Eur Respir J 2007; 29: 128–133
DOI: 10.1183/09031936.00050706

Gefitinib monotherapy in advanced nonsmall cell lung cancer: a large Western community implementation study

R. van Puijenbroek*, L. Bosquée#, A-P. Meert¶, D. Schallier+, J-C. Goeminne§, G. Tits[f], P. Collard, K. Nackaerts*, J-L. Canon##, F. Duplaquet¶¶, D. Galdermans++, P. Germonpré§§, M-A. Azerad[ff], G. Vandenhoven[ff], J. De Greve+ and J. Vansteenkiste***

ABSTRACT: **Epidermal growth factor receptor tyrosine kinase inhibitors represent a new treatment option for patients with advanced nonsmall cell lung cancer (NSCLC). This retrospective study examined to what extent previous clinical trial experience matches large-scale Western community implementation of this treatment.**

In the Belgian expanded access programme, the data from 513 patients with advanced or metastatic NSCLC, not suitable for further chemotherapy and receiving oral gefitinib 250 mg·day^{-1} until disease progression, death or unacceptable toxicity, were analysed.

The median (range) duration of gefitinib treatment was 2.3 months (0.0–32.7). Its use was predominantly in second- or third-line treatment. The overall response and disease control rates were 8.9 and 41.2%, respectively. In univariate analysis, response was more common in females and never-smokers. In multivariate analysis, female sex was the only significant predictive factor (odds ratio (OR) (95% confidence interval (CI)) 0.329 (0.129–0.839)). Symptom improvement was reported in 108 patients of whom 32 (29.6%) had an objective response, 66 (61.1%) experienced disease stabilisation and 10 (9.3%) progressed. Gefitinib was well tolerated; only 7.8% of the patients reported grade 3 or 4 toxicity. The overall median survival was 4.7 months, with a 1-yr survival rate of 21%. Survival was strongly influenced by a better performance status (PS) (good PS: hazard ratio (HR) (95%CI) 0.110 (0.077–0.157)) and adenocarcinoma with bronchioloalveolar carcinoma features histology (HR (95%CI) 0.483 (0.279–0.834)).

In conclusion, the activity of gefitinib was confirmed in the present large Western community implementation study. Response, present in a small subgroup, led to a rewarding survival and could be predicted by sex only. Baseline performance status and adenocarcinoma with bronchioloalveolar carcinoma features histology were significant factors for survival.

KEYWORDS: **Community implementation study, epidermal growth factor, expanded access, gefitinib, nonsmall cell lung cancer, treatment outcome**

The treatment of advanced nonsmall cell lung cancer (NSCLC) has improved over the past decade. Cisplatin-based chemotherapy improves the outcome of patients with early [1] or locally advanced NSCLC [2]. In metastatic disease, modern regimens combining platinum with gemcitabine or taxanes have brought the 1-yr survival rate from 15 to 30%. However, a therapeutic plateau has been reached with the current chemotherapeutic options. Furthermore, better options for patients who relapse after first- and second-line chemotherapy are needed [3]. Consequently, targeted therapy gained a central place in current cancer therapeutics development. The most striking example is the success of imatinib in the treatment of gastrointestinal stromal tumours [4]. As NSCLC is characterised by frequent expression of the epidermal growth factor receptor (EGFR), this target was studied extensively. Based on the results of two randomised phase II studies (Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL) 1 and 2) showing encouraging response and symptom improvement rates in heavily pretreated patients, the EGFR tyrosine kinase inhibitor (TKI) gefitinib became the first available targeted therapy for the treatment of NSCLC [5, 6]. Gefitinib was approved for the treatment of relapsed NSCLC in several countries, including Japan and the USA. In the meanwhile, no

AFFILIATIONS
*Univ. Hospital, Catholic University, Leuven,
#Citadelle Hospital, Liège
¶Jules Bordet Institute,
+University Hospital VUB,
**Cliniques Universitaires St.-Luc, and
[ff]Astra Zeneca Medical, Brussels,
§St-Elisabeth Hospital, Namur,
[f]St-Andries Hospital, Tielt,
##Notre Dame Hospital, Charleroi,
¶¶Univ. Hospital UCL, Yvoir,
++Middelheim Hospital, and
§§Univ. Hospital UIA, Antwerp, Belgium.

CORRESPONDENCE
J. Vansteenkiste
Respiratory Oncology Unit (Pneumology)
University Hospital Gasthuisberg
Herestraat 49
3000 Leuven
Belgium
Fax: 32 16346803
E-mail: johan.vansteenkiste@uz.kuleuven.ac.be

Received:
April 12 2006
Accepted after revision:
August 29 2006

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

additional benefit could be demonstrated when gefitinib was added to standard first-line chemotherapy in the Iressa NSCLC Trial Assessing Combination Treatment (INTACT) studies [7, 8]. In the phase III Iressa Survival Evaluation in Lung Cancer (ISEL) study in patients failing after previous chemotherapy, gefitinib improved survival compared to best supportive care alone. However, this difference did not reach significance except in pre-defined subgroups, such as never-smokers or Asian patients [9].

In a worldwide Expanded Access Program (EAP), patients with advanced NSCLC and no alternative therapeutic options were able to receive gefitinib treatment. As a variable degree of selection is always present in the context of prospective clinical trials, it is important to study the applicability of their results in community settings. The present study represents the retrospective analysis of the patients enrolled in the EAP in Belgium. The purpose of the analysis is to examine the response and outcome with gefitinib and the tolerability within the general community setting as well as to identify clinical parameters that may predict for response or survival. In an ancillary study, a set of genetic parameters that could predict gefitinib sensitivity will be analysed and reported separately.

PATIENTS AND METHODS

Cohort assembly

Patient data were retrieved from the Belgian EAP, which involved a total of 1,464 patients enrolled between January 2001 and December 2004. All patients with proven advanced NSCLC failing previous chemotherapy or without alternative therapeutic options were able to receive gefitinib 250 $mg \cdot day^{-1}$ until disease progression, death or unacceptable toxicity occurred. Inherent to this type of study, response assessment was not prospectively structured according to, for example, Response Evaluation Criteria in Solid Tumours (RECIST) parameters, but performed at each centre according to local standards. In general, a first evaluation of response with clinical factors [10], chest radiography and/or computed tomography scan took place after 4-6 weeks of treatment. Symptom improvement (SI) was evaluated according to the clinical judgement of the treating physician. All participating patients gave written informed consent. All centres that had $\geqslant$10 patients in the EAP participated in the present study, except for one refusal in a centre with 14 cases. A standardised questionnaire listing data on demographics, tolerability, response, symptom improvement and outcome was used to sample the data. Baseline assessment included smoking history, World Health Organization (WHO) performance status (PS), tumour assessment and previous local therapy (surgery or radiotherapy). Detailed information about previous chemotherapy was included, *i.e.* number of lines, drugs administered, duration of treatment, treatment-free intervals and best objective response to each line.

Statistics

Descriptive data are presented as median (range). The relationship between patients' characteristics and likelihood of response, disease control (*i.e.* response or stabilisation) or symptom improvement were tested using a Chi-squared test in the univariate analysis and logistic regression in the multivariate analysis. The variables of interest were sex, performance status, smoking history, histology and number of lines of prior chemotherapy. Overall survival was defined as the period between the start of gefitinib treatment and the date of last follow-up for censored cases or date of death. For survival, the same set of variables was studied. The relationship with survival was studied with the Kaplan-Meier analysis and log-rank test and with Cox regression for multivariate analysis. A p-value <0.05 was considered to be statistically significant.

RESULTS

Data from 513 patients were retrieved from different academic (six centres, 267 patients) and nonacademic (five centres, 246 patients) hospitals.

The patients' demographics are listed in table 1. Male and stage IV subgroups were ~75% of the total number of patients each. There were 40 (7.8%) never-smokers and 34 (6.7%) patients with adenocarcinoma with bronchioloalveolar carcinoma features (AD/BAC). Almost 60% of the patients had received $\geqslant$2 lines of chemotherapy before entering the EAP with gefitinib. This chemotherapy mostly consisted of platinum (81.5%), gemcitabine (71.4%) or vinorelbine (30.2%), and a taxane (50.7%), as currently accepted first- and second-line treatment. Gefitinib was used as primary treatment in patients non amenable to chemotherapy due to low PS, comorbidity or refusal. The median (range) duration of gefitinib treatment was 2.3 months (0.0–32.7) in the total group.

The overall observed response rate (RR) was 8.9%, with four complete responders (table 2). The median (range) duration of intake of gefitinib in responders was 8.1 months (1.9–25.4), with 13 patients still taking gefitinib at the time of analysis. The RR was significantly higher in females compared with males (16.2 *versus* 6.2%, p=0.002) and lifetime never-smokers compared with ever-smokers (21.8 *versus* 8.0%, p=0.009).

The overall observed disease control rate (DCR) was 41.2%. The median (range) duration of intake of gefitinib in these patients was 6.8 months (0.6–32.7) with 21 patients still taking gefitinib at the time of analysis. DCR correlated significantly with a better PS (good *versus* intermediate *versus* poor: 55.7 *versus* 36.7 *versus* 12.5%; p<0.0001), number of previous chemotherapy regimens (none *versus* one *versus* two: 60.0 *versus* 48.1 *versus* 34.9%; p=0.004) and with AD/BAC histology compared to non-AD/BAC histology (60.0 *versus* 39.9%, p=0.049).

In the multivariate analysis, likelihood of response was significantly determined by female sex (odds ratio (OR) (95% confidence interval (CI)) 0.329 (0.129–0.839), p=0.020). For disease control the only significant factor was a good PS (OR (95%CI) 0.105 (0.035–0.320), p<0.0001). A never-smoking history was nonpredictive.

In patients for whom sufficient symptom data were available (unknown in 118 patients), 29% (108 patients) experienced an improvement in overall symptoms. Of these, 32 (29.6%) had an objective response, 66 (61.1%) experienced disease stabilisation and 10 (9.3%) progressed. In univariate analysis, there was a statistically significant association between SI and PS (good *versus* intermediate *versus* poor: 40.3 *versus* 22.5 *versus* 7.5%;

TABLE 1 Demographics of the study patients

Characteristics	
Age yrs	63 (32–89)
Sex	
Male	372 (72.5)
Female	141 (27.5)
Disease stage	
III	123 (24.0)
IV	384 (74.8)
Other	6 (1.2)
WHO performance status	
Good (0–1)	191 (37.3)
Intermediate (2)	133 (25.9)
Poor (3–4)	73 (14.2)
Unknown	116 (22.6)
Smoking status	
Never	40 (7.8)
Ever	448 (87.3)
Unknown	25 (4.9)
Histology	
Adenocarcinoma	252 (49.1)
AD/BAC	34 (6.7)
Squamous cell	135 (26.3)
Other NSCLC	92 (17.9)
Prior local treatment	
Yes	230 (44.8)
No	283 (55.2)
Prior chemotherapy regimens	
0	42 (8.2)
1	170 (33.1)
⩾2	301 (58.7)
Prior chemotherapy agents	
Platinum	418 (81.5)
Taxane	260 (50.7)
Gemcitabine	366 (71.4)
Vinorelbine	155 (30.2)
Other	177 (34.5)

Data are presented as median (range) and n (%), unless otherwise stated. WHO: World Health Organization; AD/BAC: adenocarcinoma with bronchioloalveolar features; NSCLC: nonsmall cell lung cancer.

p<0.0001) and AD/BAC histology (AD/BAC *versus* non-AD/BAC, 73.7 *versus* 26.8%; p=0.048), but not with sex or smoking status.

The median overall survival time (MST) after the start of treatment with gefitinib was 4.7 months, with a 1-yr survival rate (1YSR) of 21% (table 3). Figure 1 shows the Kaplan-Meier estimates of overall survival comparing patients with good, intermediate or poor PS (p<0.0001). Other factors associated with better survival rates were AD/BAC histology (p=0.033) (fig. 2) and the number of prior chemotherapy treatments (p=0.013). In the multivariate Cox regression, better PS (good PS: HR (95%CI) 0.110 (0.077–0.157), p<0.0001; and intermediate PS: HR (95%CI) 0.283 (0.202–0.396), p<0.0001) and AD/BAC histology (HR (95%CI) 0.483 (0.279–0.834), p=0.009) remained significant predictive factors for survival.

The favourable tolerability of gefitinib was confirmed: only 7.8% of the patients were reported with grade 3 or 4 toxicity. A serious adverse event of pulmonary nature was reported in eight of the 513 patients. Five of these belonged to another category: cardiogenic pulmonary oedema (n=1), diffuse progression of tumour with bronchioloalveolar features (n=1), infectious pneumonia (n=2) and infectious pneumonia plus pulmonary embolism (n=1). Three instances of interstitial lung disease (ILD) were reported. One of these was unlikely to be related to gefitinib, as the ILD occurred 13 months after discontinuation of gefitinib. Two others were probably related, occurring 31 and 33 days after the start of gefitinib treatment, respectively. In both patients, other causes of ILD were ruled out. Both improved with cessation of gefitinib and administration of corticosteroids.

DISCUSSION

This retrospective analysis of the treatment with gefitinib for advanced NSCLC in a mixed academic and nonacademic setting in the Belgian EAP demonstrated clear antitumour activity (RR 8.9%; DCR 41.2%) in the absence of major toxicity (grade 3 or 4 toxicity 7.8%). The median duration of intake of gefitinib was 8.1 months in responding patients and 6.8 months in patients with disease stabilisation. Although the present authors do not really have the exact time to progression based on rigorous radiological follow-up, the results suggest a clinically meaningful duration of the effect of gefitinib in many patients. Symptom improvement was reported in 29.0% of the patients. As a whole, the findings in this large Western community implementation study demonstrate that the findings from previous prospective clinical trials [5, 6] are reproducible in a probably less selected group of patients coming from daily practice.

In the multivariate analysis, only female sex could be retained as a predictive factor for activity, but not histology or smoking status. Based on prospective trials and retrospective series, Asian origin, never-smoking status, adenocarcinoma histology and female sex are the most often reported predictors of response [5, 11–15]. Ethnicity was not a factor in the present series, as all patients were Caucasians. The never-smoking status of lung cancer patients is probably the strongest indicator of activity in Western populations [9, 11, 12, 15, 16]. This factor was significant in the current univariate analysis (p=0.009), but was not withheld in the multivariate analysis probably due to the lower number of known never-smokers in the series or due to overlap with other clinical factors. The RR was similar in patients with adenocarcinoma compared with nonadenocarcinoma (9.4 *versus* 8.4%) and AD/BAC compared with non-AD/BAC histology (12.0 *versus* 8.7%). This is in contrast with most other studies, where adenocarcinoma histology, especially the AD/BAC subtype, is usually associated with higher likelihood of response [11–13, 17]. The fact that different centres and, as such, different pathologists participated in the present study may be a factor in this apparent discrepancy. Nevertheless, responses in patients with squamous cell carcinoma were also reported in a recent large phase III study with the EGFR-TKI erlotinib [16].

A correlation was also found between PS and activity of gefitinib. As patients with a very low performance status (3 or 4) are in

TABLE 2 Univariate analysis of predictive factors for response or disease stabilisation[#]

	Patients n	Responders n	RR %	p-value	DC patients n	DCR %	p-value
All patients	403	36	8.9		166	41.2	
Sex				0.002			0.950
Female	111	18	16.2		46	41.4	
Male	292	18	6.2		120	41.1	
WHO performance status				0.098			<0.0001
0–1	176	19	10.8		98	55.7	
2	98	5	5.1		36	36.7	
3–4	40	1	2.5		5	12.5	
Smoking status				0.009			0.145
Never-smoker	32	7	21.9		17	53.1	
Smoker	351	28	8.0		140	39.9	
Histology				0.728			0.578
Adenocarcinoma	224	21	9.4		95	42.4	
Nonadenocarcinoma	179	15	8.4		71	39.7	
Histology				0.579			0.049
AD/BAC	25	3	12.0		15	60.0	
Non-AD/BAC	378	33	8.7		151	39.9	
Prior chemotherapy regimens				0.295			0.004
0	30	4	13.3		18	60.0	
1	135	15	11.1		65	48.1	
⩾2	238	17	7.1		83	34.9	

RR: response rate; DC: disease control; DCR: disease control rate; WHO: World Health Organization; AD/BAC: adenocarcinoma with bronchioloalveolar features. [#]: totals and subtotals can be lower than expected in certain cells due to missing values.

TABLE 3 Univariate analysis of survival and predictors of survival[#]

	Subjects n	MST months	1YSR %	p-value
All patients	513	4.7	21.4	
Sex				0.123
Female	141	5.7	26.8	
Male	372	4.7	19.3	
WHO performance status				<0.0001
0–1	191	8.0	36.3	
2	133	2.9	10.0	
3–4	73	1.1	0.0	
Smoking status				0.283
Never-smoker	40	7.3	25.2	
Smoker	448	4.6	20.3	
Histology				0.429
Adenocarcinoma	286	4.9	24.4	
Nonadenocarcinoma	227	4.6	17.4	
Histology				0.033
AD/BAC	34	8.9	39.1	
Non-AD/BAC	479	4.5	20.3	
Prior chemotherapy regimens				0.013
0	42	8.0	27.0	
1	170	5.3	26.1	
⩾2	301	3.8	16.4	

MST: median survival time; 1YSR: 1-yr survival rate; WHO: World Health Organization; AD/BAC: adenocarcinoma with bronchioloalveolar features. [#]: totals and subtotals can be lower than expected in certain cells due to missing values.

general not considered for chemotherapy, the issue has been raised whether this group could benefit from better-tolerated targeted therapies like gefitinib. These patients were, however, excluded from the prospective trials with gefitinib. The activity of gefitinib was poor in the present low PS population, suggesting that they are unlikely to benefit from this therapy, but as there was no comparator arm in the present study, it is not possible to ascertain that there would not be a benefit over best supportive care alone in such patients.

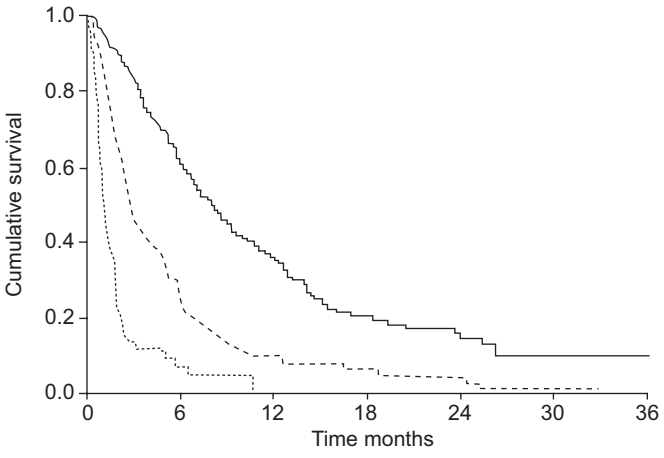

FIGURE 1. Survival according to the performance status (PS) at the start of gefitinib treatment. ——: PS 0-1; ------: PS 2; ·····: PS 3-4.

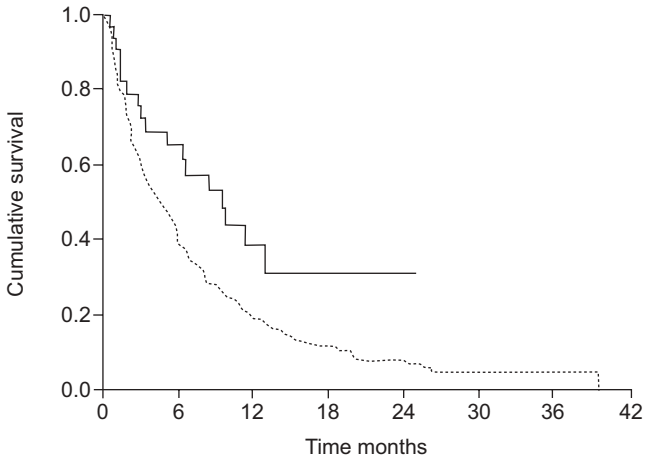

FIGURE 2. Survival according to adenocarcinoma with bronchioloalveolar features (AD/BAC; ——) or non-AD/BAC (·····) histology.

The MST of the total group was 4.7 months after the start of treatment with gefitinib, with a 1YSR of 21%. This is somewhat inferior to the survival data in the IDEAL studies [5, 6], probably due to a lower degree of patient selection in the present implementation study, as can be illustrated by the inclusion of 73 patients with very poor PS. This subgroup performed very badly, with a MST of only 1.1 month. The importance of PS for outcome has been reported by others as well [11, 14, 17, 18]. Apart from PS, AD/BAC histology was retained as a predictor of survival in the multivariate analysis. The longer MST of the patients with AD/BAC in the present series is probably an indicator of the more indolent course of this special type of NSCLC [19].

A favourable outcome in a subpopulation of NSCLC patients who respond to gefitinib was observed. Some responding patients experienced long-term benefit of the treatment, as can be suggested from the median duration of gefitinib treatment of 8.1 months in responders, up to a total of >2 yrs in a few patients. It is, however, urgently needed to have unequivocal predictors of activity of this important targeted agent for NSCLC. As it is obvious from the present community series and the experience of others, the ''clinical'' predictors of response are not well established in Western populations, with the exception of a never-smoking status in some series [9, 16]. Better and more targeted use of agents such as gefitinib is clearly needed to bring this breakthrough in the treatment of NSCLC to those patients who really benefit in a way that can be afforded by the health security systems. Increasing the understanding of the mechanism of action of these agents and deriving an unequivocal and specific predictive test from this knowledge is the way forward. At the present moment, such a test is not available for clinical practice. Expression of EGFR on the cell surface, measured by grading immunohistochemical staining with an EGFR antibody, is in general poorly predictive for a response [20, 21]. A frequent occurrence of EGFR domain mutations, reported in responders to EGFR-TKIs [22, 23], could not be confirmed in a recent phase III study [16]. The presence of a high EGFR gene copy number identified by fluorescence *in situ* hybridisation may become the most promising molecular predictor for gefitinib efficacy in NSCLC [24]. Further molecular analysis in the group of patients from the present series is ongoing.

The strengths of the present study are: the fact that it represents a large sample of patients of both university-affiliated and community hospitals from across the country, the collection of data during a defined time window and the use of a standardised data collection tool. The present study also has several potential limitations. The inclusion of some chemo-naive patients in the EAP for reasons of poor PS or comorbidity was allowed, despite the fact that this did not correspond to standard treatment guidelines. Less structured or less detailed documentation of patient data in the medical record is inherent to all retrospective chart audits, like the present implementation study.

Finally, it was not the aim of the present authors to measure safety and toxicity in detail, as this had already been performed in prospective series [5–8]. The data query sheet used only asked for the severe toxicity (grade 3 or 4 according to the National Cancer Institute Common Toxicity Criteria) occurring during gefitinib treatment. No further information on lower grade toxicity was asked in order to avoid the use of a too complex sheet for several nonacademic centres. One side-effect, drug-induced ILD is, however, of particular concern due to its potential severity, especially in Asian patients [25]. Most probably, the incidence in Western populations is only slightly elevated. In a large phase III study, an incidence of ILD of 1.5% for patients taking gefitinib 250 $mg \cdot day^{-1}$ and 0.9% for patients taking placebo was reported, a difference of 0.6% [8]. In another phase III study, the overall incidence of ILD-type events was <1% [7]. In the present series, which is one of the largest EAPs with a pure Caucasian population, no serial pulmonary function tests were in place, but clinically relevant ILD probably related to gefitinib could be withheld in two instances (0.4%). Both patients recovered with cessation of the drug and corticosteroid medication.

In summary, the present large Western community implementation study of gefitinib for advanced nonsmall cell lung cancer confirmed the good tolerability of this agent. Response, present in a subpopulation, led to very rewarding survival outcomes. Clinically meaningful symptom improvement was linked to disease response and disease stabilisation. Response could be predicted by sex only. Better predictive tests of activity of gefitinib are urgently needed to allow us to offer this therapy in a true targeted approach to those nonsmall cell lung cancer patients who would really benefit from this therapy while keeping the expenses for society at an acceptable level.

ACKNOWLEDGEMENTS

The authors would like to thank all colleagues who contributed to the analysis: L. Bosquée, J-L. Canon, P. Collard, F. Duplaquet, J. De Greve, D. Galdermans, P. Germonpré, J-C. Goeminne, A-P. Meert, K. Nackaerts, T. Pieters, D. Schallier, G. Tits and J. Vansteenkiste. The authors would also like to thank Astra Zeneca (Brussels, Belgium) for providing the EAP and for their help in the acquisition of the database (K. Geeroms) and all the patients who participated in the EAP.

REFERENCES

1 Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 2004; 350: 351–360.

2 Rowell NP, O'Rourke NP. Concurrent chemoradiotherapy in non-small cell lung cancer. *Cochrane Database Syst Rev* 2004; 4: CD002140.

3 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.

4 Demetri GD, Von Mehren M, Blanke CD, *et al.* Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2005; 347: 472–480.

5 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 (The IDEAL 1 Trial). *J Clin Oncol* 2003; 21: 2237–2246.

6 Kris MG, Natale RB, Herbst RS, *et al.* Efficacy of gefinitib, 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: 2149–2158.

7 Giaccone G, Herbst RS, Manegold C, *et al.* Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial (INTACT 1). *J Clin Oncol* 2004; 22: 777–784.

8 Herbst RS, Giaccone G, Schiller JH, *et al.* Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial (INTACT 2). *J Clin Oncol* 2004; 22: 785–794.

9 Thatcher N, Chang A, Parikh P, *et al.* Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 2005; 366: 1527–1537.

10 Therasse P, Arbuck SG, Eisenhauer EA, *et al.* New guidelines to evaluate the response to treatment in solid tumours. *J Natl Cancer Inst* 2000; 92: 205–216.

11 Haringhuizen A, Van Tinteren H, Vaessen HF, Baas P, Van Zandwijk N. Gefitinib as a last treatment option for non-small-cell lung cancer: durable disease control in a subset of patients. *Ann Oncol* 2004; 15: 786–792.

12 Miller VA, Kris MG, Shah N, *et al.* Bronchioloalveolar pathologic subtype and smoking history predict sensitivity to gefitinib in advanced non-small-cell lung cancer. *J Clin Oncol* 2004; 22: 1103–1109.

13 Konishi J, Yamazaki K, Kinoshita I, *et al.* Analysis of the response and toxicity to gefitinib of non-small cell lung cancer. *Anticancer Res* 2005; 25: 435–441.

14 Lim ST, Wong EH, Chuah KL, *et al.* Gefitinib is more effective in never-smokers with non-small-cell lung cancer: experience among Asian patients. *Br J Cancer* 2005; 93: 23–28.

15 Veronese ML, Algazy K, Bearn L, *et al.* Gefitinib in patients with advanced non-small cell lung cancer (NSCLC): the expanded access protocol experience at the University of Pennsylvania. *Cancer Invest* 2005; 23: 296–302.

16 Shepherd FA, Rodrigues Pereira J, Ciuleanu T, *et al.* Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005; 353: 123–132.

17 Park J, Park BB, Kim JY, *et al.* Gefitinib (ZD1839) monotherapy as a salvage regimen for previously treated advanced non-small cell lung cancer. *Clin Cancer Res* 2004; 10: 4383–4388.

18 Cappuzzo F, Bartolini S, Ceresoli GL, *et al.* Efficacy and tolerability of gefitinib in pretreated elderly patients with advanced non-small cell lung cancer (NSCLC). *Br J Cancer* 2004; 90: 82–86.

19 Miller VA, Hirsch FR, Johnson DH. Systemic therapy of advanced bronchioloalveolar cell carcinoma: challenges and opportunities. *J Clin Oncol* 2005; 23: 3288–3293.

20 Parra HS, Cavina R, Latteri F, *et al.* Analysis of epidermal growth factor receptor expression as a predictive factor for response to gefitinib (''Iressa'', ZD1839) in non-small-cell lung cancer. *Br J Cancer* 2004; 91: 208–212.

21 Bailey LR, Kris M, Wolf M, *et al.* Tumor EGFR membrane staining is not clinically relevant for predicting response in patients receiving gefitinib (''Iressa'', ZD1839) monotherapy for pretreated advanced non-small cell lung cancer: IDEAL 1 and 2. *Proc Am Assoc Cancer Res* 2003; 44: 170A.

22 Paez JG, Janne PA, Lee JC, *et al.* EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004; 304: 1497–1500.

23 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: 2129–2139.

24 Cappuzzo F, Hirsch FR, Rossi E, *et al.* Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small cell lung cancer. *J Natl Cancer Inst* 2005; 97: 643–655.

25 Inoue A, Saijo Y, Maemondo M, *et al.* Severe acute interstitial pneumonia and gefitinib. *Lancet* 2003; 361: 137–139.