

Evaluation of erlotinib for the treatment of patients with non-small cell lung cancer with epidermal growth factor receptor wild type

FUMIHIKO HIRAI, MAKOTO EDAGAWA, SHINICHIRO SHIMAMATSU,
 RYO TOYOZAWA, GOUJI TOYOKAWA, KANAME NOSAKI, MASAFUMI YAMAGUCHI,
 TAKASHI SETO, MITSUHIRO TAKENOYAMA and YUKITO ICHINOSE

Department of Thoracic Oncology, National Kyushu Cancer Center, Fukuoka 811-1395, Japan

Received August 13, 2015; Accepted February 7, 2017

DOI: 10.3892/ol.2017.6118

Abstract. Erlotinib is one of the treatment choices for patients with advanced non-small cell lung cancer (NSCLC), regardless of the epidermal growth factor receptor (*EGFR*) mutation status. However, its efficacy for the treatment of patients with NSCLC with *EGFR* wild type or who are beyond the usage of gefitinib remains controversial. The present study therefore retrospectively assessed the efficacy of erlotinib in patients with wild type *EGFR* who had previously undergone gefitinib therapy. A total of 222 patients with NSCLC who received chemotherapeutic treatment with erlotinib between July 2007 and February 2013 were evaluated. The background variables, response rates, progression-free survival (PFS) and overall survival rates were retrospectively analyzed. The male/female ratio of patients was 103/119, and patients had a median age of 63 years (range, 33-95 years). A total of 10 of the 222 patients had clinical stages IIIB/IV, 191 had adenocarcinoma, 5 had large cell carcinoma, 10 had squamous cell carcinoma and 6 had NSCLC of a variety not otherwise specified. The *EGFR* mutation was positive, wild type or unknown in 95, 52 and 75 patients, respectively. In the 52 patients with *EGFR* wild type, there were 3 partial responders, 25 with stable disease and 24 with progressive disease, for a response rate of 6% [95% confidence interval (CI), 1.3-15%]. The median PFS of *EGFR* wild type and positive were 1.1 months (95% CI, 1.04-1.16 months) and 5.42 months (95% CI, 5.43-5.68 months), respectively. The results of the study demonstrated that erlotinib is not sufficiently effective for patients with NSCLC who possess the *EGFR* wild type status.

Introduction

Lung cancer remains the leading cause of malignancy-associated mortality worldwide (1). Non-small cell lung cancer (NSCLC) comprises ~80% of all cases, and the majority of patients present with locally advanced or metastatic disease (2). Systemic chemotherapy (with or without bevacizumab) or tyrosine kinase inhibitor (TKI) therapy currently represent the primary treatment options for prolonging a patient's survival rate and improving their quality of life (3-6). At present, the standard first-line chemotherapy for unselected advanced NSCLC is platinum doublet regimens using a third-generation anti-cancer agent (7,8).

Erlotinib, a small molecule inhibitor of the intracellular tyrosine kinase of epidermal growth factor receptor (*EGFR*), has been approved as second-line therapy for patients with advanced NSCLC in numerous countries. A phase III trial (the BR.21 trial) demonstrated that unselected patients with advanced NSCLC, progressing subsequent to first-line chemotherapy, gained a survival benefit when treated with erlotinib compared with best supportive care (9). At the start of BR.21, *EGFR* mutations in NSCLC had not yet been identified; therefore, the study included molecularly unselected patients. The discovery and characterization of *EGFR* mutations in 2004 was a key example of oncogene addiction, associated with a high efficacy of biomarker-driven treatment (10-12). As a result, *EGFR* TKIs are currently the treatment of choice for patients with *EGFR* mutations. Several phase III studies have demonstrated that erlotinib and gefitinib are superior to chemotherapy in first-line treatment, but only in *EGFR*-mutated patients (5,13-15). The value of erlotinib as a second-line and third-line treatment of patients with wild type or unknown *EGFR* mutation status remains controversial.

In previous years, the Tarceva Italian Lung Optimization (TAILOR) phase III trial demonstrated that chemotherapy was more effective compared with erlotinib for second-line treatment for previously treated patients with NSCLC who possess wild type *EGFR* tumors (16). The present study was undertaken to evaluate the efficacy of erlotinib in second-line or more advanced NSCLC, in particular for patients with *EGFR* wild type status and who received pretreatment with gefitinib.

Correspondence to: Dr Fumihiko Hirai, Department of Thoracic Oncology, National Kyushu Cancer Center, 3-1-1 Notame, Minami-ku, Fukuoka 811-1395, Japan
 E-mail: hirai.f@nk-cc.go.jp

Key words: non-small cell lung cancer, erlotinib, gefitinib, epidermal growth factor receptor, wild type

Patients and methods

Patients. A total of 222 patients with NSCLC received erlotinib treatment as a first-line or further chemotherapy at the National Kyushu Cancer Center (Fukuoka, Japan) between July 2007 and the end of February 2013. Erlotinib therapy was applied for patients who satisfied all the following requirements: Age ≥ 20 years; pathologically or cytologically diagnosed as exhibiting NSCLC; clinical stage III or IV disease (including IIIA, non-applicable for radical radiotherapy) according to the seventh edition of the 'tumor, node, metastasis' classification of lung cancer (17); presenting evaluable lesions (cases without measurable lesions were acceptable); freedom from severe disorders in major organs (bone marrow, heart, lungs, liver and kidneys); without interstitial lung disease (ILD); and laboratory test data at the commencement of treatment indicating a neutrophil count $\geq 2,000$ cells/mm³ (normal range, 3,300-8,600 cells/mm³), a hemoglobin level ≥ 9.0 g/dl (normal range, 13.7-16.8 g/dl), a platelet count $\geq 10.0 \times 10^4$ cells/mm³ (normal range, 15.8-34.8 $\times 10^4$ cells/mm³), aspartate aminotransferase [normal range 13-30 international units (IU)/l] and alanine aminotransferase (normal range 10-42 IU/l) levels ≤ 100 IU/l, a total bilirubin level ≤ 1.5 mg/dl (normal range, 0.4-1.5 mg/dl), a serum creatinine level ≤ 1.2 mg/dl (normal range, 0.65-1.07 mg/dl) and a peripheral O₂ saturation level of $\geq 90\%$ (normal range, $\geq 90\%$). Treatment was provided subsequent to each patient providing written consent on the basis of receiving sufficient information regarding the treatment plan. All patients signed a consent form prior to entry to the study. The present study was approved by the National Kyushu Cancer Center Local Research Ethics Committee.

Treatment and study design. Eligible patients received oral erlotinib at a dose of 150 mg/day until disease progression (PD) or unacceptable toxicity. Dose reductions (in 50-mg decrements) were permitted to manage adverse events associated with erlotinib treatment. If a patient had a confirmed diagnosis of ILD, erlotinib was discontinued immediately.

Evaluation of the response and statistical analysis. Prior to the start of erlotinib therapy, diagnostic imaging with computed tomography scanning was performed to yield baseline information. Tumor response evaluation was scheduled every 6 weeks. Responses to treatment were evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (18). The progression free survival (PFS) was defined as the time from the start of treatment to PD or mortality. The overall survival (OS) was defined as the time from the start of treatment to mortality. The follow-up period concluded on May 31, 2013 for patients either still receiving treatment or beginning to receive the next treatment.

Statistical analysis. Survival curves were produced using the Kaplan-Meier method. Data were expressed as means \pm standard deviation. Univariate analysis was initially undertaken, followed by Cox's multivariate analysis that included all variables with a significance level of $P < 0.05$, to identify variables associated with a risk of mortality. Analysis of linear correlation was used to evaluate the correlation between two variables; analysis of variance with Dixon's Q-test was used to

compare multiple variables. Two-sided $P < 0.05$ was considered to indicate a statistically significant difference. Statistics were produced using StatView version 5.0 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics. Table I summarizes the background variables of the 222 patients who received erlotinib in the present study. There were 119 males and 103 females, with a median age of 63 years (range, 33-95 years). The Eastern Cooperative Oncology Group (19) performance status (PS) was 0-1, 2 and 3-4 in 181, 21 and 20 cases, respectively. The histological types were adenocarcinoma, squamous cell carcinoma, large cell carcinoma and NSCLC (NOS; not otherwise specified) in 191, 10, 5 and 16 cases, respectively. The clinical stage was IIIA, IIIB and IV in 1, 15 and 206 cases, respectively. The *EGFR* mutation status was positive in 95 patients [exon 18 (G719A or G719S) in 3 cases, exon 19 deletion in 47 cases (with T790M in 3 cases), exon 21 (L858R or L861Q) in 43 cases (with T790M in 5 cases) and NOS in 2 cases], wild type in 52 cases and unknown in 75 cases, respectively. A total of 92/222 patients received gefitinib prior to erlotinib treatment. The median follow-up time for the 222 patients who received erlotinib therapy was 858 days (range, 27-4543 days).

Response and survival analysis of all patients. The efficacy was evaluated by each attending physician in accordance with the RECIST criteria, version 1.1. Among the 222 patients who received erlotinib therapy, the best overall response was a partial response (PR) in 31 patients, stable disease (SD) in 101 patients and progressive disease (PD) in 90 patients. The best response rate (RR) of all patients was 14% [95% confidence interval (CI), 10.0-19.1%]. The median PFS and OS were 2.14 months (95% CI, 2.09-2.16 months) and 8.87 months (95% CI, 8.65-9.61 months), respectively. In a subset analysis, the PFS of *EGFR* wild type and unknown status were 1.08 months and 1.48 months, respectively, whereas the PFS of *EGFR* active mutation was 5.29 months (Fig. 1).

Analysis of the RR according to the *EGFR* mutation status. According to the RECIST criteria, the RR of 95 patients with an *EGFR* mutation was 25% (24/43/28, PR/SD/PD; 95% CI, 15-34%). Conversely, the RR of 52 *EGFR* wild type and 75 unknown patients were 6% (3/25/24, PR/SD/PD; 95% CI, 1.3-15%) and 5% (4/33/38, PR/SD/PD; 95% CI, 2.1-13%), respectively (Table II).

Univariate and multivariate survival analyses. To rule out potential confounding interaction between efficacy and other factors, the present study performed univariate and multivariate analyses of the PFS. Kaplan-Meier analyses compared by the log-rank test were used to calculate the effect of the clinicopathological factors on the PFS (Table III). A univariate analysis demonstrated that male gender [hazard ratio (HR) 1.63; $P < 0.001$], poor PS (PS 3 or 4; HR 1.75; $P = 0.028$), current or former smoking history (HR 1.64; $P < 0.001$), prior regimens (2 or more) (HR 1.44; $P = 0.036$) and *EGFR* wild type or unknown (HR 2.09; $P < 0.001$) status significantly predicted a decreased PFS. Furthermore, a multivariate analysis identified

Table I. Patient characteristics.

Clinical features	All patients (n=222)	EGFR wild type (n=52)	EGFR mutated (n=95)	EGFR status unknown (n=75)
Gender				
Male/female	119/103	33/19	33/62	37/38
Age				
Median (range)	63 (33-95)	64 (36-85)	63 (37-95)	61 (33-83)
ECOG performance status				
0/1/2/3/4	63/118/21/15/5	17/28/3/3/1	38/35/10/8/4	8/55/8/4/0
Smoking history				
Never	122	13	55	32
Current/former	100	23/16	15/25	20/23
Histological type				
Adenocarcinoma	191	43	88	60
Large cell carcinoma	5	3	1	1
Squamous cell carcinoma	10	3	1	6
NSCLC (NOS)	16	3	5	8
Stage				
IIIA/IIIB/IV	1 ^a /15/206	0/7/45	1/2/92	0/5/70
Prior gefitinib treatment				
Yes/no	91/131	9/43	50/45	32/43
Prior regimens				
0/1/2/3 or more	3/55/107	0/6/30	3/20/32	0/9/21/45

^aUnresectable and non-applicable for radiotherapy. EGFR, epidermal growth factor receptor; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; NOS, not otherwise specified.

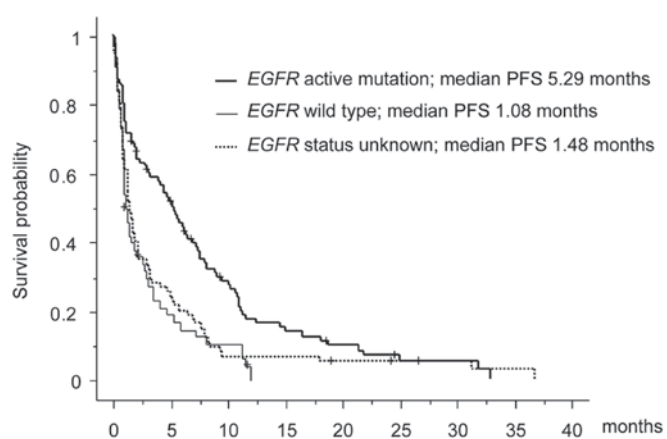


Figure 1. Survival curve of each *EGFR* mutation status. EGFR, epidermal growth factor receptor; PFS, progression free survival.

only *EGFR* mutation (HR 1.89; $P < 0.001$) to be an independent prognostic factor for PFS.

Association between the PFS and prior gefitinib therapy. Of the 222 patients treated with erlotinib, 91 patients previously received gefitinib. To evaluate the potential cofounding interaction between erlotinib and previous gefitinib therapy, the

present study performed univariate and multivariate analyses of the PFS (Table III). A univariate analysis demonstrated that non-adenocarcinoma (HR 4.78; $P = 0.035$) and poor response of gefitinib (HR 2.27; $P = 0.014$) significantly predicted a decreased PFS. However, the multivariate analysis identified no association between the characteristics and the PFS of erlotinib. Furthermore, as it was speculated that a response to erlotinib treatment may be associated with a long interval of a previous gefitinib therapy or a long duration from erlotinib to gefitinib therapy, the present study investigated the impact of a long disease control interval on the survival outcome among patients treated with gefitinib who achieved ≥ 12 months PFS (Table IV). However, no significant correlation was detected between previous gefitinib therapy and the PFS of erlotinib therapy (Fig. 2).

Discussion

At present, several *EGFR* TKIs are commercially available for patients with *EGFR* mutations: Gefitinib, erlotinib and afatinib (20). Erlotinib, an orally available *EGFR* TKI, has proven to be effective as a second- or third-line treatment for patients with NSCLC, regardless of the *EGFR* mutation status (9). Additionally, maintenance therapy with erlotinib for patients with NSCLC is well-tolerated and significantly prolongs the PFS compared with placebo (21). In these trials,

Table II. Subset analysis of the EGFR mutation status.

EGFR mutation status	Gefitinib treatment status	n=222	Response (%)					95% CI (%)
			CR	PR	SD	PD	RR	
Mutated	Total (Prior gefitinib treatment)	95	0	24	43	28	25	15-34
	Yes	50	0	7	29	14	14	7-26
	No	45	0	17	14	14	38	25-52
Wild type	Total (Prior gefitinib treatment)	52	0	3	25	24	6	1.3-15
	Yes	10	0	0	7	3	0	-
	No	42	0	3	17	22	7	2-19
Unknown	Total (Prior gefitinib treatment)	75	0	4	33	38	5	2.1-13
	Yes	32	0	2	18	12	6	2-20
	No	43	0	2	15	26	5	1-15

EGFR, epidermal growth factor receptor; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; RR, response rate; CI, confidence interval.

Table III. Univariate and multivariate analyses of factors associated with the progression-free survival (all patients).

Variable	No. of patients	Univariate hazard ratio (95% CI)	P-value	Multivariate hazard ratio (95% CI)	P-value
Gender			0.0009		0.164
Male	119	1.626 (1.219-2.169)		1.333 (0.889-2.004)	
Female	103	1		1	
ECOG performance status			0.0278		0.629
3-4	20	1.754 (1.063-2.894)		1.635 (0.974-2.746)	
0-2	202	1		1	
Smoking history			0.0009		0.534
Current or former	100	1.639 (1.225-2.192)		1.142 (0.752-1.730)	
Never	122	1		1	
Histological type			0.1370		
Non-adenocarcinoma	31	1.371 (0.904-2.079)			
Adenocarcinoma	191	1			
Prior gefitinib treatment			0.3890		
No	131	1.135 (0.851-1.515)			
Yes	91	1			
Prior regimens			0.0364		0.867
>2	164	1.438 (1.023-2.020)		1.034 (0.701-1.529)	
0-1	58	1		1	
EGFR status			<0.0001		<0.001
Wild type or unknown	170	2.087 (1.548-2.814)		1.892 (1.346-2.662)	
Mutation	52	1		1	

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

subgroup analyses of the PFS according to the clinical characteristics also suggested an improved PFS with erlotinib treatment compared with the placebo; this benefit was observed

irrespective of histology and *EGFR* mutation status. However, erlotinib was compared with BCS or placebo for unselected patients with NSCLC, which included patients with wild type

Table IV. Univariate and multivariate analyses of factors associated with the progression-free survival (patients who received previous gefitinib treatment).

Variable	No. of patients	Univariate hazard ratio (95% CI)	P-value	Multivariate hazard ratio (95% CI)	P-value
Gender			0.235		
Male	24	1.342 (0.825-2.183)			
Female	67	1			
ECOG performance status			0.587		
3-4	9	1.226 (0.588-2.556)			
0-2	82	1			
Smoking history			0.615		
Current or former	31	1.123 (0.714-1.766)			
Never	60	1			
Histological type			0.035	3.74 (0.850-16.393)	0.809
Non-adenocarcinoma	2	4.784 (1.116-20.408)			
Adenocarcinoma	89	1			
Prior regimens			0.125		
>2	77	1.690 (0.864-3.303)			
0-1	14	1			
EGFR status			0.388		
Wild type or unknown	41	1.210 (0.784-1.865)			
Mutation	50	1			
Response of gefitinib			0.0139	2.141 (1.101-4.164)	0.249
PD	12	2.271 (1.181-4.365)			
CR-SD	79	1			
Duration of gefitinib treatment			0.6125		
<12	58	1.122 (0.718-1.754)			
>12	33	1			
Interval between gefitinib and erlotinib treatment			0.429		
<12	57	1.197 (0.766-1.871)			
>12	34	1			

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; PD, progressive disease; CR, complete response; SD, stable disease.

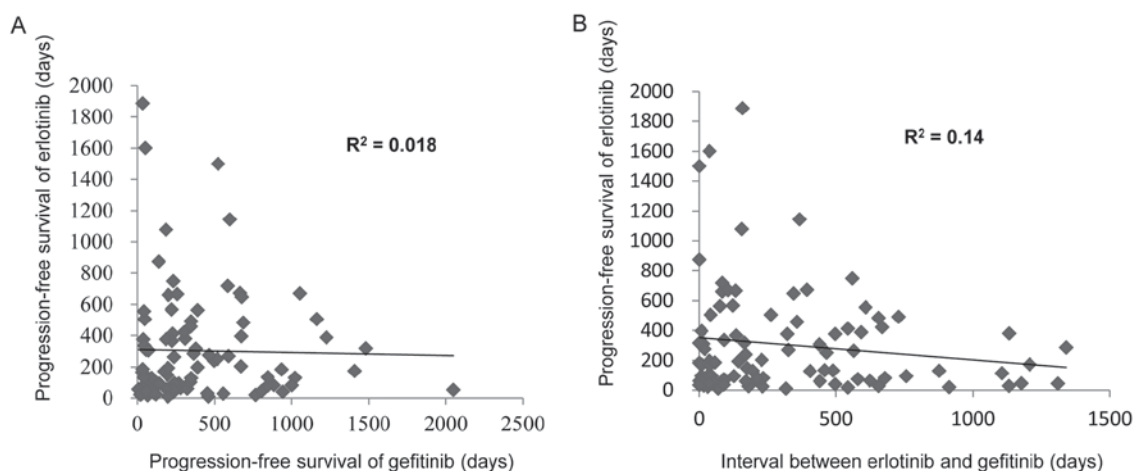


Figure 2. Correlations were assessed between previous gefitinib therapy and the progression free survival of erlotinib therapy. (A) Correlation between the PFS of erlotinib and the PFS of gefitinib. (B) Correlation between the PFS of erlotinib against the interval from gefitinib to erlotinib. PFS, progression free survival.

EGFR in the BR.21 and Sequential Tarceva in Unresectable NSCLC trials (9,21).

As the benefit of *EGFR* TKIs varies widely between patients with *EGFR* mutations and those with wild type *EGFR*, it is crucial to establish which second- or third-line treatment is preferable, particularly for patients with wild type *EGFR* (22). The TAILOR phase III trial, conducted to compare erlotinib with docetaxel in patients who failed first-line platinum-based chemotherapy and who had *EGFR* wild type, demonstrated that chemotherapy was more effective compared with erlotinib for the second-line treatment for previously treated patients with NSCLC with *EGFR* wild type (16). Erlotinib had low efficacy for patients with wild type *EGFR* compared with patients who had *EGFR* active mutations. In addition, the effectiveness of erlotinib subsequent to gefitinib therapy remains controversial.

The present study analyzed the characteristics of 222 patients according to the response to erlotinib. The multivariate analysis revealed that the *EGFR* mutation status (with active mutation) was only associated with a longer PFS and good response to erlotinib treatment. Patients with wild type *EGFR* or unknown status had a poor PFS (1.1 and 1.5 months, respectively) and RR (6 and 5%, respectively). Similarly, the TAILOR phase III trial, which compared erlotinib with standard chemotherapy in patients with wild type *EGFR* as second-line chemotherapy, demonstrated that the RR of erlotinib in wild type *EGFR* patients was 3-5.6%, whereas that of standard chemotherapy was 10.3-20% (16). In addition, a randomized phase III trial (Docetaxel and Erlotinib Lung cancer trial) of erlotinib vs. docetaxel in Japanese patients with advanced NSCLC who had an *EGFR* wild type status demonstrated the poor effectiveness of erlotinib as a second or third-line therapy. The RR of chemotherapy for patients with NSCLC as a second-line therapy was 7.1-22.7% (23-25). The present study therefore considered erlotinib to be invalid for patients with NSCLC with wild type *EGFR* as a second or third-line therapy.

The current study analyzed the characteristics of 95 patients according to the response and interval time on erlotinib subsequent to gefitinib failure. In these patients, a significantly altered response following erlotinib therapy was observed in patients who had exhibited SD for a long period of time during gefitinib treatment. Thus, it appeared that erlotinib is a potential therapeutic option for the treatment of patients with advanced NSCLC with wild type *EGFR* who had SD while receiving gefitinib, as previously suggested (26). However, there was no association between the erlotinib and gefitinib treatments. The predictive factor of erlotinib subsequent to gefitinib therapy was associated with the *EGFR* mutation status alone.

Although the PFS was markedly improved with *EGFR* TKI treatment compared with chemotherapy in such *EGFR* mutated patients, patients who had initially responded to *EGFR* TKI treatment eventually relapsed (27). This acquired resistance to *EGFR* TKI treatment may be linked to a number of molecular mechanisms, including secondary mutations in the *EGFR* gene coding for the intracellular kinase domain of this receptor, a T790M mutation and other factors, including *MET* amplification and hepatocyte growth factor overexpression (28-30). Thus, oncologists may consider a repeat biopsy

prior to retreatment with *EGFR* TKI subsequent to the initial *EGFR* TKI failure.

In conclusion, the efficacy of erlotinib therapy was closely associated with the *EGFR* mutation status. Erlotinib treatment is therefore considered to be limited for patients with NSCLC with *EGFR* mutations, at least as a second or third-line therapy.

References

- Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T and Thun MJ: Cancer statistics, 2008. *CA Cancer J Clin* 58: 71-96, 2008.
- Potosky AL, Saxman S, Wallace RB and Lynch CF: Population variations in the initial treatment of non-small-cell lung cancer. *J Clin Oncol* 22: 3261-3268, 2004.
- Ramalingam S and Belani C: Systemic chemotherapy for advanced non-small cell lung cancer: Recent advances and future directions. *Oncologist* 13 (Suppl 1): S5-S13, 2008.
- Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, *et al*: Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 361: 947-957, 2009.
- Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, Palmero R, Garcia-Gomez R, Pallares C, *et al*: Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced *EGFR* mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 13: 239-246, 2012.
- Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R and Johnson DH: Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 355: 2542-2550, 2006.
- Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J and Johnson DH: Eastern Cooperative Oncology Group: Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 346: 92-98, 2002.
- Ohe Y, Ohashi Y, Kubota K, Tamura T, Nakagawa K, Negoro S, Nishiwaki Y, Saijo N, Ariyoshi Y and Fukuoka M, *et al*: Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol* 18: 317-323, 2007.
- Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, Campos D, Maoleekoonpiroj S, Smylie M, Martins R, *et al*: Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 353: 123-132, 2005.
- Pao W, Miller V, Zakowski M, Doherty J, Politi K, Sarkaria I, Singh B, Heelan R, Rusch V, Fulton L, *et al*: *EGF* receptor gene mutations are common in lung cancers from 'never smokers' and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci USA* 101: 13306-13311, 2004.
- Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, *et al*: 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, 2004.
- Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, *et al*: *EGFR* mutations in lung cancer: Correlation with clinical response to gefitinib therapy. *Science* 304: 1497-1500, 2004.
- Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I, *et al*: Gefitinib or chemotherapy for non-small-cell lung cancer with mutated *EGFR*. *N Engl J Med* 362: 2380-2388, 2010.
- Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, Seto T, Satouchi M, Tada H, Hirashima T, *et al*: 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.
- Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, Zhang S, Wang J, Zhou S, Ren S, *et al*: Erlotinib versus chemotherapy as first-line treatment for patients with advanced *EGFR* mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): A multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 12: 735-742, 2011.

16. Garassino MC, Martelli O, Brogгинi M, Farina G, Veronese S, Rulli E, Bianchi F, Bettini A, Longo F, Moscetti L, *et al*: Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): A randomised controlled trial. *Lancet Oncol* 14: 981-988, 2013.
17. Postmus PE, Brambilla E, Chansky K, Crowley J, Goldstraw P, Patz EF Jr and Yokomise H; International Association for the Study of Lung Cancer International Staging Committee; Cancer Research and Biostatistics; Observers to the Committee; Participating Institutions: The IASLC lung cancer staging project: Proposals for revision of the M descriptors in the forthcoming (seventh) edition of the TNM classification of lung cancer. *J Thorac Oncol* 2: 686-693, 2007.
18. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, *et al*: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 45: 228-247, 2009.
19. Zubrod CG, Ipsen J, Frei E, Lasagna Lc, Lipsett Mb, Gehan E and Escher Gc: Newer techniques and some problems in cooperative group studies. *Natl Cancer Inst Monogr* 3: 277-292, 1960.
20. Lee CK, Brown C, Gralla RJ, Hirsh V, Thongprasert S, Tsai CM, Tan EH, Ho JC, Chu da T, Zaatar A, *et al*: Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: A meta-analysis. *J Natl Cancer Inst* 105: 595-605, 2013.
21. Cappuzzo F, Ciuleanu T, Stelmakh L, Cicens S, Szczésna A, Juhász E, Esteban E, Molinier O, Brugger W, Melezínek I, *et al*: Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: A multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol* 11: 521-529, 2010.
22. Laurie SA and Goss GD: Role of epidermal growth factor receptor inhibitors in epidermal growth factor receptor wild-type non-small-cell lung cancer. *J Clin Oncol* 31: 1061-1069, 2013.
23. Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, Levitan N, Gressot L, Vincent M, Burkes R, *et al*: Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 18: 2095-2103, 2000.
24. Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, Kalman L, Miller V, Lee JS, Moore M, *et al*: Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 non-small cell lung cancer study group. *J Clin Oncol* 18: 2354-2362, 2000.
25. Kudoh S, Takeda K, Nakagawa K, Takada M, Katakami N, Matsui K, Shinkai T, Sawa T, Goto I, Semba H, *et al*: Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small-cell lung cancer: Results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). *J Clin Oncol* 24: 3657-3663, 2006.
26. Cho BC, Im CK, Park MS, Kim SK, Chang J, Park JP, Choi HJ, Kim YJ, Shin SJ, Sohn JH, *et al*: Phase II study of erlotinib in advanced non-small-cell lung cancer after failure of gefitinib. *J Clin Oncol* 25: 2528-2533, 2007.
27. Remon J, Morán T, Majem M, Reguart N, Dalmau E, Márquez-Medina D and Llanes P: Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in EGFR-mutant non-small cell lung cancer: A new era begins. *Cancer Treat Rev* 40: 93-101, 2014.
28. Yun CH, Mengwasser KE, Toms AV, Woo MS, Greulich H, Wong KK, Meyerson M and Eck MJ: The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. *Proc Natl Acad Sci USA* 105: 2070-2075, 2008.
29. Bean J, Brennan C, Shih JY, Riely G, Viale A, Wang L, Chitale D, Motoi N, Szoke J, Broderick S, *et al*: MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. *Proc Natl Acad Sci USA* 104: 20932-20937, 2007.
30. Yano S, Wang W, Li Q, Matsumoto K, Sakurama H, Nakamura T, Ogino H, Kakiuchi S, Hanibuchi M, Nishioka Y, *et al*: Hepatocyte growth factor induces gefitinib resistance of lung adenocarcinoma with epidermal growth factor receptor-activating mutations. *Cancer Res* 68: 9479-9487, 2008.