

Keywords: non-small cell lung cancer; *EGFR* mutation; exon 19; exon 21; erlotinib; gefitinib

A phase III randomised controlled trial of erlotinib vs gefitinib in advanced non-small cell lung cancer with *EGFR* mutations

J J Yang¹, Q Zhou¹, H H Yan¹, X C Zhang¹, H J Chen¹, H Y Tu¹, Z Wang¹, C R Xu¹, J Su¹, B C Wang¹, B Y Jiang¹, X Y Bai¹, W Z Zhong¹, X N Yang¹ and Y L Wu^{*,1}

¹Guangdong Lung Cancer Institute, Guangdong General Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China

Background: A phase III trial was conducted to compare the safety and efficacy of erlotinib with that of gefitinib in advanced non-small cell lung cancer harbouring epidermal growth factor receptor mutations in exon 19 or 21.

Methods: Eligible patients were randomised to receive erlotinib (150 mg per day) or gefitinib (250 mg per day) orally until disease progression or unacceptable toxicity. We aimed to determine whether erlotinib is superior to gefitinib in efficacy. The primary end point was progression-free survival.

Results: A total of 256 patients were randomised to receive erlotinib ($N=128$) or gefitinib ($N=128$). Median progression-free survival was not better with erlotinib than with gefitinib (13.0 vs 10.4 months, 95% confidence interval (CI) 0.62–1.05, $P=0.108$). The corresponding response rates and median overall survival were 56.3% vs 52.3% ($P=0.530$) and 22.9 vs 20.1 months (95% CI 0.63–1.13, $P=0.250$), respectively. There were no significant differences in grade 3/4 toxicities between the two arms ($P=0.172$).

Conclusions: The primary end point was not met. Erlotinib was not significantly superior to gefitinib in terms of efficacy in advanced non-small cell lung cancer with epidermal growth factor receptor mutations in exon 19 or 21, and the two treatments had similar toxicities.

Both gefitinib and erlotinib are first-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) for advanced non-small cell lung cancer (NSCLC) patients. Two phase III trials (the Iressa Survival Evaluation in Lung Cancer study and the BR.21 trial) comparing gefitinib or erlotinib to placebo in previously treated advanced NSCLC showed that erlotinib significantly prolonged median overall survival (OS; 6.7 vs 4.7 months, hazard ratio (HR) 0.70, $P<0.001$; Shepherd *et al*, 2005), but gefitinib did not (Thatcher *et al*, 2005). In 2004, two milestone studies identified somatic mutations in *EGFR* that predicted sensitivity and response to EGFR TKIs (Lynch *et al*, 2004; Paez *et al*, 2004). The frequency of these activating mutations, including

EGFR exon 19 deletions and exon 21 (L858R) point mutations, was reported to be increased in specific NSCLC populations such as women, patients of Asian origin, and patients without a history of smoking (Fukuoka *et al*, 2003; Giaccone *et al*, 2004; Shepherd *et al*, 2005; Thatcher *et al*, 2005).

Until 2009, gefitinib and erlotinib had been considered valid treatment options for patients with advanced NSCLC who had received prior treatment (on the basis of several phase III trials (Shepherd *et al*, 2005; Thatcher *et al*, 2005; Kim *et al*, 2008) and were registered in many countries for this indication, particularly in Asian countries (Guan *et al*, 2005; Maruyama *et al*, 2008; Uhm *et al*, 2009). However, it was unclear how to choose between these

*Correspondence: Dr YL Wu; E-mail: syylwu@live.cn.

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two EGFR TKIs in the clinic. Although some differences in the trial results for erlotinib and gefitinib led to differences in regulatory policy, no head-to-head randomised controlled trials were published to provide a final treatment strategy. In addition, there were no significant differences in progression-free survival (PFS) or OS between first-line and second-line EGFR TKI treatment in EGFR-mutant NSCLC (Massuti *et al*, 2009). We were faced with the challenging problem of how to customise EGFR TKI treatment for advanced NSCLC patients with EGFR activating mutations.

Robust data were lacking, so it was difficult to make an informed choice, even though these two EGFR TKIs were available in the clinic. Therefore, in July 2009, we initiated a randomised controlled trial of erlotinib vs gefitinib in advanced NSCLC harbouring EGFR exon 19 or 21 mutations and enrolled patients regardless of the line of treatment (Chinese Thoracic Oncology Group (CTONG) 0901) to determine whether erlotinib is superior to gefitinib in terms of response and survival.

PATIENTS AND METHODS

Eligibility criteria. Eligible patients were adults aged ≥ 18 years with histologically or cytologically confirmed and locally advanced or metastatic (stage IIIB without any indications for curative chemoradiation or other local treatments to stage IV) NSCLC (AJCC/UICC version 6) harbouring EGFR exon 19 or 21 mutations detected by direct DNA sequencing as previously described (Jiang *et al*, 2008); measurable disease according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (Eisenhauer *et al*, 2009); Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2; and adequate bone marrow, liver, and kidney function. Patients without exposure to any EGFR inhibitors were eligible for recruitment. Those with clinically unstable brain metastases, a history of cardiac disease, uncontrolled hypertension, other active malignancies, or any active infectious diseases were excluded.

Treatment schedule. After screening, patients were randomly assigned at a 1:1 ratio to receive oral erlotinib 150 mg or gefitinib 250 mg once daily. Second- and further-line treatments were

defined as second line in the present study. Treatment continued until unacceptable toxicity, disease progression, or another discontinuation criterion was met. Erlotinib or gefitinib dose delays of ≤ 14 days were permitted for grade ≥ 3 nonhaematological toxicities until resolution to grade 1 or baseline, and treatment was reintroduced at a reduced dosage depending on the toxicity.

Tumour response was assessed by investigators according to RECIST version 1.1 (Eisenhauer *et al*, 2009). The initial response was assessed after 5 weeks of treatment, and the baseline assessments were repeated every 2 months. Toxicities were assessed by the investigators based on the incidence and severity of adverse events (AEs), according to the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 3.0.

Study design and objectives. In June 2009, this study was a head-to-head phase II randomised controlled trial (CTONG 0901; clinicaltrials.gov No. NCT01024413) comparing erlotinib with gefitinib for patients with exon 21 mutations. The primary end point was response rate (RR), and the secondary endpoints included PFS, OS, and safety. The sample size was 70 (35 in each arm).

However, the protocol was amended in January 2010, and the study was redesigned and approved as a phase III randomised controlled trial by the appropriate independent ethics committees at the Guangdong Lung Cancer Institute, Guangdong General Hospital; this study was conducted according to the Declaration of Helsinki. EGFR exon 19 or 21 mutation-positive patients with advanced NSCLC were allowed to be recruited into this phase III trial. All patients provided written informed consent before study participation.

In this phase III trial, the primary end point was PFS, and the secondary end points included OS, RR, and safety. An exploratory end point was efficacy between the exon 19 and 21 mutation groups.

Statistical considerations. The study hypothesis was that erlotinib would improve PFS relative to gefitinib in advanced NSCLC harbouring EGFR exon 19 or 21 mutations. Based on the median PFS of 9.5 months with gefitinib and 14.0 months with erlotinib

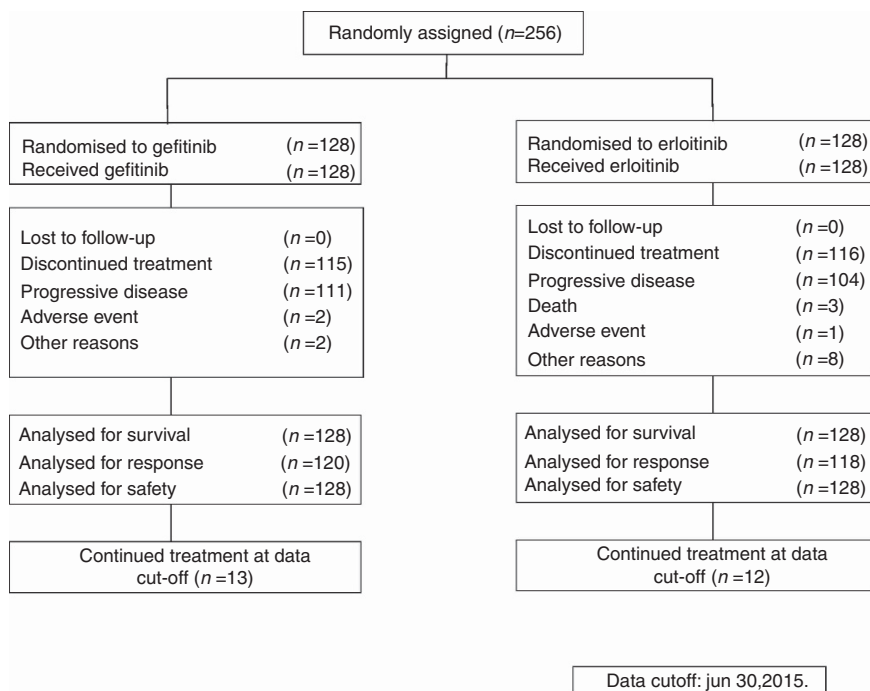


Figure 1. Trial profile. The study flowchart is shown from randomisation to data cutoff.

(Mok *et al*, 2008; Massuti *et al*, 2009), 80% power to detect a HR of 0.65 at a two-sided significance level of 0.05, 12 months of enrolment, 48 months of study duration, and a 5% rate of loss to follow-up, the appropriate sample size was calculated to be 254 patients with 127 in each arm, with statistical analysis of median survival time by log-rank test.

Chi-square or Fisher's exact tests were used to compare qualitative data. PFS was defined as the time of randomisation to the first documentation of progressive disease (PD) or death from any cause. OS was calculated from randomisation to the last visit or death from any cause. Efficacy analyses were completed for the intent-to-treat population.

The Kaplan-Meier method was used to generate survival curves. The log-rank test was used to compare survival curves among patient groups. All statistical tests were two-sided, and 0.05 was deemed to indicate statistical significance. PASS version 11.0 (NCSS, Inc., Kaysville, Utah, USA) was used for the analyses.

RESULTS

Patient population and characteristics. Between July 2009 and 2014, 256 patients at the Guangdong Lung Cancer Institute satisfied the inclusion or exclusion criteria and were randomly assigned (128 in each arm; Figure 1). The first and last patients with exon 21 mutations were recruited on 13 July 2009, and 11 July 2014, respectively. The first and last patients with exon 19 mutations were recruited on 26 February 2010 and 29 January 2014, respectively. In the erlotinib arm, 10 patients did not have an assessment of tumour response (three did not return to the hospital for evaluation; two discontinued treatment by themselves within one month; and two died within 1 month of treatment) or a confirmed response (three had an initial response of SD but did not undergo further imaging). In the gefitinib arm, eight patients did not undergo an assessment of tumour response (four died within 1 month of treatment, and four discontinued treatment by themselves within 1 month due to AEs or financial problems and refused to undergo imaging investigation). The compliance of the enrolled patients was 95.3% (244/256).

Patient characteristics. The 256 randomized patients formed well-balanced treatment arms in terms of baseline demographics and clinicopathological characteristics (Table 1). The median age was 58.5 years (range, 30–85 years); 57.8% of the patients had EGFR exon 19 deletions, and 66.0% were in the first-line setting.

Efficacy analysis. The last follow-up was on 30 June 2015, and the median follow-up time was 22.1 months. When 218 progression events (85.2%) and 184 survival events (71.9%) had occurred, both PFS and OS were mature. PFS did not differ significantly between the treatment arms in the intent-to-treat population (HR 0.81, 95% CI 0.62–1.05, $P=0.108$; Figure 2A). Median PFS was 13.0 (95% CI 11.1–14.9) vs 10.4 (95% CI 8.8–11.9) months for the erlotinib and gefitinib arms, respectively (Figure 2A). Similarly, OS was not significantly different (median OS: erlotinib, 22.9 months; gefitinib, 20.1 months; HR 0.84, 95% CI 0.63–1.13, $P=0.250$; Figure 2B). Post-discontinuation therapies are listed in Supplementary Table S1. There was no significant difference in RR between the two arms in the intent-to-treat population (56.3% (76/128) vs 52.3% (67/128), $P=0.530$). The waterfall plots for the best percentage change in target lesion size are shown for the two arms (Figure 3).

Baseline demographic characteristics for the EGFR exon 19 and 21 mutation arms are shown in Table 2. Except for age and line of EGFR TKI treatment, the other baseline demographics were well-balanced between the two arms. Upon receiving erlotinib or gefitinib treatment, patients with EGFR exon 19 mutations were

Table 1. Baseline demographics between the erlotinib and gefitinib arms

Demographics	Gefitinib N (%)	Erlotinib N (%)	Sum N (%)	P
Gender				0.900
Male	59 (46.1)	60 (46.9)	119 (46.5)	
Female	69 (53.9)	68 (53.1)	137 (53.5)	
Age				0.900
≤ 60 yrs	72 (56.3)	71 (55.5)	143 (55.9)	
> 60 yrs	56 (43.8)	57 (44.5)	113 (44.1)	
ECOG PS				0.448
0–1	124 (96.9)	126 (98.4)	250 (97.7)	
2	4 (3.1)	2 (1.6)	6 (2.3)	
Smoking				0.073
No	93 (72.7)	105 (82.0)	198 (77.3)	
Yes	35 (27.3)	23 (18.0)	58 (22.7)	
Prior lung surgery				0.447
No	97 (75.8)	92 (71.9)	189 (73.8)	
Yes	31 (24.2)	36 (28.1)	67 (26.2)	
Chemotherapy ^a				0.483
No	83 (64.8)	83 (64.8)	166 (64.8)	
Single agent	1 (0.8)	4 (3.1)	5 (2.0)	
Doublet	44 (34.4)	41 (32.0)	85 (33.2)	
Prior radiation				0.512
No	118 (92.2)	115 (89.8)	233 (91.0)	
Yes	10 (7.8)	13 (10.2)	23 (9.0)	
Brain metastasis				0.628
No	106 (82.8)	103 (80.5)	209 (81.6)	
Yes	22 (17.2)	25 (19.5)	47 (18.4)	
Clinical staging ^a				1.000
IIIB	3 (2.3)	4 (3.1)	7 (2.7)	
IV	125 (97.7)	124 (96.9)	249 (97.3)	
Histology ^b				1.000
Adeno	123 (96.1)	123 (96.1)	246 (96.1)	
Non-adeno	5 (3.9)	5 (3.9)	10 (3.9)	
EGFR mutations				1.000
Exon 19	74 (57.8)	74 (57.8)	148 (57.8)	
Exon 21	54 (42.2)	54 (42.2)	108 (42.2)	
Line of EGFR TKI				0.695
First-line	84 (65.6)	81 (63.3)	165 (64.5)	
Second-line ^c	44 (34.4)	47 (36.7)	91 (35.5)	
Sum	128 (50.0)	128 (50.0)	256 (100.0)	

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; Adeno = adenocarcinoma; EGFR = epidermal growth factor receptors; EGFR TKI = epidermal growth factor receptors tyrosine kinase inhibitors; yrs = years.

^aFISH exact method.

^bIncluding four with adenosquamous cell carcinoma, four with squamous cell carcinoma, and two with sarcoma-like carcinoma.

^cIncluding nine cases in the third-line or fourth-line settings.

superior to those with exon 21 mutations in terms of median OS (22.9 vs 17.8 months, HR 0.71, 95% CI 0.53–0.95, $P=0.022$; Figure 2D) and RR (62.2% vs 43.5%, $P=0.003$; Table 3), even though there was no significant difference in median PFS (11.4 vs 11.2 months, HR 0.82, 95% CI 0.63–1.08, $P=0.160$; Figure 2C).

However, in the first-line setting, the erlotinib and gefitinib arms had an RR of 58.0% (47/81) vs 52.4% (44/84) ($P=0.466$), a median PFS of 13.2 vs 11.1 months (HR 0.96, 95% CI 0.69–1.35, $P=0.827$), and a median OS of 22.4 vs 20.7 months (HR 0.98, 95% CI 0.67–1.42, $P=0.902$).

Safety. In the safety population of 256 patients who received any dose of study drug, no significant difference was observed in the frequency of Grade ≥ 3 AEs in the erlotinib and gefitinib arms (5.4% vs 1.6%, $P=0.172$). No cases of interstitial lung disease were recorded. The treatment-emergent AEs that were observed in $\geq 10\%$ of the patients in each arm are shown in Table 4.

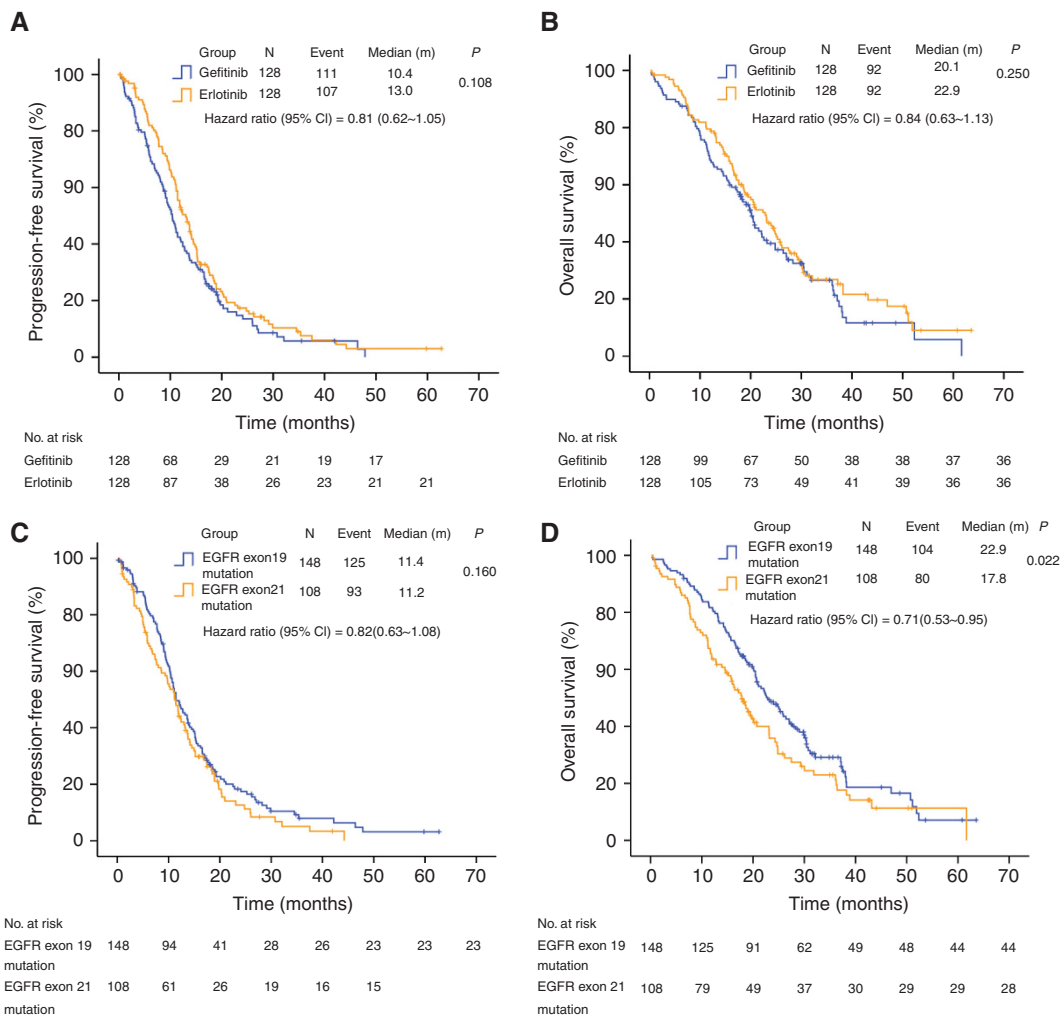


Figure 2. Kaplan-Meier curves of PFS and OS in 256 patients. (A) Median PFS in the erlotinib and gefitinib arms. (B) Median OS in the erlotinib and gefitinib arms. (C) Median PFS in the EGFR exon 19 and 21 mutation arms. (D) Median OS in the EGFR exon 19 and 21 mutation arms. EGFR, epidermal growth factor receptor.

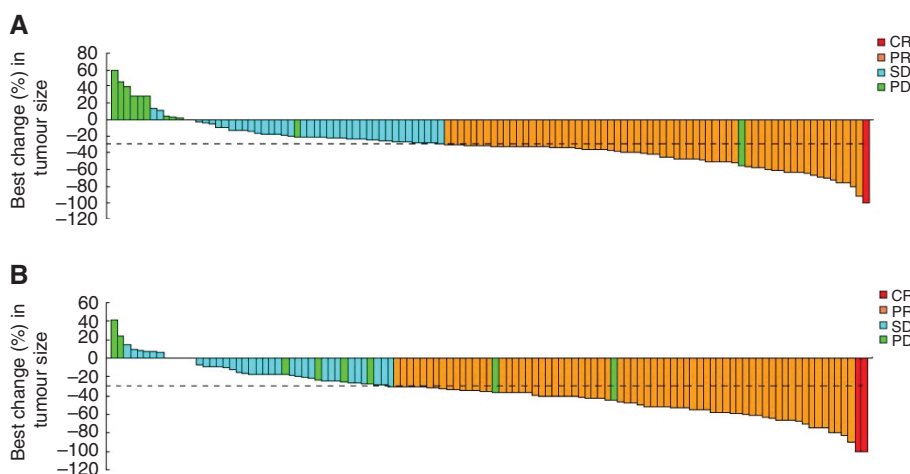


Figure 3. Waterfall plots of the best percentage change in target lesions at baseline. (A) Gefitinib arm. (B) Erlotinib arm. CR, complete remission; PR, partial response; SD, stable disease; and PD, progressive disease.

DISCUSSION

To the best of our knowledge, the present study was the first head-to-head phase III randomised controlled trial comparing erlotinib

with gefitinib in EGFR activating mutation-positive NSCLC. The results did not support the hypothesis described in the study design, namely, that the primary end point, PFS, would be significantly prolonged with erlotinib compared with gefitinib. These two EGFR TKIs produced similar results for RR, OS, and

Table 2. Baseline demographics between the exon 19 and 21 mutation arms

Demographics	Exon 19 N (%)	Exon 21 N (%)	Sum N (%)	P
Gender				0.648
Male	67 (45.3)	52 (48.1)	119 (46.5)	
Female	81 (54.7)	56 (51.9)	137 (53.5)	
Age				<0.001
≤ 60 yrs	100 (67.6)	43 (39.8)	143 (55.9)	
> 60 yrs	48 (32.4)	65 (60.2)	113 (44.1)	
ECOG PS				0.406
0-1	143 (96.6)	107 (99.1)	250 (97.7)	
2	5 (3.4)	1 (0.9)	6 (2.3)	
Smoking				0.643
No	116 (78.4)	82 (75.9)	198 (77.3)	
Yes	32 (21.6)	26 (24.1)	58 (22.7)	
Prior lung surgery				0.431
No	112 (75.7)	77 (71.3)	189 (73.8)	
Yes	36 (24.3)	31 (28.7)	67 (26.2)	
Chemotherapy ^a				0.159
No	89 (60.1)	77 (71.3)	166 (64.8)	
Single agent	4 (2.7)	1 (0.9)	5 (2.0)	
Doublet	55 (37.2)	30 (27.8)	85 (33.2)	
Prior radiation				0.895
No	135 (91.2)	98 (90.7)	233 (91.0)	
Yes	13 (8.8)	10 (9.3)	23 (9.0)	
Brain metastasis				0.300
No	124 (83.8)	85 (78.7)	209 (81.6)	
Yes	24 (16.2)	23 (21.3)	47 (18.4)	
Clinical staging ^a				0.702
IIIB	5 (3.4)	2 (1.9)	7 (2.7)	
IV	143 (96.6)	106 (98.1)	249 (97.3)	
Histology ^b				0.639
Adeno	141 (95.3)	105 (97.2)	246 (96.1)	
Non-adeno	7 (4.7)	3 (2.8)	10 (3.9)	
Line of EGFR TKI				0.027
First-line	87 (58.8)	78 (72.2)	165 (64.5)	
Second-line ^c	61 (41.2)	30 (27.8)	91 (35.5)	
Type of EGFR TKI				1.000
Gefitinib	74 (50.0)	54 (50.0)	128 (50.0)	
Erlotinib	74 (50.0)	54 (50.0)	128 (50.0)	
Sum	148 (57.7)	108 (42.3)	256 (100.0)	

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; Adeno = adenocarcinoma; EGFR = epidermal growth factor receptors; EGFR TKI = epidermal growth factor receptors tyrosine kinase inhibitors; yrs = years.

^aFISH exact method.

^bIncluding four with adenocarcinoma, four with squamous cell carcinoma, and two with sarcoma-like carcinoma.

^cIncluding nine cases in the third-line or fourth-line settings.

toxicity. To some extent, the conclusion of the present study was almost the same as that of the earlier randomised phase II study, in which gefitinib and erlotinib showed similar efficacy and tolerable toxicity profiles as second-line treatments for molecularly selected (*EGFR* activating mutations accounted for 17.7% (17/96) of all enrolled patients) or clinically selected populations of patients with NSCLC (Kim *et al*, 2012). However, patients with *EGFR* exon 19 or 21 mutations in any line setting were enrolled in the present study, leading to precision medicine in advanced NSCLC. In addition, the present study had a larger sample size ($N = 256$; 128 in each arm) than the previous phase II study ($N = 96$; 48 in each arm; Kim *et al*, 2012).

A prospective study showed no significant difference in PFS (14.0 vs 13.0 months, $P = 0.62$) or OS (28.0 vs 27.0 months, $P = 0.67$) between first- and second-line erlotinib treatment in *EGFR*-mutant NSCLC (Massuti *et al*, 2009; Rosell *et al*, 2009). Furthermore, in recent years, several phase III randomised

Table 3. Response to erlotinib or gefitinib between the exon 19 and 21 mutation arms

Best response	Exon 19 (%)	Exon 21 (%)	P
	N = 148	N = 108	
CR	3 (2.0)	0 (0.0)	
PR	89 (60.1)	47 (43.5)	
SD	42 (28.4)	38 (35.2)	
PD	6 (4.1)	13 (12.0)	
NA	8 (5.4)	10 (9.3)	
ORR	92 (62.2)	47 (43.5)	0.003
DCR	134 (90.5)	85 (78.7)	0.008

Abbreviations: CR = complete remission; PR = partial response; SD = stable disease; PD = progressive disease; NA = not available; ORR = objective response rate; DCR = disease control rate.

Table 4. Treatment-emergent AEs ≥ 10% of patients in either treatment arm

AE	Gefitinib (n = 128) no. (%)		Erlotinib (n = 128) no. (%)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Rash	80 (62.5)	0 (0.0)	89 (69.5)	3 (2.3)
Cough	38 (29.7)	0 (0.0)	30 (23.4)	0 (0.0)
Diarrhoea	24 (18.8)	0 (0.0)	22 (17.2)	0 (0.0)
Hand and foot syndrome	16 (12.5)	0 (0.0)	8 (6.3)	0 (0.0)
Nail changes	16 (12.5)	0 (0.0)	24 (18.8)	0 (0.0)
Anorexia	15 (11.7)	0 (0.0)	7 (5.4)	0 (0.0)
ALT increase	13 (10.2)	0 (0.0)	6 (4.7)	0 (0.0)
Bilirubin increase	13 (10.2)	0 (0.0)	7 (5.4)	3 (2.3)
Dry skin	11 (8.6)	0 (0.0)	13 (10.2)	0 (0.0)

Abbreviations: AE = adverse event; ALT = alanine aminotransferase.

controlled trials have demonstrated no significant difference in OS between first-line *EGFR* TKIs and chemotherapy for patients with *EGFR*-mutant advanced NSCLC, probably owing to subsequent *EGFR* TKI treatment for those receiving first-line chemotherapy (Mok *et al*, 2009; Maemondo *et al*, 2010; Mitsudomi *et al*, 2010; Zhou *et al*, 2011; Rosell *et al*, 2012; Sequist *et al*, 2013; Wu *et al*, 2014). Taken together, the design of the present study, comparing erlotinib with gefitinib in both first- and second-line settings, was evidence-based and could be rationalised in 2009.

In the present study, subgroup analyses showed that patients with *EGFR* exon 19 mutations had a significantly higher RR (62.2% vs 43.5%, $P = 0.003$) and longer median OS (22.9 vs 17.8 months, $P = 0.022$) than those with exon 21 mutations treated with erlotinib or gefitinib, similar to the results of several retrospective studies in which better efficacy was observed in patients with *EGFR* exon 19 deletions than in those with exon 21 L858R mutations (Jackman *et al*, 2006; Riely *et al*, 2006; Rosell *et al*, 2012); however, the present study had a relatively large sample size ($N = 148$ vs $N = 108$) and a prospective design based on our translational data (Zhu *et al*, 2008). Recently, an analysis of OS data from two randomised phase III trials suggested that *EGFR* del19-positive disease might be distinct from L858R-positive disease and that these subgroups should be analysed separately in future trials (Sequist *et al*, 2013; Wu *et al*, 2014; Yang *et al*, 2015). However, the above differences were found in subgroup analyses. Therefore, it could be very challenging to draw a definitive conclusion.

Recently, first-line gefitinib was approved by the FDA for patients with EGFR-mutant advanced NSCLC (FDA approves targeted therapy for first-line treatment of patients with a type of metastatic lung cancer, 2015). The present study identified no significant differences in efficacy or toxicity profile between first-line erlotinib and gefitinib for patients with EGFR-mutant disease, and these results could be considered globally. Recently, in the LUX LUNG 7 trial, first-line afatinib (an irreversible ErbB family blocker) significantly improved PFS vs gefitinib in EGFR-mutant patients (HR 0.73, 95% CI 0.57–0.95, $P = 0.0165$; Park *et al*, 2016). However, the LUX LUNG 7 trial was a global randomised phase IIb study, and the results will be validated by future phase III trials. The question remains as to the acceptable length of the survival benefit in the clinic. More investigations are warranted to determine which generation EGFR TKIs will be the best choice for the treatment of EGFR-mutant patients.

There are a few limitations to the present study. First, it took 5 years to complete recruitment at a single centre, and several competitive trials might have affected enrolment during this long period, possibly leading to an enrolment bias. Second, the present study was not sponsored by any pharmaceutical companies, and patients self-paid for study drugs and imaging investigations, so a few were not fully compliant. Finally, the efficacy data for erlotinib and gefitinib indicated that a much larger sample size was necessary in the present study.

In conclusion, the primary end point was not met in the present study, and erlotinib was not significantly superior to gefitinib in advanced NSCLC with EGFR exon 19 or 21 mutations in terms of response or survival, and it had similar toxicity. Meanwhile, upon treatment with erlotinib or gefitinib, patients with exon 19 mutations had markedly better outcomes than those with exon 21 mutations.

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CONFLICT OF INTEREST

YLW received speaker fees from Eli Lilly, Roche, AstraZeneca, Pfizer, and Sanofi. The remaining authors declare that they have no competing interest.

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