical Center, Maywood, Ill (Dr Albain); Northwestern University, Evanston, Ill (Dr Cella); AstraZeneca Pharmaceuticals, Wilmington, Del (Drs Wolf, Averbuch, Ochs, and Kay).

©2003 American Medical Association. All rights reserved.

Financial Disclosures: Drs Kris, Natale, Prager, Belani, Schiller, Sandler, and Cella have received research support, speaking honoraria, and/or consulting fees from AstraZeneca Pharmaceuticals. Dr Natale has also received such funding from Amgen, Aventis, Eli Lilly, Pharmacia, Pfizer, and Ortho-Biotech.
Author Contributions: Dr Kris, as principal investigator of this study, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.
Study concept and design: Kris, Natale, Herbst, Lynch, Belani, Wolf, Averbuch, Ochs, Kay.
Acquisition of data: Kris, Natale, Herbst, Lynch, Prager, Belani, Kelly, Spiridonidis, Albain, Averbuch, Ochs, Kay.
Analysis and interpretation of data: Kris, Natale, Herbst, Belani, Schiller, Sandler, Albain, Cella, Wolf, Averbuch, Ochs, Kay.
Drafting of the manuscript: Kris, Natale, Herbst, Lynch, Belani, Kelly, Wolf, Ochs.
Critical revision of the manuscript for important intellectual content: Kris, Natale, Herbst, Lynch, Prager, Belani, Schiller, Kelly, Spiridonidis, Sandler, Albain, Cella, Wolf, Averbuch, Ochs, Kay.
Statistical expertise: Kris, Cella, Wolf.
Obtained funding: Ochs.
Administrative, technical, or material support: Kris, Natale, Belani, Ochs, Kay.
Study supervision: Kris, Lynch, Prager, Belani, Wolf, Averbuch.
Patient measurement: Cella.
Participating investigators, research coordinators, and institutions: *Alabama:* Birmingham: University of Alabama (Francisco Robert, MD, investigator; Liz Busby, study coordinator); *Arkansas:* Little Rock: Arkansas Cancer Research Center (Anne-Marie Maddox, MD, investigator; Courtney Terry, study coordinator); *California:* Los Angeles: Cedars Sinai Comprehensive Cancer Center (Lupe Escamilla, study coordinator); UCLA Medical Center (Polly Candela, study coordinator); Sacramento: University of California Davis Cancer Center (David R. Gandara, MD, investigator; Leora Tanaka, study coordinator); *Colorado:* Aurora: Anshutz Cancer Pavilion (Lynn Magree, study coordinator); *Florida:* Boca Raton: Comprehensive Cancer Care Specialists (Mohammad Jahanzeb, MD, investigator; Lori Kronish, study coordinator); Miami: Oncology/Hematology Group of South Florida (Leonard A. Kalman, MD, investigator; Kathy Maxwell, study coordinator); Miami Beach: Mt Sinai Cancer Center (Rogerio Lilienbaum, MD, investigator; Patricia Gutterman, study coordinator); *Georgia:* Marietta: Georgia Cancer Specialist (Mansoor Saleh, MD, investigator; Amy Bome, study coordinator); *Illinois:* Maywood: Loyola University Medical Center (Anita Brown, study coordinator); Naperville: Edwards Hospital Cancer Center (Joseph Kash, MD, investigator; Kathy Seymour, study coordinator); *Kentucky*: Louisville: Norton Healthcare Inc (John Hamm, MD, investigator; Lolita Stribinskiene, study coordinator); *Louisiana*: New Orleans: Ochsner Cancer Institute (John Cole, MD, investigator; Gary Lagasse, study coordinator); *Maryland:* Baltimore: Johns Hopkins (Julie R. Brahmer, MD, investigator; Joelle Mahkovec, study coordinator); *Massachusetts:* Boston: Dana Farber Cancer Institute (Arthur Skarin, MD, investigator; Jeffrey Hellman, study coordinator); Massachusetts General Hospital (Elizabeth Kennedy, study coordinator); *Michigan:* Ann Arbor: University of Michigan Cancer Center Network (Philip Stella, MD, investigator; Anne Novak, study coordinator); *North Carolina:* Durham: Duke University Medical Center (Jeffrey Crawford, MD, investigator; Carolyn Andrews, study coordinator); *North Dakota:* Bismark: Mid Dakota Clinic (M. Roy Thomas, MD, investigator; Jeannie Wright, study coordinator); *New Jersey:* New Brunswick: Cancer Institute of New Brunswick (Stuart Lutzker, MD, investigator; John Biondi, study coordinator); *New York:* Great Neck: Cancer Research of Long Island (Hal Gerstein, MD, investigator; Desiree Galli, study coordinator); *Ohio:* Columbus: Hematology Oncology Consultants Inc (Kelly Koesters, study coordinator); *Pennsylvania:* Philadelphia: Fox Chase Cancer Center (Corey Langer, MD, investigator; Kris Padavic, study coordinator); Pittsburgh: University of Pittsburgh Cancer Institute (Jill Tauch, study coordinator); *Tennessee:* Knoxville: Thompson Cancer Survival Center (Timothy J. Panella, MD, investigator; Sue Bales, study coordinator); Nashville: Vanderbilt University Medical School (Peggy Krozely, study coordinator); *Texas*: Houston: University of Texas M. D. Anderson Cancer Center (Pamela Lee, study coordinator); San Antonio: Cancer Therapy Research Center (Lisa Hammond, MD, investigator; Heather McCreery, study coordinator); *Wisconsin*: Madison: University of Wisconsin Cancer Center (Marilyn Larson, study coordinator).
Funding/Support: Research support for this trial was provided by AstraZeneca Pharmaceuticals, Wilmington, Del.
Role of Sponsor: The funding and infrastructure to conduct this trial were provided by AstraZeneca Pharmaceuticals, which also provided the study drug and placebo and hired a contract research organization to collect the data from the study sites. The data analyses were conducted at AstraZeneca by Dr Wolf, and the data analyses were then given to Dr Kris by AstraZeneca along with the individual patient data. There was no formal approval from AstraZeneca.
Previous Presentation: Presented in part at the 38th annual meeting of the American Society of Clinical Oncology; May 18-21, 2002; Orlando, Fla.

REFERENCES

1. Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ. Cancer statistics, 2003. *CA Cancer J Clin*. 2003;53:5-26.
2. Eton DT, Fairclough DL, Cella D, Yount SE, Bonomi P, Johnson DH. Early change in patient-reported health during lung cancer chemotherapy predicts clinical outcomes beyond those predicted by baseline report: results from Eastern Cooperative Oncology Group Study 5592. *J Clin Oncol.* 2003;21:1536-1543.
3. Mendelsohn J. Blockade of receptors for growth factors: an anticancer therapy—the fourth annual Joseph H. Burchenal American Association for Cancer Research Clinical Research Award Lecture. *Clin Cancer Res.* 2000;6:747-753.
4. Arteaga CL. The epidermal growth factor receptor: from mutant oncogene in nonhuman cancers to therapeutic target in human neoplasia. *J Clin Oncol.* 2001;19(18 suppl):32S-40S.
5. Wakeling AE, Guy SP, Woodburn JR, et al. ZD1839 (Iressa): an orally active inhibitor of epidermal growth factor signaling with potential for cancer therapy. *Cancer Res.* 2002;62:5749-5754.
6. Moyer JD, Barbacci EG, Iwata KK, et al. Induction of apoptosis and cell cycle arrest by CP-358,774, an inhibitor of epidermal growth factor receptor tyrosine kinase. *Cancer Res.* 1997;57:4838-4848.
7. Allen LF, Cerna C, Gomez L, Yochmowitz M, Medina L, Weitman S. Investigation of the effects of CP-358,774 on various human tumor specimens taken directly from patients. *Clin Cancer Res.* 2000;6:4543S.
8. Al Hazaa A, Birchall MA, Bowen ID. ZD1839 (Iressa™), an EGFR-TK1, and cisplatin have an additive effect on programmed cell death in human head and neck squamous carcinoma cells in vitro. *Clin Cancer Res.* 2000;6:4542S.
9. Ciardiello F, Caputo R, Bianco R, et al. Antitumor effect and potentiation of cytotoxic drugs activity in human cancer cells by ZD-1839 (Iressa), an epidermal growth factor-selective tyrosine kinase inhibitor. *Clin Cancer Res.* 2000;6:2053-2063.
10. Hirsch FR, Varella-Garcia M, Bunn PA Jr, et al. Epidermal growth factor receptor in non-small cell lung carcinomas: correlation between gene copy number and protein expression and impact on prognosis. *J Clin Oncol.* In press.
11. Brabender J, Danenberg KD, Metzger R, et al. Epidermal growth factor receptor and HER2-neu mRNA expression in non-small cell lung cancer is correlated with survival. *Clin Cancer Res.* 2001;7:1850-1855.
12. Rusch V, Baselga J, Cordon-Cardo C, et al. Differential expression of the epidermal growth factors receptor and its ligands in primary non-small cell lung cancers and adjacent benign lung. *Cancer Res.* 1993; 53:2379-2385.
13. Fujino S, Enokibori T, Tezuka N, et al. A comparison of epidermal growth factor receptor levels and other prognostic parameters in non-small cell lung cancer. *Eur J Cancer.* 1996;32A:2070-2074.
14. Rusch V, Klimstra D, Venkatraman E, Pisters PW, Langenfeld J, Dmitrovsky E. Overexpression of the epidermal growth factor receptor and its ligand transforming growth factor alpha is frequent in resectable non-small cell lung cancer but does not predict tumor progression. *Clin Cancer Res.* 1997;3:515-522.
15. Pfeiffer P, Clausen PP, Andersen K, Rose C. Lack of prognostic significance of epidermal growth factor receptor and the oncoprotein p185HER-2 in patients with systemically untreated non-small-cell lung cancer: an immunohistochemical study on cryosections. *Br J Cancer.* 1996;74:86-91.
16. Albanell J, Rojo F, Averbuch S, et al. Pharmacodynamic studies of the epidermal growth factor receptor inhibitor ZD1839 in skin from cancer patients: histopathologic and molecular consequences of receptor inhibition. *J Clin Oncol.* 2001;20:110-124.
17. Ranson M, Hammond LA, Ferry D, et al. ZD1839, a selective oral epidermal growth factor receptor-tyrosine kinase inhibitor, is well tolerated and active in patients with solid, malignant tumors: results of a phase I trial. *J Clin Oncol.* 2002;20:2240-2250.
18. Herbst RS, Maddox A-M, Rothenberg ML, et al. Selective oral epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 is generally well-tolerated and has activity in non-small-cell lung cancer and other solid tumors: results of a phase I trial. *J Clin Oncol.* 2002;20:3815-3825.
19. Baselga J, Rischin D, Ranson M, et al. Phase I safety, pharmacokinetic, and pharmacodynamic trial of ZD1839, a selective oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with five selected solid tumor types. *J Clin Oncol.* 2002;20: 4292-4302.
20. Kusaba H, Tamura T, Nakagawa K, et al. A phase I intermittent dose-escalation trial of ZD1839 (Iressa™) in Japanese patients with solid malignant tumors. *Clin Cancer Res.* 2000;6:4543S.
21. Kris MG, Herbst R, Rischin D, et al. Objective regressions in non-small cell lung cancer patients treated in Phase I trials of oral ZD1839 (Iressa™), a selective tyrosine kinase inhibitor that blocks the epidermal growth factor receptor (EGFR). *Lung Cancer.* 2000; 29(suppl 1):72.
22. Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest.* 1997;111:1710-1717.
23. Cella DF, Bonomi AE, Lloyd SR, Tulsky DS, Kaplan E, Bonomi P. Reliability and validity of the Functional Assessment of Cancer Therapy- Lung (FACT-L) quality of life instrument. *Lung Cancer.* 1995;12:199-220.
24. Cella D, Eton DT, Fairclough DL, et al. What is a clinically meaningful change on the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire? results from Eastern Cooperative Oncology Group (ECOG) Study 5592. *J Clin Epidemiol.* 2002;55:285-295.
25. Green S, Weiss GR. Southwest Oncology Group standard response criteria, endpoint definitions and toxicity criteria. *Invest New Drugs.* 1992;10:239-253.
26. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: develop-

©2003 American Medical Association. All rights reserved.

ment and validation of the general measure. *J Clin Oncol.* 1993;11:570-579.
27. Bailey R, Kris M, Wolf M, et al. Tumor epidermal growth factor receptor (EGFR) expression levels does not predict for response in patients (pts) receiving gefitinib ("Iressa," ZD1839) monotherapy for pretreated advanced non-small-cell lung cancer (NSCLC): IDEAL 1 and 2. *Proc Am Assoc Cancer Res.* 2003;1362.
28. Fleiss J. *Statistical Methods for Rates and Proportions*. London, England: John Wiley & Sons; 1981.
29. Natale RB, Skarin A, Maddox A-M, et al. Improvement in symptoms and quality of life for advanced non-small-cell lung cancer patients receiving ZD1839 ("Iressa") in IDEAL 2. *Proc Am Soc Clin Oncol.* 2002;21:292a.
30. Massarelli E, Andre F, Liu DD, et al. A retrospective analysis of the outcome of patients who have received two prior chemotherapy regimens including platinum and docetaxel for recurrent non-small cell lung cancer. *Lung Cancer.* 2003;39:55-61.
31. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol.* 2000;18:2095-2103.
32. Fossella FV, DeVore R, Kerr RN, et al, the TAX 320 Non-Small Cell Lung Cancer Study Group. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. *J Clin Oncol.* 2000;18:2354-2362.
33. Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. *J Clin Oncol.* 2003;21:2237-2246.
34. Perez-Soler R, Chachoua A, Huberman M, et al. A phase II trial of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor OSI-774, following platinum-based chemotherapy, in patients with advanced, EGFR-expressing, non-small cell lung cancer (NSCLC). Presented at: American Society of Clinical Oncology Annual Meeting; May 12-15, 2001; San Francisco, Calif.
35. Inoue A, Saijo Y, Maemondo M, et al. Severe acute interstitial pneumonia and gefitinib. *Lancet.* 2003; 361:137-139.
36. Cooper JA Jr, White DA, Matthay RA. Drug-induced pulmonary disease, part 1: cytotoxic drugs. *Am Rev Respir Dis.* 1986;133:321-340.
37. Bergeron A, Bergot E, Vilela G, et al. Hypersensitivity pneumonitis related to imatinib mesylate. *J Clin Oncol.* 2002;20:4271-4272.
38. Saltz L, Rubin M, Hochster H, et al. Acne-like rash predicts response in patients treated with cetuximab (IMC-C225) plus irinotecan (CPT-11) in CPT-11-refractory colorectal cancer (CRC) that expresses epidermal growth factor receptor (EGFR). *Clin Cancer Res.* 2001;7(suppl):3766S.
39. Shah NT, Miller VA, Kris MG, et al. Bronchioloalveolar histology and smoking history predict response to gefitinib (Iressa) [abstract]. *Proc Am Soc Clin Oncol.* 2003;22:628.
40. O'Connell J, Kris MG, Gralla RJ, et al. Frequency and prognostic importance of pretreatment clinical characteristics in patients with advanced non-small cell lung cancer treated with combination chemotherapy. *J Clin Oncol.* 1986;4:1604-1614.
41. Savage D, Antman K. Imatinib mesylate—a new oral targeted therapy. *N Engl J Med.* 2002;346:683-693.
42. Heinrich MC, Blanke CD, Druker BJ, Corless CL. Inhibition of KIT tyrosine kinase activity: a novel molecular approach to the treatment of KIT-positive malignancies. *J Clin Oncol.* 2002;20:1692-1703.
43. Heinrich MC, Corless CL, Blanke C, et al. KIT mutational status predicts clinical response to STI571 in patients with metastatic gastrointestinal stromal tumors (GISTs). *Proc Am Soc Clin Oncol.* 2002;21: 2a.
44. Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. *Science.* 2003;299:708-710.
45. Mauro MJ, O'Dwyer M, Heinrich MC, Druker BJ. STI571: a paradigm of new agents for cancer therapeutics. *J Clin Oncol.* 2002;20:325-334.
46. Stallings-Mann M, Wharen R, Thomas CY. Resistance of glioblastoma cells to an EGFR kinase inhibitor is associated with maintenance of signaling by phosphatidylinositol-3-kinase (P13K) and constitutive phosphorylation of the Gab1/Gab2 adapter proteins. *Proc Am Soc Clin Oncol.* 2002;21:19a.
47. Sirotnak F, Zakowski M, Miller V, Scher H, Kris M. Efficacy of cytotoxic agents against human tumor xenografts is markedly enhanced by co-administration of ZD1839 (Iressa), an inhibitor of EGFR tyrosine kinase. *Clin Cancer Res.* 2000;6:4885-4892.
48. Soria JC, Lee HY, Lee JI, et al. Lack of PTEN expression in non-small cell lung cancer could be related to promoter methylation. *Clin Cancer Res.* 2002; 8:1178-1184.
49. Singh B, Reddy PG, Goberdhan A, et al. p53 regulates cell survival by inhibiting PIK3CA in squamous cell carcinomas. *Genes Dev.* 2002;16:984-993.
50. Hainaut P, Pfeifer GP. Patterns of p53 G toT transversions in lung cancer reflect the primary mutagenic signature of DNA-damage by tobacco smoke. *Carcinogenesis.* 2001;22:367-374.
51. Schindler T, Bornmann W, Pellicena P, Miller WT, Clarkson B, Kuriyan J. Structural mechanism for STI-571 inhibition of abelson tyrosine kinase. *Science.* 2000;289:1938-1942.

The purpose of science is to extend our knowledge of forces of nature. The whole history of civilization is witness to the compelling necessity of this process. Any danger to mankind lies in the destructive use of discoveries which could have been used for its benefit. It does not lie in the discoveries themselves.
—Enrico Fermi (1901-1954)

©2003 American Medical Association. All rights reserved.