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Gefitinib monotherapy in advanced non-small cell lung cancer: Experience from a large, Western community, implementation study.

Running title: Gefitinib for advanced non-small cell lung cancer (NSCLC).

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Abstract

Background: Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR TKI's) represent a new treatment option for patients with advanced NSCLC. This retrospective study examined to what extent previous clinical trial experience matches large-scale Western community implementation of this treatment.

Patients and methods: In the Belgian expanded access programme, the data of 513 patients with advanced or metastatic NSCLC, not suitable for further chemotherapy and receiving oral gefitinib 250mg/day until disease progression, death or unacceptable toxicity, were analysed.

Results: Median duration of gefitinib treatment was 2.3 months (range 0.0-32.7). 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 (*P*=0.002) and never-smokers (*P*=0.009). In multivariate analysis female gender was the only significant predictive factor (OR 0.329, 95%CI 0.129-0.839, *P*=0.020). 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. Overall median survival was 4.7 months, with a 1-year survival of 21%. Survival was strongly influenced by a better performance status (PS) (good PS: HR 0.110, 95%CI 0.077-0.157, *P*<0.0001) and adenocarcinoma with bronchioloalveolar carcinoma features (AD/BAC) histology (HR 0.483, 95%CI 0.279-0.834, *P*=0.009).

Conclusion: The activity of gefitinib was confirmed in this large Western community implementation study. Response, present in a small subgroup, led to a rewarding survival and could be predicted by gender only. Baseline PS and AD/BAC histology were significant factors for survival.

Keywords

Non-small cell lung cancer; Gefitinib; Epidermal Growth Factor; Treatment outcome; Community implementation study; Expanded access.

Introduction

The treatment of advanced non-small 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-year 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 1st and 2nd line chemotherapy are wanted [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 randomized phase II studies (IDEAL 1 and 2), showing encouraging response and symptom improvement rates in heavily pre-treated 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 United States. In the meanwhile, no additional benefit could be demonstrated when gefitinib was added to standard first-line chemotherapy in the INTACT studies [7,8]. In the phase III ISEL study in patients failing after previous chemotherapy, gefitinib improved survival compared to best supportive care alone, but this difference did not reach significance, except in predefined 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. This report represents the retrospective analysis of the patients enrolled in the EAP in Belgium. The purpose of this analysis was to examine the response and outcome with gefitinib and the tolerability within the general community setting and 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 as well.

Patients and Methods

Cohort assembly

Patient data were retrieved from the Belgian EAP (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 per day until disease progression, death or unacceptable toxicity. Inherent to this type of study, response assessment was not prospectively structured according to e.g. RECIST criteria, but performed at each centre according to local standards. In general, a first evaluation of response with clinical factors, chest X-ray and/or CT-scan took place after 4 to 6 weeks of treatment. Symptom improvement was evaluated according to the clinical judgement of the treating physician. All participating patients gave written informed consent. All centres that had at least 10 patients in the EAP participated in this 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, WHO performance status (PS), tumour assessment and previous local therapy (surgery or radiotherapy). Detailed information about previous chemotherapy was included: number of lines, drugs administered, duration of treatment, treatment-free intervals, and best objective response to each line.

Statistics

Descriptive data are given with their median value and range. The relationship between patients' characteristics and likelihood of response, disease control (i.e. response or stabilisation) or symptom improvement were tested using an X^2-test in the univariate analysis and logistic regression in the multivariate analysis. Variables of interest were gender, performance status, smoking history, histology and number of lines of prior chemotherapy. Overall survival was defined as the period between the start of gefitinib and 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. Probability

values <0.05 were considered to be statistically significant. All analyses were performed with Stat View 5.0.1.

Results

Data of 513 patients were retrieved from different academic (6 centres, 267 patients) and non-academic (5 centres, 246 patients) hospitals. The patients' demographics are listed in Table 1. Male and stage IV subgroups were about three quarters each. There were 40 (7.8%) never-smokers and 34 (6.7%) patients with adenocarcinoma with bronchioloalveolar carcinoma features (AD/BAC). Most of the patients had received at least two lines of chemotherapy before they entered 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 as first and second line treatment. Gefitinib was used as primary treatment in patients non amenable to chemotherapy because of low PS, co-morbidity or refusal of chemotherapy. The median duration of gefitinib treatment was 2.3 months in the total group (range 0.0-32.7).

The overall observed response rate (RR) was 8.9%, with 4 complete responders (Table 2). The median duration of intake of gefitinib in responders was 8.1 months (range 1.9-25.4); with 13 patients still taking gefitinib at the time of analysis. The RR was significantly higher in females compared to males (16.2% vs 6.2%, *P*=0.002) and lifetime never-smokers compared to ever-smokers (21.8% vs 8.0%, *P*=0.009).

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

In the multivariate analysis likelihood of response was significantly determined by female gender (OR 0.329, 95%CI 0.129-0.839, *P*=0.020). For disease control the only significant factor was a good

performance status (OR 0.105, 95%CI 0.035-0.320, *P*<0.0001). A never smoking history was non predictive.

In patients for whom sufficient symptom data were available (unknown in 118 patients), 29% experienced an improvement in overall symptoms. 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. In univariate analysis, there was a statistically significant association between SI and PS (good vs intermediate vs poor, 40.3% vs 22.5% vs 7.5%; *P*<0.0001) and AD/BAC histology (AD/BAC vs non-AD/BAC, 73.7% vs. 26.8%; *P*=0.048), but not with gender or smoking status.

Median overall survival time (MST) after start of treatment with gefitinib was 4.7 months, with a 1-year survival rate (1YS) 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 were AD/BAC histology (*P*=0.033) (Figure 2) and the number of prior chemotherapy treatments (*P*=0.013). In the multivariate Cox regression, better PS (good PS: HR 0.110, 95%CI 0.077-0.157, *P*<0.0001 and intermediate PS: HR 0.283, 95%CI 0.202-0.396, *P*<0.0001) and AD/BAC histology (HR 0.483, 95%CI 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**. In the 513 patients, a serious adverse event of pulmonary nature was reported in eight. Five of these belonged to another category: cardiogenic pulmonary edema (1), diffuse progression of tumour with bronchioloalveolar features (1), infectious pneumonia (2) and infectious pneumonia plus pulmonary embolism (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 start of gefitinib, 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 non-academic setting in the Belgian EAP demonstrated clear anti-tumour 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 we 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 therefore 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 gender 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 gender are the most often reported predictors of response [5,10-14]. Ethnicity was not a factor in our series, as all patients were Caucasians. The never-smoking status of lung cancer patients is probably the strongest indicator of activity in Western populations [9-11,14,15]. This factor was significant in our univariate analysis (P=0.009), but was not withheld in the multivariate analysis probably due to the lower number of known never-smokers in this series or due to overlap with other clinical factors. The RR was similar in patients with adenocarcinoma compared to non-adenocarcinoma (9.4% vs 8.4%) and AD/BAC compared to non-AD/BAC histology (12.0% vs 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 [10-12,16]. The fact that different centres, and as such different pathologists,

participated in this 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 [15].

We also found a correlation between PS and activity of gefitinib. As patients with a very low performance status (3 or 4) are in general not considered for chemotherapy, the issue has been raised if this group could perhaps benefit from better tolerated targeted therapies like gefitinib. These patients were, however, excluded from the prospective trials with gefitinib. Activity of gefitinib was poor in our low PS population, suggesting that they are unlikely to benefit from this therapy, but as there was no comparator arm in this study, it is not possible to ascertain that there would not be a benefit over best supportive care alone in such patients.

Median overall survival of the total group was 4.7 months after the start of gefitinib, with a 1YS of 21%. This is somewhat inferior to the survival data in the IDEAL studies [5,6], probably because of the 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 did very badly, with a MST of only 1.1 month. The importance of PS for outcome was reported by others as well [10,13,16,17]. 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 our series probably is an indicator of the more indolent course of this special type of NSCLC [18].

A favourable outcome in a subpopulation of NSCLC patients who respond to gefitinib is observed. Some responding patients experience 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 more than 2 years in a few patients. It is however urgently needed to have unequivocal predictors of activity of this important targeted agent for NSCLC. As was obvious from our 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 [9,15]. Better and more targeted use of targeted

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 our Health Security Systems. Increasing our 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 this 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 response [19,20]. A frequent occurrence of EGFR domain mutations, reported in responders to EGFR-TKIs [21,22], could not be confirmed in a recent phase III study [15]. The presence of a high EGFR gene copy number identified by fluorescence in-situ hybridisation (FISH) may become the most promising molecular predictor for gefitinib efficacy in NSCLC [23]. Further molecular analysis in the group of patients from our series is ongoing.

The strengths of our study are the fact that it represents a large sample of patients of both university-affiliated and community hospitals from across the country, data collection during a defined time window and use of a standardised data collection tool. Our study also has several potential limitations. Inclusion of some chemonaive patients in the EAP, for reasons of poor PS or co-morbidity, 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 this implementation study.

Finally, it was not our aim to measure safety and toxicity in detail, as this had already been done in prospective series [5-8]. Our data query sheet only asked for the severe toxicity (grade 3 or 4 according to the NCI-CTC) occurring during gefitinib treatment. No further information on lower grade toxicity was asked in order not to use a too complex sheet for several non-academic centres. **One side-effect, drug-induced ILD, however, is of particular concern, because of its potential severity, especially in Asian patients [24]. 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/d 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 less than 1% [7]. In our series, which is one of the largest EAP's with a pure Caucasian population, no serial pulmonary function tests were in place, but clinically relevant ILD likely related to gefitinib could be withheld in two instances (0.4%). Both patients recovered with cessation of the drug and corticosteroid medication.

In summary, our large Western community implementation study of gefitinib for advanced NSCLC 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 gender 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 NSCLC patients who would really benefit from this therapy while keeping the expenses for society at an acceptable level.

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Legends to the figures

Figure 1: Survival according to the performance status at the start of gefitinib.

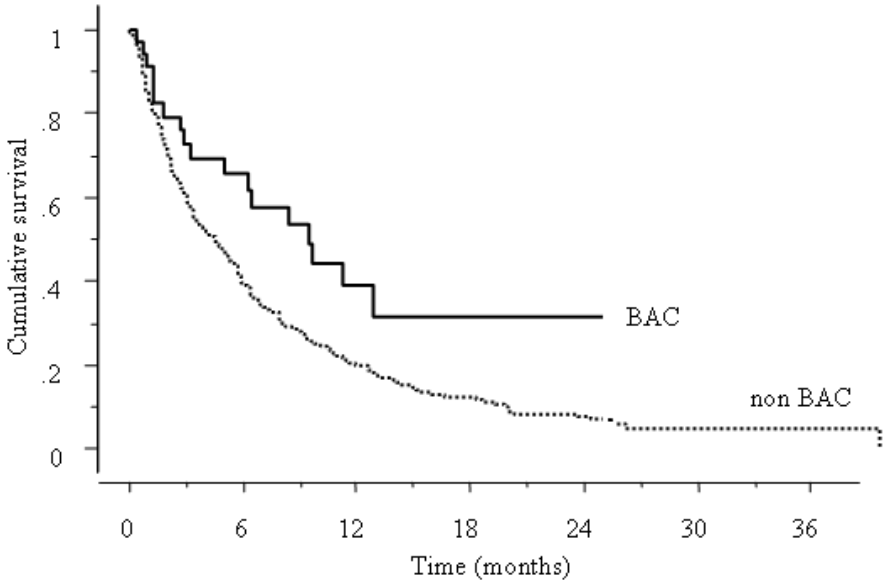
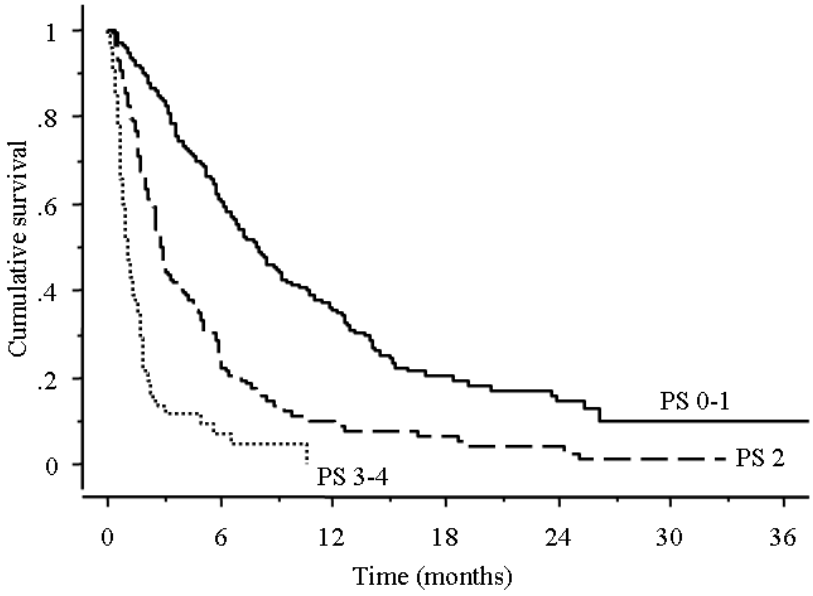


Figure 2: Survival according to BAC or non-BAC histology. BAC: adenocarcinoma with bronchioloalveolar features.


Cumulative survival
1
.8
.6
.4
.2
0
PS 0-1
PS 2
PS 3-4
0
6
12
18
24
30
36
Time (months)

Tables

Table 1: Demographics of the 513 patients.

	N	%
Age		
Median	63	
Range	32-89	
Gender		
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

N: number of patients; AD/BAC: adenocarcinoma with bronchioloalveolar features.

Table 2: Univariate analysis of predictive factors for response or disease stabilisation.

	N	Nresp	RR (%)	*P*	Ncontr	DCR (%)	*P*
All patients	403	36	8.9		166	41.2	
Gender				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	
Non-adenocarcinoma	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	

Totals and subtotals can be lower than expected in certain cells, due to missing values

N: number of patients; Nresp: number of responders; RR: response rate; Ncontr: number of patients with disease control; DCR: disease control rate; AD/BAC: adenocarcinoma with bronchioloalveolar features.

Table 3: Univariate analysis of survival and predictors of survival.

	N	MST (mo)	1YS (%)	*P*
All patients	513	4.7	21.4	
Gender				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	
Non-adenocarcinoma	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	

Totals and subtotals can be lower than expected in certain cells, due to missing values

N: number of patients; MST (mo): median survival time in months; 1YS (%): percent one-year survival rate; AD/BAC: adenocarcinoma with bronchioloalveolar features.

References

1. The International Adjuvant Lung Cancer Trial Collaborative Group, 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; CD002140

3. Massarelli E, Andre F, Liu DD, Lee JJ, Wolf M, Fandi A, Ochs J, Le Chevalier T, Fossella F, Herbst RS. 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, Van den Abbeele AD, Eisenberg B, Roberts PJ, Heinrich MC, Tuveson DA, Singer S, Janicek M, Fletcher JA, Silverman SG, Silberman SL, Capdeville R, Kiese B, Peng B, Dimitrijevic S, Druker BJ, Corless C, Fletcher CD, Joensuu H. 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, Tamura T, Douillard JY, Nishiwaki Y, Vansteenkiste J, Kudo S, Rischin D, Eek R, Horai T, Noda K, Takata I, Smit E, Averbuch S, Macleod A, Wolf M, Feyereislova A, Dong RP, Baselga J. 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

6. Kris MG, Natale RB, Herbst RS, Lynch TJ, Prager D, Belani CP, Schiller JH, Kelly K, Spiridonidis H, Sandler A, Albain KS, Cella D, Wolf MK, Averbuch SD, Ochs JJ, Kay AC. 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, Scagliotti G, Rosell R, Miller V, Natale RB, Schiller JH, Von Pawel J, Pluzanska A, Gatzemeier U, Grous J, Ochs JS, Averbuch SD, Wolf MK, Rennie P, Fandi A, Johnson DH. 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, Natale RB, Miller V, Manegold C, Scagliotti G, Rosell R, Oliff I, Reeves JA, Wolf MK, Krebs AD, Averbuch SD, Ochs JS, Grous J, Fandi A, Johnson DH. 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, Rodrigues Pereira J, Ciuleanu T, Von Pawel J, Thongprasert S, Tan EH, Pemberton K, Archer V, Carroll K. 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. 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

11. Miller VA, Kris MG, Shah N, Patel J, Azzoli C, Gomez J, Krug LM, Pao W, Rizvi N, Pizzo B, Tyson L, Venkatraman E, Ben-Porat L, Memoli N, Zakowski M, Rusch V, Heelan RT. Bronchioloalveolar pathologic subtype and smoking history predict sensitivity to gefitinib in advanced non-small cell lung cancer. *J Clin Oncol* 2004; 22:1103-1109

12. Konishi J, Yamazaki K, Kinoshita I, Isobe H, Ogura S, Sekine S, Ishida T, Takashima R, Nakadate M, Nishikawa S, Hattori T, Asahina H, Imura M, Kikuchi E, Kikuchi J, Shinagawa N, Yokouchi H, Munakata M, Dosaka-Akita H, Nishimura M. Analysis of the response and toxicity to gefitinib of non-small cell lung cancer. *Anticancer Res* 2005; 25:435-441

13. Lim ST, Wong EH, Chuah KL, Leong SS, Lim WT, Tay MH, Toh CK, Tan EH. Gefitinib is more effective in never-smokers with non-small cell lung cancer: experience among Asian patients. *Br J Cancer* 2005; 93:23-28

14. Veronese ML, Algazy K, Bearn L, Eaby B, Alavi J, Evans T, Stevenson JP, Shults J. 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

15. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, Campos D, Maoleekoonpiroj S, Smylie M, Martins R, Van Kooten M, Dediu M, Findlay B, Tu D, Johnston D, Bezjak A, Clark G, Santabarbara P, Seymour L. Erlotinib in previously treated non-small cell lung cancer. *N Engl J Med* 2005; 353:123-132

16. Park J, Park BB, Kim JY, Lee SH, Lee SI, Kim HY, Kim JH, Park SH, Lee KE, Park JO, Kim K, Jung CW, Park YS, Im YH, Kang WK, Lee MH, Park K. Gefitinib (ZD1839) monotherapy as a salvage regimen for previously treated advanced non-small cell lung cancer. *Clin Cancer Res* 2004; 10:4383-4388

17. Cappuzzo F, Bartolini S, Ceresoli GL, Tamberi S, Spreafico A, Lombardo L, Gregorc V, Toschi L, Calandri C, Villa E, Crino L. Efficacy and tolerability of gefitinib in pretreated elderly patients with advanced non-small cell lung cancer (NSCLC). *Br J Cancer* 2004; 90:82-86

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

19. Parra HS, Cavina R, Latteri F, Zucali PA, Campagnoli E, Morenghi E, Grimaldi GC, Roncalli M, Santoro A. 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

20. Bailey, L. R., Kris, M., Wolf, M., Kay, A., Averbuch, S., Askaa, J., Sanas, M., Schmidt, K., and Fukuoka, M. 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.

21. Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, Fujii Y, Eck MJ, Sellers WR, Johnson BE, Meyerson M. EGFR mutations in lung cancer: correlation with clinical response to Gefitinib therapy. *Science* 2004; 304:1497-1500

22. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, Settleman J, Haber DA. 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

23. Cappuzzo F, Hirsch FR, Rossi E, Bartolini S, Ceresoli GL, Bemis L, Haney J, Witta S, Danenberg K, Domenichini I, Ludovini V, Magrini E, Gregorc V, Doglioni C, Sidoni A, Tonato M, Franklin WA, Crino L, Bunn PA, Varella-Garcia M. Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small cell lung cancer. *J Natl Cancer Inst* 2005; 97:643-655

24. Inoue A, Saijo Y, Maemondo M, Gomi K, Tokue Y, Kimura Y, Ebina M, Kikuchi T, Moriya T, Nukiwa T. Severe acute interstitial pneumonia and gefitinib. *Lancet* 2003; 361:137-139