Phase II Study of Erlotinib for Acquired Resistance to Gefitinib in Patients with Advanced Non-small Cell Lung Cancer

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Abstract. *Background: Gefitinib and erlotinib are used to treat advanced non-small cell lung cancer (NSCLC). Gefitinib is a common first-line treatment, but most patients develop resistance. This phase II study evaluated the efficacy of erlotinib after acquired resistance to gefitinib. Patients and Methods: Between January 2008 and September 2009, we enrolled 50 patients with advanced NSCLC who had received one or more chemotherapy regimens, including gefitinib monotherapy to which they had partial responses (PR) or stable disease (SD). Erlotinib (150 mg) was administered until disease progression or unacceptable toxicity. Patients were 11 males, 39 females; median age 65 years (range=36-81 years); 46 with adenocarcinoma; performance status 0/1/2: 24/19/7; and smoking status, never/former/current: 33/15/2. Prior gefitinib response, PR/SD: 36/14. Median duration of prior gefitinib therapy was 419 days (range=63-1,540 days). Median interval after gefitinib therapy was 29 days (range=13-1,198 days). Results: Of 47 patients on erlotinib, four showed PR and 29 showed SD [response rate, 8.5%; disease control rate (DCR), 70.2%]. DCR for patients who continued gefitinib treatment for more than one year was significantly higher (81.5%) than for patients who could not continue (57.1%; p=0.018); but was not affected by prior gefitinib response or treatment interval. Median tiMETo treatment failure: 100 days (95% confidence interval=90-110 days); median overall survival: 342 days (95% confidence interval=242-442 days). Rash (78%) and diarrhea (68%) were the most common adverse reactions; grade 5 pneumonitis occurred in one patient (2%). Conclusion: Erlotinib treatment after gefitinib failure may prolong the efficacy of epidermal growth factor receptor tyrosine kinase inhibitors treatment.*

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Gefitinib and erlotinib are orally-active epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI), which are available in current clinical practice. Gefitinib is the first EGFR-TKI developed and approved for non-small cell lung cancer (NSCLC) (1, 2). Gefitinib therapy elicits extraordinary responses in female patients, patients who have never smoked, patients with adenocarcinomas, patients of Asian origin, and patients with *EGFR* mutations (3-6). In addition, the IPASS study showed that gefitinib monotherapy improved progression-free survival (PFS) compared to platinum-doublet chemotherapy in Asian patients who had adenocarcinomas and were non-smokers or light smokers (7). Furthermore, two Japanese phase III studies demonstrated that gefitinib dramatically prolonged PFS in patients who had *EGFR* mutations (8, 9). Therefore, gefitinib is usually used as a first EGFR-TKI treatment in Japan. Unfortunately, even patients who initially respond to gefitinib may eventually develop resistance to gefitinib. This happens over time, almost without exception. Currently, no optimal treatment has been identified for NSCLC after failure of gefitinib treatment.

Erlotinib was the second EGFR-TKI developed and approved for NSCLC (10). Erlotinib prolonged overall survival in a phase III study compared with placebo in non-selected previously treated patients with NSCLC (11). Erlotinib also appeared to improve survival not only for never-smokers and Asians but also most of the other patient subsets.

Several explanations have been considered for the different efficacies of gefitinib and erlotinib. The standard doses of erlotinib and gefitinib are not biologically-equivalent because erlotinib is administered at the maximum tolerated dose

(MTD), whereas gefitinib is administered at approximately one-third of its MTD; differences in tumor sensitivity might be associated with these different concentrations. The half-maximal (50%) inhibitory concentration (IC_{50}) value of erlotinib is lower than that of gefitinib (12). Several studies showed that erlotinib may be efficacious in patients with resistant tumors that had previously responded to gefitinib (13, 14). However, these studies used small sample sizes or retrospective analyses. To our knowledge, no studies have evaluated the efficacy in limited patients with resistant tumors that had previously responded to gefitinib prospectively. We conducted a phase II study to evaluate the efficacy of erlotinib against acquired resistance to gefitinib.

Patients and Methods

Study design. This phase II study was conducted in patients whose advanced NSCLC had previously responded to gefitinib. The primary objective of this study was disease control rate (DCR). Secondary objectives included adverse reactions, time to treatment failure (TTF), response rate (RR), and overall survival (OS).

Eligibility criteria. The eligibility criteria for enrollment in this study were as follows: histologically confirmed NSCLC, age 20 years or over, relapsed after gefitinib treatment which obtained complete response (CR), partial response (PR), or stable disease (SD), one or more prior chemotherapy regimens, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, life expectancy of at least three months, adequate organ function [leukocytes ≥3,000/mm^3, hemoglobin ≥7.5 g/dl, platelets ≥100,000/mm^3, serum creatinine ≤1.5 mg/dl, total bilirubin ≤1.5 mg/dl, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤100 IU/l and PaO2 ≥60.0 torr]. Patients were excluded from the trial for any of the following reasons: uncontrolled malignant pleural or pericardial effusion, a concomitant serious illness contraindicating chemotherapy, history of interstitial lung disease (ILD) during prior gefitinib therapy, pregnancy, or breast-feeding. All patients provided written informed consent. The study protocol was approved by the Institutional Ethics Committee of each of the participating institutions.

Treatment. All patients received 150 mg erlotinib once daily before breakfast, and were treated with this dose daily until disease progression or unacceptable toxicity. In the event of treatment-related toxicity, two dose reductions were permitted per patient. The first reduction was to 100 mg/day, the second reduction was to 50 mg/day. Erlotinib treatment could be interrupted within four weeks. No dose escalations were permitted. For grade 3 or intolerable grade 2 rash or stomatitis, treatment was discontinued until improvement to grade 2 or less, and then a lower dose of erlotinib was started.

Assessment. Adverse reactions were monitored, graded, and recorded according to the National Cancer Institute Common Toxicity Criteria version 3.0 (15). Efficacy was assessed by a physician on the basis of antitumor effect according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 (16). The response was confirmed for at least four weeks for a CR or PR, or six weeks for SD, after it was first documented. TTF was defined as the time during which patients were treated with erlotinib. OS was defined as the time from registration to death from any cause.

Statistics. Simon's two-stage optimal design was used to determine the sample size. A DCR of 50% would be the target activity level of interest, whereas a rate of 30% would be the lower activity level of interest. With α=0.10 and β=0.10, the estimated accrual number was 46 patients. Allowing for a 10% loss to follow-up, a total of 50 patients were planned to be enrolled. DCR was compared between demographic factors using Pearson's chi-square test. The survival distribution was estimated by the Kaplan–Meier method. A value of $p \leq 0.05$ was considered significant.

Results

Patients' characteristics. From January 2008 to September 2009, 50 eligible patients were enrolled in this study. All patients received erlotinib treatment. Patient characteristics are summarized in Table I. The median age of patients entering this study was 65 years. Four-fifths of the patients were female (78%); adenocarcinoma was the major histological type (92%); and 33 patients (66%) had never smoked. All patients had received previous chemotherapies; approximately half had received more than three chemotherapy regimens. Prior responses to gefitinib were PR in 35 patients (70%), and SD in 15 patients (30%). The median duration of prior gefitinib treatment was 424 days. The median interval from gefitinib treatment was 32 days. *EGFR* mutations were analyzed in 24 out of 50 patients (48%) before initiation of gefitinib therapy, and were detected in 20 of those 24 patients (83%).

Efficacy. Out of 50 patients, 47 (94%) were included in the response analysis. Of the three patients who were not included, one patient moved to another hospital because of personal circumstances, another was not able to take erlotinib tablets, and the third patient stopped erlotinib treatment due to severe toxicity (ILD) before their first response analyses. Four patients had PR, 29 patients had SD, and 14 patients had PD (Table II). The DCR and RR were 70.2% and 8.5%, respectively. Figure 1 shows the best response to erlotinib treatment as compared with pre-treatment baseline. Numbers along the x axis indicate arbitrarily assigned participant numbers from 1 to 43. The bars indicate the percentage change in tumor burden from baseline. Four patients are not included in this plot. They were clinically assessed as having had PD, although their response analyses were evaluated in non-target lesions. Twenty patients (46.5%) had some degree of tumor shrinkage. The median TTF was 100 days [95% confidence interval (CI)=90-110 days], the median OS was 342 days (95% CI=185-303 days), and the 1-year survival rate was 50.0%.

Safety. Adverse reactions were evaluated in 50 patients (Table III). The most common adverse reactions were rash (78%) and diarrhea (68%). Only one patient developed ILD. He was 74-year-old smoker with a history of stage IV left

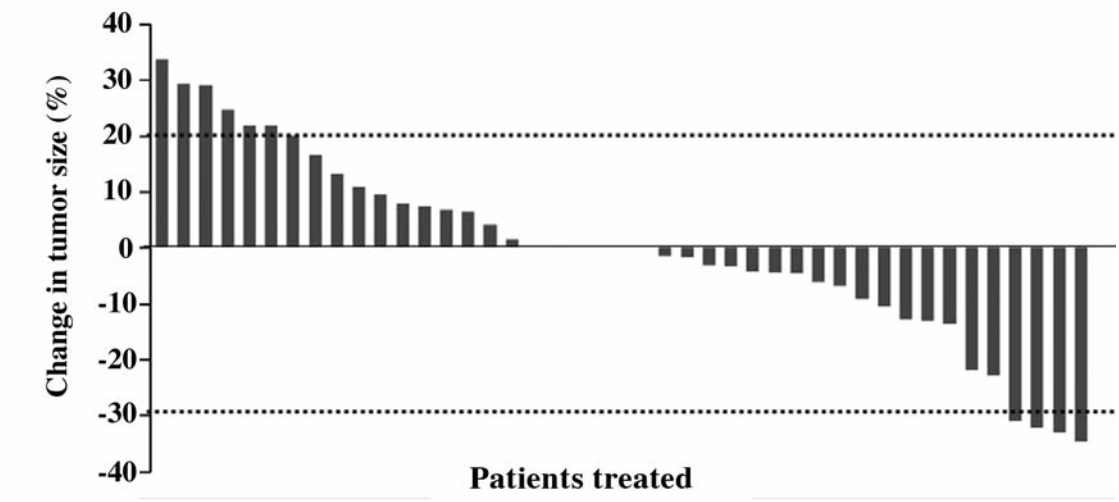

Figure 1. *Best response of target lesions by the RECIST criteria.*

Table I. *Patients' characteristics.*

Characteristic	N
Patients	50
Gender	
Male	11
Female	39
Age (years)	
Median	65
Range	36-81
Performance status	
0	24
1	19
2	7
Smoking status	
Current	2
Former	15
Never	33
Histology	
Adenocarcinoma	46
Squamous cell carcinoma	2
Large cell carcinoma	2
EGFR mutation status	
Positive	20
Negative	4
Unknown	26
Number of prior chemotherapy regimens	
1	6
2	17
3	15
4	10
5	2
Prior gefitinib response	
PR	35
SD	15

EGFR, Epidermal growth factor receptor; N, number of patients; PR, partial response; SD, stable disease.

Table II. *Patients' response (N=47).*

Response	N	%
CR	0	0.0
PR	4	8.5
SD	29	61.7
PD	14	29.8
DCR		70.2
RR		8.5

CR, Complete response; DCR, disease control rate; N, number of patients; PD, progressive disease; PR, partial response; SD, stable disease; RR, response rate.

upper lobe adenocarcinoma for which he had received three successive regimens (S-1 and cisplatin with concurrent thoracic radiotherapy, docetaxel, and gefitinib), followed two weeks later by erlotinib. He received gefitinib for about three months. He did not develop ILD during gefitinib therapy. Ground-glass opacity was detected in the bilateral lung fields by chest computed tomography 26 days after the start of erlotinib administration; the patient immediately received oxygen, corticosteroids and, later, cyclophosphamide. However, his respiratory failure progressed, his condition deteriorated and he died on day 39.

EGFR mutation analysis and clinical outcome. EGFR mutation analyses were performed in 24 out of 50 patients (48%) before initial gefitinib therapy. *EGFR* mutations were detected in 20 out of 24 patients (83%). In these 20 patients, three had PR, 11 had SD, five had PD and one was not evaluable (NE). In patients with wild-type *EGFR*, three had

Table III. *Adverse reactions.*

Adverse reaction	N						
	NCI-CTC grade					≥Grade 3 (%)	Total (%)
	1	2	3	4	5		
Rash	14	23	2	0	0	2 (4%)	39 (78%)
Dry skin	15	10	0	0	0	0 (0%)	25 (50%)
Diarrhea	27	7	0	0	0	0 (0%)	34 (68%)
Stomatitis	10	6	0	0	0	0 (0%)	16 (32%)
Anorexia	11	4	0	0	0	0 (0%)	15 (30%)
Infection	0	4	1	0	0	1 (2%)	5 (10%)
Pneumonitis	1	0	0	0	1	1 (2%)	2 (4%)
Leucocytes	7	2	0	0	0	0 (0%)	9 (18%)
Hemoglobin	6	2	2	0	0	2 (4%)	10 (20%)
Bilirubin	12	5	1	0	0	1 (2%)	18 (36%)
AST	8	2	1	0	0	1 (2%)	11 (22%)
ALT	5	3	0	1	0	1 (2%)	9 (18%)
Creatinine	7	3	0	0	0	0 (0%)	10 (20%)

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; N, number of patients.

Table IV. *Correlation of the disease control rate (DCR) of erlotinib with prior gefitinib therapy.*

			p-Value	
	N	DCR	Univariate analysis	Multivariate analysis
Response to gefitinib			0.508	
PR	32	71.9		
SD	15	60.0		
Interval from gefitinib			0.401	
Within 1 month	24	62.9		
Over 1 month	23	73.4		
Duration of gefitinib treatment			0.038	0.043
Within 1 year	21	52.4		
Over 1 year	26	80.8		

N, Number of patients; DCR, disease control rate; PR, partial response; SD, stable disease.

SD, and one had PD. In patients who did not know their *EGFR* mutation status, one had PR, 14 had SD, nine had PD and two were NE. The RR and DCR of patients with *EGFR* mutation were 15.8% and 73.7%, respectively. Data are summarized in Table IV. These patients did not undergo re-biopsy after initial gefitinib and erlotinib treatments.

Subgroup analysis specified to treatment effects. We analyzed three subgroups of patients with prior gefitinib therapy to specify treatment effects of erlotinib after failure of gefitinib. The effect of erlotinib on DCR was greatest in patients who continued gefitinib for more than one year, for whom it was significantly higher than in patients who took gefitinib for one year or less (80.8% *vs.* 52.4%, p=0.038). The DCR did not depend on response to gefitinib or interval from gefitinib therapy (Table IV). When modeled in a multi-variable setting using logistic regression, duration of gefitinib treatment was significantly associated with DCR of erlotinib.

Discussion

Our study showed that RR and DCR with erlotinib were 8.5% and 70.2% in patients previously treated with gefitinib, respectively. The DCR of our study was higher than that of the previous prospective phase II study, which evaluated the efficacy of erlotinib after failure of gefitinib (13). In that study, the RR and the DCR were 9.5% and 28.6%, respectively. Their study and ours differed in eligibility criteria regarding patient enrolment. In our study, only patients who showed CR, PR or SD from gefitinib treatment were enrolled, whereas patients who had been previously treated with gefitinib were enrolled in the previous study. Actually, half of patients in their study did not respond to gefitinib. Jackman *et al.* proposed criteria for acquired resistance to EGFR-TKIs in lung cancer (17). The criteria they proposed are the following: previous treatment with a single-agent EGFR-TKI (*i.e.* gefitinib or erlotinib); either a tumor that harbors an *EGFR* mutation known to be associated with drug sensitivity, or objective clinical benefit from treatment with an EGFR-TKI; systemic progression of disease (by RECIST or WHO standards) while on continuous treatment with gefitinib or erlotinib within the previous 30 days; and no intervening systemic therapy between cessation of gefitinib or erlotinib and initiation of new therapy. In our study, half of the patients (25 patients) acquired resistance and the other half were sensitive to EGFR-TKI, per Jackman *et al.*'s criteria. However, we did not observe a significant difference in DCR to erlotinib between patients who met these criteria and those who did not (65.2% *vs.* 70.8%, p=0.680).

Several mechanistic explanations have been already identified for acquired gefitinib resistance in patients with NSCLC with *EGFR* mutations. Two major mechanistic explanations are second-site *EGFR* mutation (T790M) and *mesenchymal–epithelial transition* (*MET*) amplification (18-21). Some irreversible EGFR-TKIs and MET inhibitors have shown antitumor activity in patients resistant to gefitinib or erlotinib in pre-clinical studies (20, 22-26). Several irreversible EGFR-TKIs were evaluated in phase II studies of patients with NSCLC with acquired resistance to gefitinib or erlotinib (27-29); RRs were 3.4% (*EGFR* mutant) and 0% (*EGFR* wild-type) to neratinib, 3% to XL647, and 7.0% to PF-00299804. Recently afatinib, an irreversible avian erythroblastosis oncogene B (ERBB) family blocker, was evaluated in a phase IIb/III randomized study for patients

Table V. *Biomarker analysis and clinical outcomes*.

Patient number	Gender	Age, years	Histology	Prior gefitinib response	*EGFR* mutation status	Response to erlotinib
1	Female	60	Adeno	PR	Ex19 deletions	PR
2	Female	56	Adeno	PR	Ex19 deletions	PR
3	Female	48	Adeno	PR	Ex19 deletions	SD
4	Female	56	Adeno	PR	Ex19 deletions	SD
5	Female	64	Adeno	PR	Ex19 deletions	SD
6	Female	64	Adeno	PR	Ex19 deletions	SD
7	Female	64	Adeno	PR	Ex19 deletions	PD
8	Female	56	Adeno	PR	Ex19 deletions	PD
9	Female	77	Adeno	PR	Ex19 deletions	NE
10	Female	70	Adeno	PR	Ex21 L858R	PR
11	Female	73	Adeno	PR	Ex21 L858R	SD
12	Female	69	Adeno	PR	Ex21 L858R	SD
13	Female	76	Adeno	PR	Ex21 L858R	SD
14	Female	74	Adeno	SD	Ex21 L858R	SD
15	Female	64	Adeno	PR	Ex21 L858R	SD
16	Male	64	Adeno	PR	Ex21 L858R	PD
17	Female	53	Adeno	PR	Ex21 L858R	PD
18	Female	61	Squamous	PR	Ex21 L858R	PD
19	Male	36	Adeno	PR	Positive	SD
20	Female	60	Adeno	SD	Ex20 codon771-9bp in-codon772	SD
21	Female	62	Adeno	PR	Wild	SD
22	Female	78	Adeno	PR	Wild	SD
23	Male	68	Large	SD	Wild	SD
24	Male	55	Adeno	SD	Wild	PD

Adeno, adenocarcinoma; Deletion, In-frame deletions; Ex; exon; Large, large cell carcinoma; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; squamous, squamous cell carcinoma; Wild, wild-type.

with NSCLC after failure of erlotinib, gefitinib, or both (LUX-Lung 1) (30). In LUX-Lung 1, patients were limited to those who had disease progression after at least 12 weeks of treatment with erlotinib or gefitinib. Among patients in the afatinib group, 91% had responded to previous courses of EGFR-TKI with CR, PR or SD, as had 94% in the placebo group. Although PFS and RR were significantly better in the afatinib-treated group, there was no significant difference in overall survival between the two groups.

Even today, there is no established treatment after failure of gefitinib. Recently, Sequist *et al*., using systematic genetic analyses of tumor biopsies in patients with acquired EGFR-TKI resistance who underwent multiple-line treatments, found that mutations for EGFR-TKI resistance were potentially reversible; a few such cases showed regained sensitivity to subsequent rounds of EGFR-TKI treatment after selective pressure from earlier EGFR-TKI treatments had ceased (31). Clinically, we also sometimes see a disease 'flare'—accelerated disease progression after discontinuation of gefitinib. Chaft *et al*. examined six clinical trials of patients with acquired EGFR-TKI resistance, and reported that 14 out of 61 patients (23%) experienced disease flares (32). Therefore, some patients are still sensitive to EGFR-TKI even after becoming resistant to gefitinib, and they may receive clinical benefits from EGFR-TKI by changing from gefitinib to erlotinib.

In conclusion, erlotinib has been shown to achieve disease control after acquired resistance to gefitinib. Erlotinib is a treatment option after gefitinib failure, and may prolong the efficacy of EGFR-TKI treatment.

References

1 Fukuoka M, Yano S, Giaccone G, Tamura T, Nakagawa K, Douillard JY, Nishiwaki Y, Vansteenkiste J, Kudoh S, Rischin D, Eek R, Horai T, Noda K, Takata I, Smit E, Averbuch S, Macleod A, Feyereislova A, Dong RP and Baselga J: Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial) [corrected]. J Clin Oncol *21*: 2237-2246, 2003.

2 Kris MG, Natale RB, Herbst RS, Lynch TJ Jr., Prager D, Belani CP, Schiller JH, Kelly K, Spiridonidis H, Sandler A, Albain KS, Cella D, Wolf MK, Averbuch SD, Ochs JJ and Kay AC: 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 *290*: 2149-2158, 2003.

3 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 and Haber DA: Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med *350*: 2129-2139. Epub 2004 Apr 2129, 2004.

4 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 and Meyerson M: *EGFR* mutations in lung cancer: Correlation with clinical response to gefitinib therapy. Science *304*: 1497-1500. Epub 2004 Apr 1429., 2004.

5 Park K and Goto K: A review of the benefit-risk profile of gefitinib in Asian patients with advanced non-small-cell lung cancer. Curr Med Res Opin *22*: 561-573, 2006.

6 Thatcher N, Chang A, Parikh P, Rodrigues Pereira J, Ciuleanu T, von Pawel J, Thongprasert S, Tan EH, Pemberton K, Archer V and 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 *366*: 1527-1537, 2005.

7 Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA and Fukuoka M: Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med *361*: 947-957, 2009.

8 Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I, Fujita Y, Okinaga S, Hirano H, Yoshimori K, Harada T, Ogura T, Ando M, Miyazawa H, Tanaka T, Saijo Y, Hagiwara K, Morita S and Nukiwa T: Gefitinib or chemotherapy for non-small-cell lung cancer with mutated *EGFR*. N Engl J Med *362*: 2380-2388, 2010.

9 Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, Seto T, Satouchi M, Tada H, Hirashima T, Asami K, Katakami N, Takada M, Yoshioka H, Shibata K, Kudoh S, Shimizu E, Saito H, Toyooka S, Nakagawa K and Fukuoka M: Gefitinib *versus* cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol *11*: 121-128, 2010.

10 Kubota K, Nishiwaki Y, Tamura T, Nakagawa K, Matsui K, Watanabe K, Hida T, Kawahara M, Katakami N, Takeda K, Yokoyama A, Noda K, Fukuoka M and Saijo N: Efficacy and safety of erlotinib monotherapy for Japanese patients with advanced non-small cell lung cancer: a phase II study. J Thorac Oncol *3*: 1439-1445, 2008.

11 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 and Seymour L: Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med *353*: 123-132, 2005.

12 Blackhall F, Ranson M and Thatcher N: Where next for gefitinib in patients with lung cancer? Lancet Oncol *7*: 499-507, 2006.

13 Cho BC, Im CK, Park MS, Kim SK, Chang J, Park JP, Choi HJ, Kim YJ, Shin SJ, Sohn JH, Kim H, and Kim JH: Phase II study of erlotinib in advanced non-small-cell lung cancer after failure of gefitinib. J Clin Oncol *25*: 2528-2533, 2007.

14 Kaira K, Naito T, Takahashi T, Ayabe E, Shimoyama R, Kaira R, Ono A, Igawa S, Shukuya T, Murakami H, Tsuya A, Nakamura Y, Endo M and Yamamoto N: Pooled analysis of the reports of erlotinib after failure of gefitinib for non-small cell lung cancer. Lung Cancer *68*: 99-104, 2009.

15 National Cancer Institute: Cancer Therapy Evaluation Program: Common Terminology Criteria for Adverse Events, version 3.0. http://ctep.cancer.gov/protocolDevelopment/electronic applications/ctc.htm

16 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC and Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst *92*: 205-216, 2000.

17 Jackman D, Pao W, Riely GJ, Engelman JA, Kris MG, Janne PA, Lynch T, Johnson BE and Miller VA: Clinical definition of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. J Clin Oncol *28*: 357-360, 2010.

18 Engelman JA, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, Park JO, Lindeman N, Gale CM, Zhao X, Christensen J, Kosaka T, Holmes AJ, Rogers AM, Cappuzzo F, Mok T, Lee C, Johnson BE, Cantley LC and Janne PA: *MET* amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science *316*: 1039-1043, 2007.

19 Pao W, Miller VA, Politi KA, Riely GJ, Somwar R, Zakowski MF, Kris MG and Varmus H: Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the *EGFR* kinase domain. PLoS Med *2*: e73, 2005.

20 Kwak EL, Sordella R, Bell DW, Godin-Heymann N, Okimoto RA, Brannigan BW, Harris PL, Driscoll DR, Fidias P, Lynch TJ, Rabindran SK, McGinnis JP, Wissner A, Sharma SV, Isselbacher KJ, Settleman J and Haber DA: Irreversible inhibitors of the EGF receptor may circumvent acquired resistance to gefitinib. Proc Natl Acad Sci USA *102*: 7665-7670, 2005.

21 Kobayashi S, Boggon TJ, Dayaram T, Janne PA, Kocher O, Meyerson M, Johnson BE, Eck MJ, Tenen DG and Halmos B: *EGFR* mutation and resistance of non-small-cell lung cancer to gefitinib. N Engl J Med *352*: 786-792, 2005.

22 Sos ML, Rode HB, Heynck S, Peifer M, Fischer F, Kluter S, Pawar VG, Reuter C, Heuckmann JM, Weiss J, Ruddigkeit L, Rabiller M, Koker M, Simard JR, Getlik M, Yuza Y, Chen TH, Greulich H, Thomas RK and Rauh D: Chemogenomic profiling provides insights into the limited activity of irreversible *EGFR* Inhibitors in tumor cells expressing the T790M EGFR resistance mutation. Cancer Res *70*: 868-874, 2010.

23 Engelman JA, Zejnullahu K, Gale CM, Lifshits E, Gonzales AJ, Shimamura T, Zhao F, Vincent PW, Naumov GN, Bradner JE, Althaus IW, Gandhi L, Shapiro GI, Nelson JM, Heymach JV, Meyerson M, Wong KK and Janne PA: PF00299804, an irreversible pan-ERBB inhibitor, is effective in lung cancer models with *EGFR* and ERBB2 mutations that are resistant to gefitinib. Cancer Res *67*: 11924-11932, 2007.

24 Gendreau SB, Ventura R, Keast P, Laird AD, Yakes FM, Zhang W, Bentzien F, Cancilla B, Lutman J, Chu F, Jackman L, Shi Y, Yu P, Wang J, Aftab DT, Jaeger CT, Meyer SM, De Costa A, Engell K, Chen J, Martini JF and Joly AH: Inhibition of the T790M gatekeeper mutant of the epidermal growth factor receptor by EXEL-7647. Clin Cancer Res *13*: 3713-3723, 2007.

25 Li J, Zhao M, He P, Hidalgo M, and Baker SD: Differential *MET*abolism of gefitinib and erlotinib by human cytochrome P450 enzymes. Clin Cancer Res *13*: 3731-3737, 2007.

26 Tang Z, Du R, Jiang S, Wu C, Barkauskas DS, Richey J, Molter J, Lam M, Flask C, Gerson S, Dowlati A, Liu L, Lee Z, Halmos B, Wang Y, Kern JA and Ma PC: Dual *MET-EGFR* combinatorial inhibition against T790M-*EGFR*-mediated erlotinib-resistant lung cancer. Br J Cancer *99*: 911-922, 2008.

27 Pietanza MC, Lynch TJ, Jr., Lara PN Jr., Cho J, Yanagihara RH, Vrindavanam N, Chowhan NM, Gadgeel SM, Pennell NA, Funke R, Mitchell B, Wakelee HA and Miller VA: XL647 – a multitargeted tyrosine kinase inhibitor: results of a phase II study in subjects with non-small cell lung cancer who have progressed after responding to treatment with either gefitinib or erlotinib. J Thorac Oncol *7*: 219-226, 2012.

28 Sequist LV, Besse B, Lynch TJ, Miller VA, Wong KK, Gitlitz B, Eaton K, Zacharchuk C, Freyman A, Powell C, Ananthakrishnan R, Quinn S and Soria JC: Neratinib, an irreversible pan-ErbB receptor tyrosine kinase inhibitor: results of a phase II trial in patients with advanced non-small-cell lung cancer. J Clin Oncol *28*: 3076-3083, 2010.

29 Janne PA, Reckamp K, Koczywas M, Engelman JA, Camidge DR, Rajan A, Khuri F, Liang JQ, O'Connell J and Giaccone G: Efficacy and safety of PF-00299804 (PF299) in patients (pt) with advanced NSCLC after failure of at least one prior chemotherapy regimen and prior treatment with erlotinib (E): A two-arm, phase II trial. *In*: 2009 ASCO Annual Meeting: J Clin Oncol, p. s422, 2009.

30 Miller VA, Hirsh V, Cadranel J, Chen YM, Park K, Kim SW, Zhou C, Su WC, Wang M, Sun Y, Heo DS, Crino L, Tan EH, Chao TY, Shahidi M, Cong XJ, Lorence RM and Yang JC: Afatinib *versus* placebo for patients with advanced, *MET*astatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol *13*: 528-538, 2012.

31 Sequist LV, Waltman BA, Dias-Santagata D, Digumarthy S, Turke AB, Fidias P, Bergethon K, Shaw AT, Gettinger S, Cosper AK, Akhavanfard S, Heist RS, Temel J, Christensen JG, Wain JC, Lynch TJ, Vernovsky K, Mark EJ, Lanuti M, Iafrate AJ, Mino-Kenudson M and Engelman JA: Genotypic and histological evolution of lung cancers acquiring resistance to *EGFR* inhibitors. Sci Transl Med *3*: 75ra26, 2011.

32 Chaft JE, Oxnard GR, Sima CS, Kris MG, Miller VA and Riely GJ: Disease flare after tyrosine kinase inhibitor discontinuation in patients with *EGFR*-mutant lung cancer and acquired resistance to erlotinib or gefitinib: implications for clinical trial design. Clin Cancer Res *17*: 6298-6303, 2011.

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