Gefitinib in Patients with Malignant Mesothelioma: A Phase II Study by the Cancer and Leukemia Group B

Ramaswamy Govindan,[1] Robert A. Kratzke,[2] James E. Herndon II,[4] Gloria A. Niehans,[3] Robin Vollmer,[5] Dorothy Watson,[4] Mark R. Green,[6] Hedy L. Kindler,[7] and on behalf of the Cancer and Leukemia Group B (CALGB 30101)

[1]Department of Medicine, Washington University School of Medicine, St. Louis, Missouri; [2]Division of Medical Oncology and [3]Department of Medicine, University of Minnesota, Minneapolis, Minnesota; Departments of [4]Biostatistics and Bioinformatics and [5]Pathology, Duke University, Medical Center, Durham, North Carolina; [6]Division of Medical Oncology, Medical University of South Carolina, Charleston, South Carolina; and [7]Department of Medicne, University of Chicago, Chicago, Illinois

ABSTRACT

Purpose: **The Cancer and Leukemia Group B conducted a phase II study of gefitinib, an inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase, in patients with previously untreated malignant mesothelioma.**

Experimental Design: **Eligible patients had unresectable pleural or peritoneal mesothelioma, measurable disease, no prior therapy, and performance status 0-1 by Cancer and Leukemia Group B criteria. Gefitinib (500 mg p.o.) was administered once a day for 21 days. Patients underwent restaging after every two cycles. Therapy was continued until disease progression or unacceptable toxicity.**

Results: **The most common grade 3 toxicities were diarrhea (16%) and nausea (12%). Of 43 patients enrolled, 1 patient (2%) had a complete response, 1 patient (2%) had a partial response, 21 (49%) had stable disease lasting two to eight cycles, 15 (35%) had progressive disease, and 5 (12%) had early deaths. One-year survival was 32% [95% confidence interval (CI), 21-50%]. Median survival and failure-free survival were 6.8% (95% CI, 3.5-10.3) and 2.6 months (95% CI, 1.5-4.0), respectively. The 3-month failure-free survival was 40% (95% CI, 25-56%). EGFR expression score by immunohistochemistry done in 28 patients was categorized as low (EGFR 1+ or 2+) or high (EGFR 3+) expression: 97% had EGFR overexpression (2+ or 3+). The median and 3-month failure-free survival were 3.6 months and 40% for those patients with low EGFR expression compared with 8.1 and 40% for those with high EGFR expression.**

Conclusions: **Although 97% of patients with mesothelioma had EGFR overexpression, gefitinib was not active in malignant mesothelioma. EGFR expression does not correlate with failure-free survival.**

INTRODUCTION

Approximately 2,500 to 3,000 patients with malignant mesothelioma are diagnosed in the United States each year. The incidence of mesothelioma is expected to decrease in the United States after reaching a peak in year 2000. However, the incidence of mesothelioma in Europe is expected to peak around 2020 before declining (1, 2). The majority of patients have unresectable disease. The median survival of patients with mesothelioma is about 6 to 15 months with a 5-year survival of <5% (3). The Cancer and Leukemia Group B (CALGB) has played a lead role in the evaluation of new drugs for mesothelioma. As single agents, several drugs have been found to have very minimal or no activity (4). The combination cisplatin and pemetrexed produced better response rates (41.3% versus 16.7%, $P < 0.0001$) and improved median survival (12.1 versus 9.3, $P = 0.02$) than cisplatin alone in a randomized phase III study (5). Based on this pivotal study, the combination of cisplatin and pemetrexed has been approved for use in malignant mesothelioma in the United States. Despite the promising results of cisplatin and pemetrexed, the long-term survival for patients with unresectable mesothelioma continues to be poor. There is a clear need to explore novel therapies for the treatment of malignant mesothelioma.

Epidermal growth factor receptor (EGFR) is overexpressed in a variety of tumors. EGFR overexpression has been associated with increased proliferation, inhibition of apoptosis and tumor angiogenesis (6). Mesothelioma cell lines have high levels of EGFR expression (7). Dazzi et al. reported that 68% of mesothelioma specimens showed EGFR overexpression (8). Govindan et al. showed EGFR overexpression in 11 of 19 mesothelioma specimens (9). The receptor tyrosine kinase inhibitor gefitinib (ZD 1839, Iressa) is a potent and selective inhibitor of EGFR tyrosine kinase (10). Gefitinib has been shown to inhibit the growth of tumors in a variety of human xenograft models in nude mice. It has also been shown to cause tumor regression in established tumor models. Gefitinib decreases proliferation and increases apoptosis in mesothelioma cell lines (11). The growth inhibitory effects of gefitinib are readily reversible on withdrawal of the compound. Both preclinical and early clinical studies indicate that the toxicities associated with gefitinib are minimal (12). Fatigue and diarrhea are the dose-limiting toxicities. Gefitinib has now been approved for use in patients with advanced non–small cell lung cancer with progressive disease after chemotherapy with platinum and docetaxel.

Received 9/21/04; revised 11/22/04; accepted 12/21/04.
Grant support: National Cancer Institute grant CA31946 (CALGB 30101, Richard L. Schilsky, M.D., Chairman) and NIH/Science Applications International Corporation–Frederick, Inc. subcontract 22XS053A.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
Requests for reprints: Ramaswamy Govindan, Division of Medical Oncology, Washington University School of Medicine, 4960 Children's Place, Suite 108, St. Louis, MO 63110. Phone: 314-362-4819; Fax: 314-362-7086; E-mail: rgovinda@im.wustl.edu.

PATIENTS AND METHODS

Eligibility Criteria. Patients were considered eligible if they had histologically confirmed malignant mesothelioma not amenable to curative surgery, unidimensionally measurable disease, and a performance status 0-1 by CALGB criteria. Patients with prior systemic therapy for malignant mesothelioma were excluded; however, prior therapy with intrapleural cytotoxic agents or sclerosing agents including bleomycin was allowed. At least 2 weeks should have elapsed since major surgery and 4 weeks since radiotherapy. Required laboratory values included the following: WBC >3,000 cells/μL; platelet count >150,000 cells/μL; total bilirubin <1.5 mg/dL; creatinine <1.5 mg/dL; and aspartate aminotransferase <2× normal. Patients with a "currently active second malignancy" other than nonmelanoma skin cancer were excluded. Patients were not considered to have active malignancy if they had completed therapy and considered by their physicians to be at <30% risk of relapse. EGFR expression or overexpression was not required for enrollment in this study. All patients signed informed consent. Baseline evaluation included history and physical examination and complete blood counts and chemistries including evaluation of hepatic and renal functions. Complete blood counts and serum chemistries were required on the first day of each cycle. Computed tomographic scans of the affected areas (chest, abdomen, and/or pelvis) were done within 4 weeks of study entry. Although central pathology review was not required, all pathology reports were reviewed by the study chair (R.G.) and unstained slides or blocks were submitted for analysis of EGFR expression. Paraffin blocks from the core biopsy or 10 unstained slides taken at the time of initial diagnosis or subsequently were assessed for EGFR expression by immunohistochemistry using standard reagents (Zymed 31G7 EGFr) as previously described (13).

Treatment Plan. Patients received gefitinib at a dose of 500 mg p.o. once a day. A cycle was defined as continuous therapy for 21 days. Patients were reevaluated with computerized tomographic scan after every two cycles and therapy was continued until there was evidence of disease progression or unacceptable toxicity.

The results of the two phase II studies establishing that a daily p.o. dose of 250 mg a day is adequate for the treatment of advanced non–small cell lung cancer were not available when this study was designed (14, 15). The side effects seem to increase when gefitinib is given at doses above 600 mg/d. In view of tolerability and activity shown, we chose a dose level of 500 mg once a day when this study was planned.

Dose Modification. Toxicity was graded using the National Cancer Institute common toxicity criteria (Version 2.0). Dose adjustments were made for grade 3 or 4 toxicities. If a patient developed grade 3 or 4 toxicity, gefitinib was initially held for a maximum of 14 days and resumed at the original dose if the toxicity decreased to grade 2 or less. If the patient subsequently experienced the same or different grade 3 or 4 toxicity, the dose was decreased to 250 mg once a day after the toxicity has resolved to grade 1 or 2. If the patients continued to have grade 3 or 4 toxicity despite holding gefitinib for 14 days, they were taken off the study. Only one dose reduction per patient was permitted. Once a dose reduction occurred, dose reescalation was not permitted. Response was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) criteria (16).

Statistical Analysis. Based on the CALGB database from 10 previous prospective studies, the 3-month failure-free survival rate among patients with good performance status (Eastern Cooperative Oncology Group PS 0-1) is ~60%. The primary end point of the study was the percentage of patients who remain alive and progression free 3 months (defined "success") after initial administration of gefitinib. A single-stage study design was used to differentiate between 55% and 75% 3-month failure-free survival rate. If the true percentage of patients who are successfully treated with gefitinib was ≥75%, it would be considered worthy of further study in malignant mesothelioma. On the other hand, if the true success rate were <55%, this regimen would not be pursued further. Specifically, the hypothesis tested was H0: $P <= 0.55$ versus H1: $P >= 0.75$, where P is the proportion of patients who remain failure-free 3 months after initial administration. Assuming a type I and II error rate of 10%, the sample size for this study was 40 patients. Based on previous data, we expected that ~60% of patients (or 24 patients) enrolled onto this study would have EGFR overexpression. Within this particular patient subgroup, there would be over 90% power to differentiate between a 55% and 80% 3-month failure-free survival rate in the test described above and conducted at the 0.10 level of significance. If 17 or more of the ~24 patients with

Table 1 Patient characteristics

Characteristic	*n* (%)
Gender	
Male	39 (91%)
Female	4 (9%)
Age	
Median (minimum, maximum)	72 (42,85)
≥70 y	24 (56%)
Histology	
Epithelial	34 (79%)
Sarcomatoid	3 (7%)
Mixed	5 (12%)
Subtype, unknown	1 (2%)
Origin	
Pleura	42 (98%)
Peritoneum	1 (2%)
Performance status	
0	16 (37%)
1	27 (73%)
Symptom duration	
<3 mo	13 (30%)
>3 mo	22 (51%)
Unknown	8 (29%)
Weight loss	
<10%	31 (73%)
>10%	11 (25%)
Unknown	1 (2%)
Platelets	
<400,000	28 (65%)
>400,000	15 (35%)
CALGB mesothelioma index	
Group 1	2 (5%)
Group 2	9 (21%)
Group 3	19 (44%)
Group 4	7 (16%)
Group 5	6 (14%)

Table 2 Grade 3 and 4 toxicities ($N = 43$)

Toxicities	Grade 3, *n* (%)	Grade 4, *n* (%)
Diarrhea	7 (16%)	
Nausea	5 (12%)	
Vomiting	4 (9%)	
Dehydration	2 (5%)	1 (2%)
Skin rash	2 (5%)	
Fatigue	2 (5%)	
Transaminase elevation		
ALT	2 (5%)	
AST	1 (2%)	
Pulmonary		1 (2%)*
Hyponatremia	1 (2%)	
Confusion	1 (2%)	
Renal failure	1 (2%)	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

*This patient died of acute respiratory failure attributed to exacerbation of chronic obstructive lung disease with no radiological features of interstitial lung disease.

EGFR amplification lived failure free for 3 months or more, additional studies in the subgroup of mesothelioma patients with EGFR overexpression would be appropriate. Kaplan-Meier curves were used to describe overall survival and failure-free survival (17). Survival time is defined as the time between registration and death. Failure-free time is computed as the time between registration and disease progression or death.

RESULTS

Forty-three patients enrolled between August 2001 and February 2002 were all eligible for assessment of response and toxicity. Table 1 summarizes the patient characteristics. Ninety-one percent were males, median age was 72 years (range, 42-85), and 56% of the patients were older than 70 years. Most patients had epitheloid histology and pleural mesothelioma. Seventy-three percent of the patients had a performance status of 1.

Median number of cycles received in this study was 2 (range, 1-31). A total of 200 cycles were administered to 43 patients. Fourteen percent of patients received more than six cycles of therapy.

Grade 3 and 4 toxicities are presented in Table 2. One patient died of respiratory failure attributed to worsening of emphysema with progressive hypercapnia, hypoxia, and absence of any interstitial infiltrates on computed tomography of the chest. One patient developed severe dehydration secondary to diarrhea and poor p.o. intake and 28% of patients developed a grade 3 toxicity, most frequently diarrhea (16%) followed by nausea (12%). Only 5% of patients experienced grade 3 skin rash. Three patients (7%) discontinued therapy because of side effects.

One patient (2%) had a complete response. One patient (2%) had a confirmed partial response, whereas 21 patients (49%) had stable disease for two to eight cycles. Progressive disease in the first 6 weeks was seen in 35% of patients whereas 12% of patients died early before completing two cycles of therapy due to progressive disease. Both the responders were men with epithelial histology and CALGB prognostic group of 3. The median failure-free survival was 2.6 months [95% confidence interval (CI), 1.5-4.0] as outlined in Table 3. EGFR expression score by immunohistochemistry on the available 28 specimens were 0+, 1+, 2+, and 3+ in 0 (0%), 1 (4%), 10 (36%), and 17 (60%), respectively. Only 40% of the patients remained failure free for at least 3 months after study entry (95% CI, 25-56%). The median failure-free survival for patients with low EGFR-expressing tumors versus those with high EGFR-expressing tumors was 2.7 months (95% CI, 1.5-∞) and 2.7 months (95% CI, 1.4-4.6), respectively. The median failure-free survival for patients with epithelial histology and nonepithelial histology was 2.7 months (95% CI, 1.4-4.2) and 1.4 months (95% CI, 1.3-2.6), respectively.

The median overall survival was 6.8 months (95% CI, 3.5-10.3) for the entire group; patients with high EGFR-over-expressing tumors had a median survival of 8.1 months (95% CI, 5.0-∞) compared with only 3.6 months (95% CI, 2.0-∞) for patients with low EGFR-expressing tumors. Kaplan-Meier plots for overall survival and failure-free survival are presented in Fig. 1. Patients with epithelial type mesothelioma had a median survival of 7.7 months (95% CI, 4.0-∞) compared with only 2.9 months (95% CI, 1.5-5.0) for patients with nonepithelial type. One-year survival for the entire study population was 32%.

DISCUSSION

Among 337 patients with malignant mesothelioma treated by CALGB in seven phase II studies, 82% had a performance status of 0 or 1 (18). The 3-month failure-free survival rates in patients with good performance status is ~60%. Treatment with single agent gefitinib resulted in a 3-month failure-free survival rate of only 40%, significantly lower than what would be predicted based on the CALGB database. The promising *in vitro* activity of gefitinib in mesothelioma cell lines was not reproduced in this phase II study. The rapid accrual rate raised the concern whether patients with poor performance status were enrolled in this study, given the appeal of a novel agent such as gefitinib and its well-known tolerability even among patients with poor performance status. However, the proportion of patients represented in the various CALGB prognostic groups (based on six variables including performance status, age, hemoglobin, white blood count, weight loss, and presence or absence of chest pain) in this

Table 3 Survival and failure-free survival

	All patients, mo (95% CI)	Patients with low EGFR expression, mo (95% CI)*	Patients with high EGFR expression, mo (95% CI)†
Overall median survival	6.8 (3.5-10.3)	3.6 (2.0-∞)	8.1 (5.0-∞)
Median failure-free survival	2.6 (1.5-4.2)	2.7 (1.5-∞)	2.7 (1.4-4.6)
Failure free survival >3 mo (%)	40	40	40

*EGFR expression 1+ or 2++.

†EGFR expression 3+.

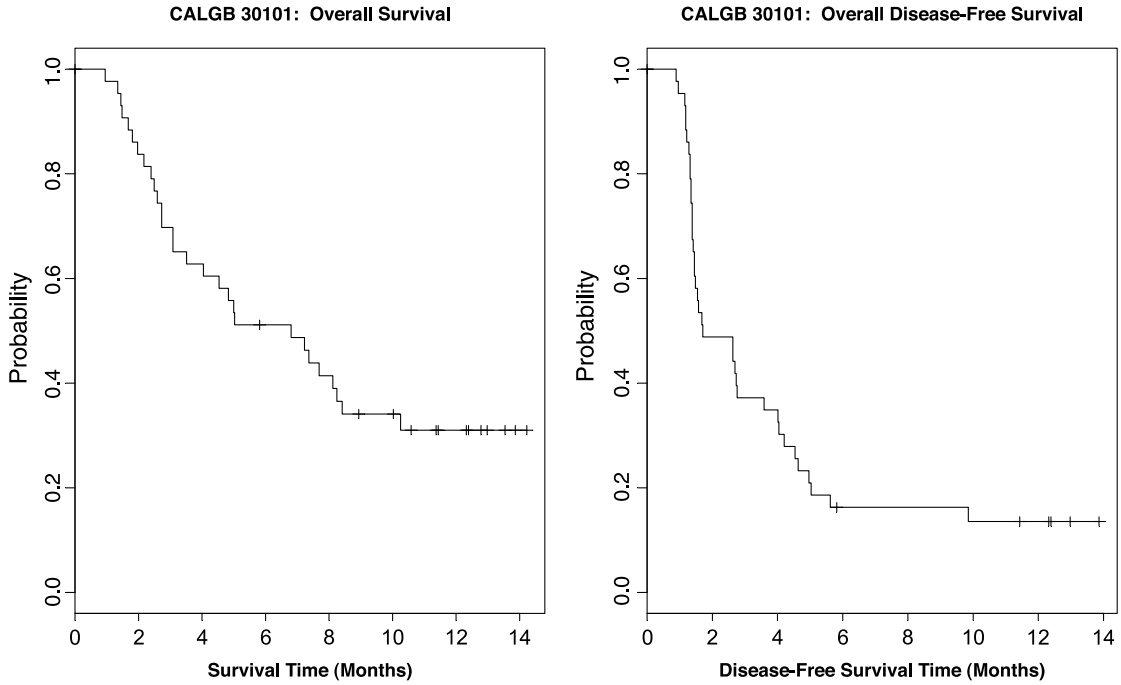

Fig. 1 Overall survival and disease-free survival of patients with malignant mesothelioma treated with gefitinib.

study is not significantly different compared with the other CALGB phase II studies and could not by itself account for the disappointing results.

EGFR overexpression did not predict response to gefitinib in this study. Similar lack of correlation between EGFR expression and response to therapy with this class of drugs has been reported in other malignancies (14, 15, 19). Mutations in EGFR tyrosine kinase domain have been associated with response in patients with metastatic NSCLC (20, 21). The prevalence of such mutations in mesothelioma is presently unknown.

It is unclear whether EGFR overexpression is a reliable predictor of poor outcome in patients with epithelial malignancies (22). EGFR overexpression is seen predominantly in patients with epitheloid malignant mesothelioma, a subtype known to have a better outcome. This fact may explain the better survival seen in this study in patients with high expression of EGFR.

It is important to study the prevalence of EGFR tyrosine kinase mutations in malignant mesothelioma and perhaps design future studies with this class of agents in patients with activating mutations in the EGFR tyrosine kinase domain. Based on the results of this phase II study, we conclude that further investigation of gefitinib in mesothelioma is not warranted in unselected group of patients with malignant mesothelioma.

APPENDIX 1

Institutions that participated in this study and corresponding grant support:

CALGB Statistical Center, Durham, NC—Stephen George, Ph.D. (CA33601).

Christiana Care Health Services, Inc. Community Clinical Oncology Program (CCOP), Wilmington, DE—Stephen Grubbs, M.D. (CA45418).

Dartmouth Medical School—Norris Cotton Cancer Center, Lebanon, NH—Marc S. Ernstoff, M.D. (CA04326).

Duke University Medical Center, Durham, NC—Jeffrey Crawford, M.D. (CA47577).

Green Mountain Oncology Group CCOP, Bennington, VT—L. Herbert Maurer, M.D. (CA35091).

Southern Nevada Cancer Research Foundation CCOP, Las Vegas, NV—John Ellerton, M.D. (CA35421).

SUNY Upstate Medical University, Syracuse, NY—Stephen L. Graziano, M.D. (CA21060).

Syracuse Hematology-Oncology Associates CCOP, Syracuse, NY—Jeffrey Kirshner, M.D. (CA45389).

The Ohio State University Medical Center, Columbus, OH—Clara D Bloomfield, M.D. (CA77658).

University of California at San Diego, San Diego, CA—Stephen L Seagren, M.D. (CA11789).

University of California at San Francisco, San Francisco, CA—Alan P. Venook, M.D. (CA60138).

University of Chicago Medical Center, Chicago, IL—Gini Fleming, M.D. (CA41287).

University of Illinois MBCCOP, Chicago, IL—Lawrence E. Feldman, M.D. (CA74811).

University of Iowa, Iowa City, IA—Gerald Clamon, MD (CA47642).

University of Missouri/Ellis Fischel Cancer Center, Columbia, MO—Michael C Perry, M.D. (CA12046).

Washington University School of Medicine, St. Louis, MO—Nancy Bartlett, MD (CA77440).

REFERENCES

1. Price B. Analysis of current trends in United States mesothelioma incidence. Am J Epidemiol 1997;145:211–8.

2. Peto J, Decarli A, La Vecchia C, Levi F, Negri E. The European mesothelioma epidemic. Br J Cancer 1999;79:666–72.

3. Kindler HL, Vogelzang N. Mesothelioma. In: Vokes EE, Golomb H, editors. Oncologic therapies. Berlin: Springer-Verlag; 2003.

4. Tomek S, Manegold C. Chemotherapy for malignant pleural mesothelioma: past results and recent developments. Lung Cancer 2004;45 Suppl 1:S103–19.

5. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003;21: 2636–44.

6. Yarden Y. The EGFR family and its ligands in human cancer. signalling mechanisms and therapeutic opportunities. Eur J Cancer 2001; 37 Suppl 4:S3–8.

7. Morocz IA, Schmitter D, Lauber B, Stahel RA. Autocrine stimulation of a human lung mesothelioma cell line is mediated through the transforming growth factor α/epidermal growth factor receptor mitogenic pathway. Br J Cancer 1994;70:850–6.

8. Dazzi H, Hasleton PS, Thatcher N, Wilkes S, Swindell R, Chatterjee AK. Malignant pleural mesothelioma and epidermal growth factor receptor (EGF-R). Relationship of EGF-R with histology and survival using fixed paraffin embedded tissue and the F4, monoclonal antibody. Br J Cancer 1990;61:924–6.

9. Govindan R, Suppiah R, Ritter J. EGFR expression in mesothelioma. Proc Am Soc Clin Oncol 2001;11. Abstract 3106.

10. Herbst RS. ZD1839: targeting the epidermal growth factor receptor in cancer therapy. Expert Opin Investig Drugs 2002;11:837–49.

11. Janne PA, Taffaro ML, Salgia R, Johnson BE. Inhibition of epidermal growth factor receptor signaling in malignant pleural mesothelioma. Cancer Res 2002;62:5242–7.

12. 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: 4292–302.

13. Nguyen PL, Swanson PE, Jaszcz W, et al. Expression of epidermal growth factor receptor in invasive transitional cell carcinoma of the urinary bladder. A multivariate survival analysis. Am J Clin Pathol 1994; 101:166–76.

14. 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: 2237–46.

15. Kris MG, Natale RB, Herbst RS, et al. 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. JAMA 2003;290:2149–58.

16. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205–16.

17. Kaplan EL, Meier PL. Nonparametric estimation of incomplete observations. J Am Stat Assoc 1958;53:457–81.

18. Herndon JE, Green MR, Chahinian AP, Corson JM, Suzuki Y, Vogelzang NJ. Factors predictive of survival among 337 patients with mesothelioma treated between 1984 and 1994 by the Cancer and Leukemia Group B. Chest 1998;113:723–31.

19. Arteaga CL. ErbB-targeted therapeutic approaches in human cancer. Exp Cell Res 2003;284:122–30.

20. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004; 304:1497–500.

21. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350: 2129–39.

22. Nicholson RI, Gee JM, Harper ME. EGFR and cancer prognosis. Eur J Cancer 2001;37 Suppl 4:S9–15.