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

Caicun Zhou, Yi-Long Wu*, Gongyan Chen, Jifeng Feng, Xiao-Qing Liu, Changli Wang, Shucai Zhang, Jie Wang, Songwen Zhou, Shengxiang Ren, Shun Lu, Li Zhang†, Chengping Hu, Chunhong Hu, Yi Luo, Lei Chen, Ming Ye, Jianan Huang, Xiuyi Zhi, Yiping Zhang, Qingyu Xiu, Jun Ma, Li Zhang‡, Changxuan You*

Summary

Background Activating mutations in *EGFR* are important markers of response to tyrosine kinase inhibitor (TKI) therapy in non-small-cell lung cancer (NSCLC). The OPTIMAL study compared efficacy and tolerability of the TKI erlotinib versus standard chemotherapy in the first-line treatment of patients with advanced *EGFR* mutation-positive NSCLC.

Methods We undertook an open-label, randomised, phase 3 trial at 22 centres in China. Patients older than 18 years with histologically confirmed stage IIIB or IV NSCLC and a confirmed activating mutation of *EGFR* (exon 19 deletion or exon 21 L858R point mutation) received either oral erlotinib (150 mg/day) until disease progression or unacceptable toxic effects, or up to four cycles of gemcitabine plus carboplatin. Patients were randomly assigned (1:1) with a minimisation procedure and were stratified according to *EGFR* mutation type, histological subtype (adenocarcinoma *vs* non-adenocarcinoma), and smoking status. The primary outcome was progression-free survival, analysed in patients with confirmed disease who received at least one dose of study treatment. The trial is registered at ClinicalTrials.gov, number NCT00874419, and has completed enrolment; patients are still in follow-up.

Findings 83 patients were randomly assigned to receive erlotinib and 82 to receive gemcitabine plus carboplatin; 82 in the erlotinib group and 72 in the chemotherapy group were included in analysis of the primary endpoint. Median progression-free survival was significantly longer in erlotinib-treated patients than in those on chemotherapy (13·1 [95% CI 10·58–16·53] *vs* 4·6 [4·21–5·42] months; hazard ratio 0·16, 95% CI 0·10–0·26; p<0·0001). Chemotherapy was associated with more grade 3 or 4 toxic effects than was erlotinib (including neutropenia in 30 [42%] of 72 patients and thrombocytopenia in 29 [40%] patients on chemotherapy *vs* no patients with either event on erlotinib); the most common grade 3 or 4 toxic effects with erlotinib were increased alanine aminotransferase concentrations (three [4%] of 83 patients) and skin rash (two [2%] patients). Chemotherapy was also associated with increased treatment-related serious adverse events (ten [14%] of 72 patients [decreased platelet count, n=8; decreased neutrophil count, n=1; hepatic dysfunction, n=1] *vs* two [2%] of 83 patients [both hepatic dysfunction]).

Interpretation Compared with standard chemotherapy, erlotinib conferred a significant progression-free survival benefit in patients with advanced *EGFR* mutation-positive NSCLC and was associated with more favourable tolerability. These findings suggest that erlotinib is important for first-line treatment of patients with advanced *EGFR* mutation-positive NSCLC.

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Introduction

Lung cancer, of which non-small-cell lung cancer (NSCLC) is the most common form, remains the leading cause of cancer-related mortality worldwide, with many patients presenting with advanced disease at initial diagnosis.[1] Recent advances in chemotherapy and targeted therapy have provided us with new treatment options for this disease. One such example is the orally administered targeted agent erlotinib, which inhibits the tyrosine kinase domain of EGFR and was approved for use in the second-line setting on the basis of the positive results of the phase 3 BR.21 trial,[2] in which erlotinib showed an improvement in overall survival versus best supportive care. Erlotinib has also shown clinical benefit in first-line advanced NSCLC, achieving tumour response rates of 10–20% and a median survival of between 10·9 and 12·9 months in phase 2 studies.[3,4] However, despite important new additions to the therapeutic armamentarium for NSCLC, 5-year survival for patients with this disease is still disappointingly low at less than 20%.[5]

Increasingly, NSCLC research has focused on efforts to identify biomarkers that are able to predict an increase in clinical benefit from new agents in selected

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*Joint lead authors

Department of Oncology, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai, China (Prof C Zhou MD, S Zhou MD, S Ren MD); Guangdong Lung Cancer Institute, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China (Prof Y-L Wu MD); Cancer Hospital of Harbin Medical University, Harbin, China (Prof G Chen PhD); Jiangsu Province Cancer Hospital, Nanjing, China (Prof J Feng MD); 307 Hospital of the Academy of Military Medical Sciences, Cancer Center, Department of Pulmonary Oncology, Beijing, China (Prof X-Q Liu MD); Tianjin Cancer Hospital, Tianjin, China (Prof C Wang MD); Beijing Chest Hospital (Prof S Zhang MD), and Xuanwu Hospital (Prof X Zhi MD), Capital Medical University, Beijing, China; Peking University School of Oncology, Beijing Cancer Hospital, Beijing, China (Prof J Wang MD); Shanghai Chest Hospital (Prof S Lu PhD) and Renji Hospital, School of Medicine (Prof M Ye MD), Shanghai Jiao Tong University, Shanghai, China; Sun Yat-sen University Cancer Center, Guangzhou, China (Prof L Zhang† MD); Xiangya Hospital (Prof Chengping Hu PhD) and Second Xiangya Hospital (Prof Chunhong Hu MD), Central South University, Changsha, China; Hunan Province Cancer Hospital, Changsha, China (Prof Y Luo MD); Cancer Hospital

Shantou University Medical College, Shantou, China (Prof L Chen MD); **First Affiliated Hospital of Suzhou University, Suzhou, China** (Prof J Huang MD); **Zhejiang Cancer Hospital, Hangzhou, China** (Prof Y Zhang MD); **Changzhen Hospital, Second Military Medical University, Shanghai, China** (Prof Q Xiu MD); **Harbin Institute of Hematology and Oncology, Harbin, China** (Prof J Ma MD); **Peking Union Medical College Hospital, Beijing, China** (Prof L Zhang‡ MD); **and Nanfang Hospital, Southern Medical University, Guangzhou, China** (Prof C You MD)

Correspondence to: Prof Caicun Zhou, Department of Oncology, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai, China **caicunzhou@yahoo.com.cn**

For the **OPTIMAL trial protocol** see http://www.shsfkyy.com/upload/html/20110627154244134.pdf

patient subgroups, thereby allowing clinicians to make informed treatment decisions about the most appropriate initial treatment option for an individual patient. The most promising of these markers to date is *EGFR* mutation status; recent data suggest that patients with tumours that harbour activating mutations in *EGFR* (ie, exon 19 deletions or exon 21 L858R point mutations) achieve a substantially increased benefit from treatment with EGFR tyrosine kinase inhibitor (TKI) therapy compared with patients whose tumours lack such mutations.[6–11] Notably, *EGFR* mutations occur with greater frequency in Asian patients compared with white patients, with typical mutation rates of around 30% and 8%, respectively.[7,12,13] Almost one in three Asian patients could therefore possess a biomarker to predict exceptional response to EGFR TKI therapy. Implementation of accurate *EGFR* mutation testing is a key factor in use of biomarker-based treatment strategies in clinical practice, although patient selection on the basis of clinical characteristics to achieve enrichment for activating *EGFR* mutations has thus far proved unsatisfactory.[6,14]

The OPTIMAL study was initiated to compare the efficacy and tolerability of first-line erlotinib as monotherapy versus the standard chemotherapy regimen in China (four cycles of gemcitabine plus carboplatin) in patients with advanced or metastatic NSCLC whose tumours carried activating mutations in *EGFR*.

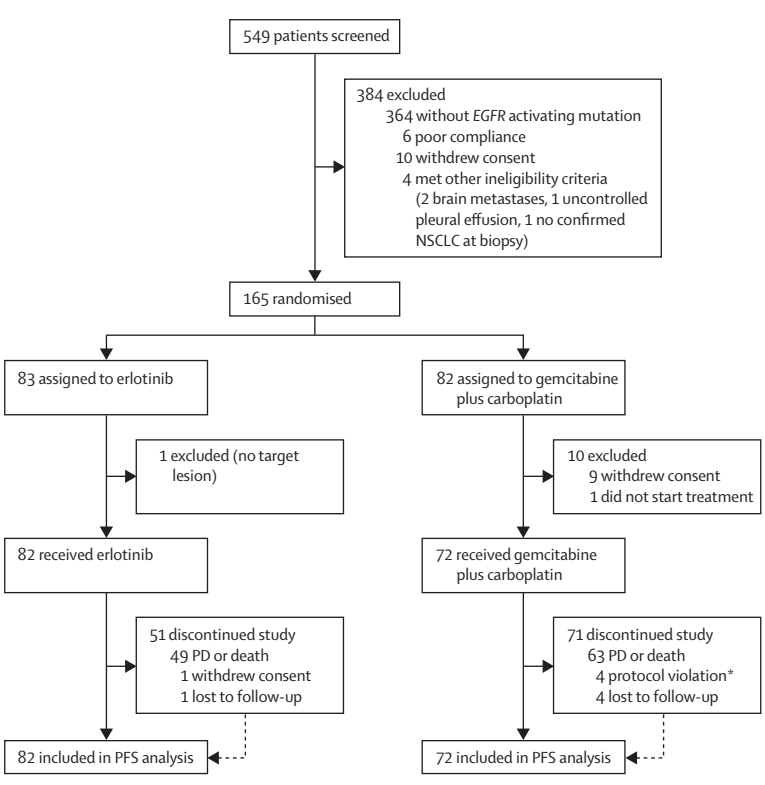

Figure 1: **Trial profile at cutoff date for analysis (Aug 16, 2010)**
NSCLC=non-small-cell lung cancer. PD=progressive disease. PFS=progression-free survival. *Received erlotinib (n=3) or gefitinib (n=1) after chemotherapy, but before PD.

Methods

Study design and patients

This phase 3, open-label, randomised study was undertaken at 22 centres in China. Eligible patients were more than 18 years of age and had histologically confirmed advanced or recurrent stage IIIB or IV NSCLC (Union for International Cancer Control classification version 6) with a confirmed activating mutation of *EGFR*—ie, an exon 19 deletion or an exon 21 L858R point mutation. They also had measurable disease according to Response Evaluation Criteria In Solid Tumors (RECIST version 1.0), an Eastern Cooperative Oncology Group performance status of 0–2, and adequate haematological, biochemical, and organ function. Patients were excluded from the study if they had uncontrolled brain metastases or had received previous systemic anticancer therapy for advanced disease (although adjuvant or neoadjuvant therapy was allowed for non-metastatic disease in which relapse had occurred ≥6 months after final treatment).

The study was undertaken in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by local ethics committees at each participating centre and all patients provided written informed consent for participation in the study and provision of tumour samples.

Randomisation

Patients were randomly assigned (1:1) to either erlotinib or chemotherapy by dynamic minimisation procedure with Mini Randomisation software (version 1·5). Central randomisation was done by a clinical research organisation (CRO; Tigermed Consulting, Shanghai, China) via email or telephone; patients were stratified according to mutation type (exon 19 mutation *vs* exon 21 mutation), histological subtype (adenocarcinoma *vs* non-adenocarcinoma), and smoking status (present or former smoker *vs* never smoker). Throughout the study, clinicians and study participants were not masked to the identity of the study treatment.

Procedures

All patients screened for entry into the study had to have sufficient tumour tissue for *EGFR* mutation testing. Only patients with confirmed *EGFR* mutations in exon 19 or exon 21 were allowed to enter the study. Testing was done on fresh or paraffin-embedded tumour samples by PCR-based direct sequencing at a central laboratory (Takara Biotechnology, Dalian, China). Other methods were applied for monitoring at the same time—eg, 4% agarose gel electrophoresis for *EGFR* exon 19 deletion mutations and Cycleave real-time PCR for *EGFR* exon 21 L858R mutations.

Eligible patients were randomly assigned to receive either oral erlotinib 150 mg once daily until disease

progression or unacceptable toxic effects, or up to four cycles of platinum-based doublet chemotherapy (intravenous gemcitabine 1000 mg/m² on days 1 and 8 and intravenous carboplatin [area under the curve=5] on day 1 of a 3-week cycle, which is a standard regimen in China). All agents were administered at the standard approved doses.

Baseline characteristics were recorded at entry into the study. Efficacy assessments took place every 6 weeks. Targeted tumour lesions were assessed with CT scan, MRI, and bone scan. Tumour response and disease progression were classified according to RECIST version 1.0. Patients were assessed for response and disease progression by the investigator, with input from the radiologists at each centre. Independent radiological review was not done. There was no predefined review by an independent committee or central review in the OPTIMAL study because this was not common practice in China when this study was designed. The study was partly supported and financial support was prioritised to central laboratory testing for *EGFR* mutations, CRO involvement in data management and monitoring of study quality, and provision of gemcitabine. At the time when independent review was considered, partway through the study, there was insufficient funding to implement this. Despite the absence of masking, however, the study quality is assured by the highly experienced CRO and its internal quality control systems. Additionally, most sites taking part in the OPTIMAL study had extensive experience in clinical trial management and have been involved in many other large trials in lung cancer, such as the IPASS and LUX-Lung 1 trials; 16 sites that were involved in these two studies contributed 117 (71%) of 165 recruited patients in the OPTIMAL study.

All adverse events and serious adverse events were recorded and classified by grade according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Strict guidelines were in place for dose adjustment or treatment interruption in case of toxic effects during study treatment. The dose of gemcitabine plus carboplatin was adjusted according to patients' tolerability on the basis of the most severe toxic effects reported during the previous treatment cycles, 7 days before the present treatment cycle, or on the basis of abnormal laboratory measurements. Treatment interruption was allowed for a maximum of 3 weeks; after this period, the patient was discontinued from the study. Erlotinib dose adjustment or interruption was allowed after grade 3 or 4 adverse events. If interstitial lung disease (ILD) was suspected, study guidelines stated that treatment should be stopped immediately. If no ILD was confirmed, treatment with the study drug could be resumed. Dose reductions were in 50 mg increments, first to 100 mg, then to 50 mg, if needed, according to the protocol. The minimum allowed dose of erlotinib was 50 mg/day; any patient receiving an erlotinib dose lower than 50 mg/day was withdrawn from the study.

	Erlotinib (N=82)	Gemcitabine plus carboplatin (N=72)
Age		
Median (years)	57 (31–74)	59 (36–78)
<65 years	63 (77%)	51 (71%)
≥65 years	19 (23%)	21 (29%)
Sex		
Male	34 (41%)	29 (40%)
Female	48 (59%)	43 (60%)
Histology		
Adenocarcinoma	72 (88%)	62 (86%)
Non-adenocarcinoma*	10 (12%)	10 (14%)
Smoking status†		
Present or former smoker	23 (28%)	22 (31%)
Non-smoker	59 (72%)	50 (69%)
***EGFR* mutation type**		
Exon 19 deletion	43 (52%)	39 (54%)
L858R mutation	39 (48%)	33 (46%)
ECOG PS		
0–1	75 (91%)	69 (96%)
2	7 (9%)	3 (4%)
Disease stage		
IIIB	11 (13%)	5 (7%)
IV	71 (87%)	67 (93%)

Data are n (%) or median (range) and are for all patients with confirmed disease who received at least one dose of study drug. ECOG=Eastern Cooperative Oncology Group. PS=performance status. *Non-adenocarcinoma included squamous-cell carcinoma (n=8), bronchoalveolar carcinoma (n=2), and other histology (n=10). †Present smoker defined as someone who had smoked more than 100 cigarettes in their lifetime and who was either currently smoking or had stopped smoking less than 1 year ago; former smoker defined as someone who had smoked more than 100 cigarettes in their lifetime and had stopped smoking 1 year or more ago; non-smoker defined as having either smoked 100 or fewer cigarettes in their lifetime or had never smoked cigarettes.

Table 1: **Baseline patient characteristics in both treatment groups**

The primary endpoint was progression-free survival, which was defined as the time from randomisation to first confirmed disease progression or death of any cause (whichever occurred first). Secondary endpoints included overall survival, objective response rate, time to progression, duration of response, safety and quality of life. Quality of life and lung cancer symptoms were assessed every 6 weeks with the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire and the Lung Cancer Subscale (LCS).

Statistical analysis

All patients with confirmed disease who were randomly assigned to treatment groups and had received at least one dose of study drug were included in the efficacy analyses. The safety population consisted of all patients who received at least one dose of study drug (which included one patient who had no target lesion and was therefore excluded from the efficacy analyses).

Statistical analyses were done to show the superiority of erlotinib over chemotherapy in terms of

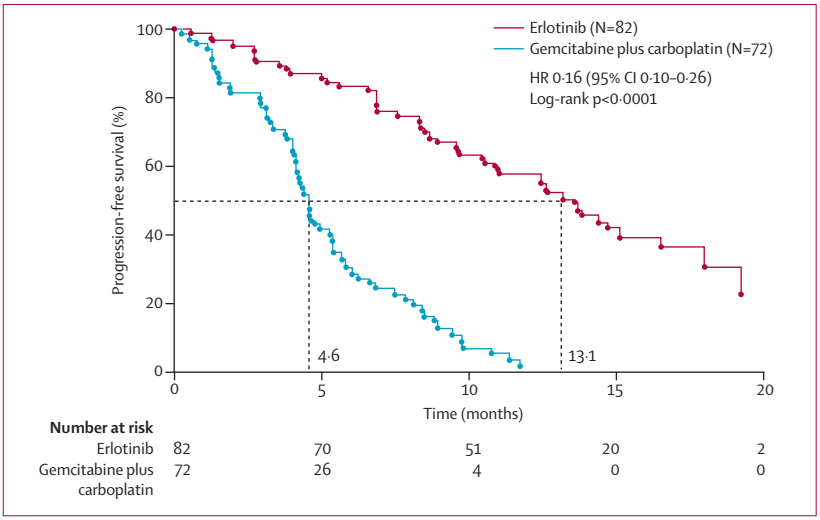

Figure 2: **Progression-free survival in both treatment groups**
PFS=progression-free survival. HR=hazard ratio.

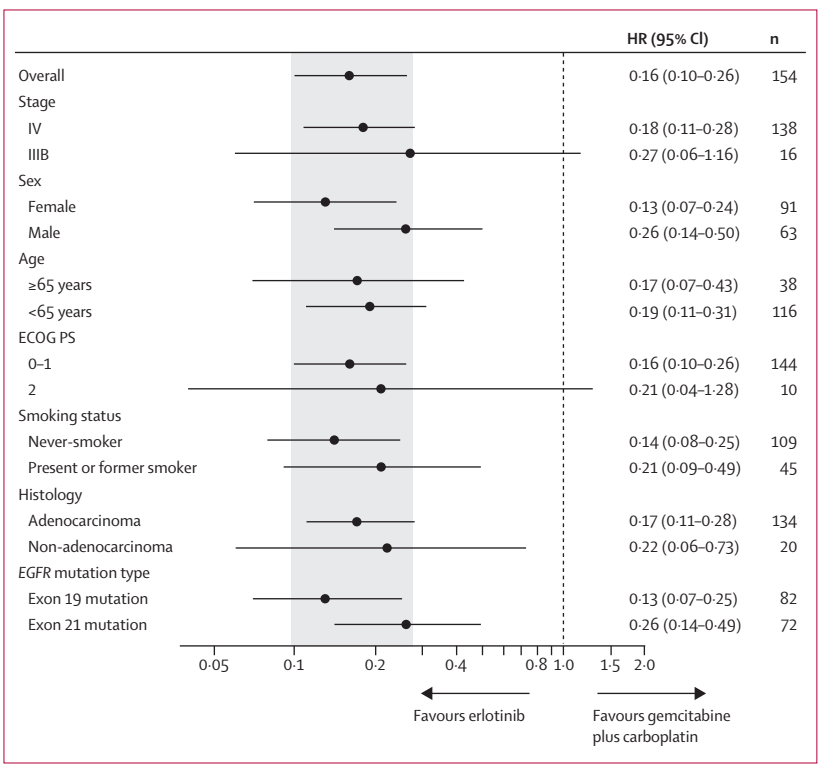

Figure 3: **Subgroup analyses of progression-free survival, by clinical characteristics**
ECOG=Eastern Cooperative Oncology Group. PS=performance status. HR=hazard ratio.

progression-free survival. The sample size was set at 152 patients (with 103 events needed) on the basis of several assumptions: a median progression-free survival of 11 months with erlotinib, on the basis of data from the Spanish Lung Cancer Group (SLCG),[7] compared with 6 months for chemotherapy; a 10% dropout rate; 80% power to detect a hazard ratio (HR) of 0·54 with an overall α level of 2·5% (α-spending for a final analysis of 0·025); and a 12-month enrolment period and 24-month follow-up, with a projected overall study period of 47 months. The software used for statistical analyses was SAS version 9.1.3.

The primary cutoff date for progression-free survival data was July 16, 2010; however, because an additional ten events occurred after this cutoff, an updated analysis was done on Aug 16, 2010, after a median follow-up of 15·6 months. These updated data are reported here. Survival was estimated with Kaplan-Meier methodology and was summarised as a median value with range and a two-sided 95% CI. A two-sided log-rank test was the main method used to compare survival between the two treatment groups. Estimates of the treatment effect were expressed as an HR for erlotinib versus chemotherapy, with a two-sided 95% CI. Exploratory and preplanned subgroup analyses of progression-free survival were done with the Cox proportional hazards model and included the stratification factors from randomisation.

This study is registered at ClinicalTrials.gov, NCT00874419.

Role of the funding source

This study was supported by partial research grants from F Hoffmann-La Roche (China) and a grant from the Science and Technology Commission of Shanghai Municipality (No 06DZ19502). F Hoffmann-La Roche had no input into the design of the study or the collection of data, although they provided financial assistance and input towards the analysis and interpretation of results, and also reviewed the study report and the Article. All authors had access to the raw data and the corresponding author had full access to all data and the final responsibility to submit for publication.

Results

Figure 1 shows the trial profile. 549 patients were screened for *EGFR* mutations and 165 were randomly assigned to treatment groups between Aug 24, 2008, and July 17, 2009. Of these patients, 154 had measurable disease and received at least one dose of study drug (82 erlotinib, 72 chemotherapy; figure 1). Both treatment groups were generally well matched with respect to baseline characteristics (table 1). Median duration of treatment was 55·5 weeks (range 3·1–93·0) for erlotinib and 10·4 weeks (range 1·0–18·9) for carboplatin plus gemcitabine. The median number of treatment cycles for the chemotherapy group was four (range 1–6). Dose reduction was necessary in five (6%) erlotinib-treated patients and 40 (56%) chemotherapy-treated patients; treatment discontinuation was needed in one (1%) patient on erlotinib and seven (10%) on chemotherapy. Dose reductions or treatment discontinuations were attributable to adverse events, except for five patients in the chemotherapy group who discontinued for personal reasons (n=3), intolerable toxic effects (n=1), or at the judgment of the investigator (n=1).

Treatment with first-line erlotinib was associated with significantly longer progression-free survival than was treatment with chemotherapy (figure 2). Median progression-free survival was 13·1 months (95% CI 10·58–16·53) in erlotinib-treated patients versus 4·6 months (4·21–5·42) for patients receiving chemotherapy (HR 0·16, 95% CI 0·10–0·26; p<0·0001). The progression-free survival benefit seemed to be consistent across all clinical subgroups irrespective of age, sex, performance status, disease stage, tumour histology, or smoking status (figure 3), suggesting that activating *EGFR* mutations are the most important factor in the progression-free survival benefit, irrespective of clinical characteristics; however, the trial was not powered to detect significant differences between subgroups. The p values of the interaction tests for smoker versus non-smoker, adenocarcinoma versus non-adenocarcinoma, exon 19 mutation versus without exon 19 mutation, and exon 21 mutation versus without exon 21 mutation were 0·34, 0·50, 0·054, and 0·054, respectively.

Two (2%) of 82 patients in the erlotinib group achieved a complete response, compared with none of the 72 patients on chemotherapy. 66 (80%) of 82 patients on erlotinib had a partial response compared with 26 (36%) of 72 patients allocated chemotherapy, giving an overall response rate of 83% (68/82) for erlotinib and 36% (26/72) for chemotherapy (p<0·0001). The disease control rate (complete response, partial response, and stable disease) was 96% (79/82) with erlotinib and 82% (59/72) with chemotherapy (p=0·0022). As with progression-free survival, response to erlotinib was similar across clinical subgroups (data not shown). Data for overall survival are not yet mature; at the time of the primary analysis (July 16, 2010) only 16 (20%) of 82 patients in the erlotinib group and 12 (17%) of 72 patients on chemotherapy had died. 88 patients remain in follow-up for overall survival as of Jan 9, 2011.

Table 2 summarises the main reported haematological and non-haematological adverse events. As expected, chemotherapy was associated with a significantly higher incidence of the haematological adverse events neutropenia (p<0·0001) and thrombocytopenia (p<0·0001) compared with erlotinib, with many events classified as grade 3 or 4. Erlotinib was associated with a significantly higher incidence of skin rash (p<0·0001) and diarrhoea (p=0·00085), but most cases were grade 1 or 2 in severity. No ILD-like events or cases of toxic death were reported in either group. Overall, chemotherapy was associated with more grade 3 or 4 toxic effects, more treatment-related serious adverse events, and a much higher rate of dose reduction and discontinuation than was erlotinib (table 3). Increased alanine aminotransferase concentration was the most common drug-related adverse event leading to dose reduction (n=3) and the only serious adverse event related to treatment (n=2) in patients on erlotinib.

Preplanned analyses showed that erlotinib provided clinically relevant improvements in quality of life compared with standard first-line chemotherapy. Logistic regression analysis with performance status, smoking history, and sex as covariates or mutation type, smoking history, and histological type as covariates showed that patients who received erlotinib had a significant improvement in their total FACT-L (p<0·0001 for both covariate analyses) and LCS scores (p<0·0001 for both covariate analyses) compared with those who received chemotherapy (data not shown).

	Erlotinib (N=83)		Gemcitabine plus carboplatin (N=72)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Neutropenia	5 (6%)	0	50 (69%)	30 (42%)
Thrombocytopenia	3 (4%)	0	46 (64%)	29 (40%)
Anaemia	4 (5%)	0	52 (72%)	9 (13%)
Infection	14 (17%)	1 (1%)	7 (10%)	0
Skin rash	61 (73%)	2 (2%)	14 (19%)	0
Diarrhoea	21 (25%)	1 (1%)	4 (6%)	0
Stomatitis	11 (13%)	1 (1%)	1 (1%)	0
Paronychia	3 (4%)	0	0	0
Vomiting or nausea	1 (1%)	0	33 (46%)	1 (1%)
Constipation	0	0	11 (15%)	0
Increased ALT	31 (37%)	3 (4%)	24 (33%)	1 (1%)
Fatigue	4 (5%)	0	17 (24%)	1 (1%)

Data are n (%) and are for the safety population (all patients who received at least one dose of study drug); each patient was only counted once even though they might have had several events across different body systems. ALT=alanine aminotransferase.

Table 2: **Most common adverse events of all grades reported in 3% of patients or more in either treatment group**

	Erlotinib (N=83)	Gemcitabine plus carboplatin (N=72)
Any AE (all grades)	77 (93%)	69 (96%)
Treatment-related AEs (all grades)	72 (87%)	68 (94%)
Grade 3 or 4 AE	14 (17%)	47 (65%)
Dose reduction due to an AE	5 (6%)*	38 (53%)
Dose reduction due to a drug-related AE	5 (6%)*	38 (53%)
Discontinuation due to AE	1 (1%)†	4 (6%)
Discontinuation due to drug-related AE	0	4 (6%)
Any SAE	10 (12%)	10 (14%)
Treatment-related SAE	2 (2%)‡	10 (14%)§
Treatment-related death	0	0
ILD-like events	0	0

Data are n (%) and are for the safety population (all patients who received at least one dose of study drug); each patient was only counted once even though they might have had several events across different body systems. AE=adverse event. ALT=alanine aminotransferase. SAE=serious adverse event. ILD=interstitial lung disease. *Increased ALT concentration (n=3), skin rash (n=1), total bilirubin increase (n=1), stomatitis (n=1); one patient had both rash and raised ALT concentration. †Spleen cyst. ‡Two cases of ALT increase. §Decreased platelet count (n=8), decreased neutrophil count (n=1), and hepatic dysfunction (n=1).

Table 3: **Summary of safety data**

Discussion

To our knowledge, OPTIMAL is the first prospective head-to-head phase 3 study to examine the efficacy and safety of first-line erlotinib versus platinum doublet

Panel: **Research in context**

Systematic review

We did a systematic review before starting this trial, searching for reports in English or Chinese up to April 30, 2008, using the search terms "lung neoplasm", "TKI", "*EGFR* mutation", and "first-line therapy", before assessing the quality of the evidence according to evidence-based medicine and giving greatest weight to data from prospective multicentre phase 2 or 3 clinical trials.

Interpretation

To our knowledge, OPTIMAL is the first phase 3 study to show that patients with *EGFR* mutation-positive NSCLC who receive erlotinib can live for more than a year without disease progression and also clearly shows the clinical usefulness of testing for a molecular biomarker in lung cancer to guide treatment and improve patient outcomes. Despite progress in recent years, lung cancer remains the leading cause of global cancer death, and increased understanding of the potential of biomarkers to inform our treatment decisions will hopefully lead to improvements in survival for this challenging disease. Our results are consistent with what was expected in view of the IPASS results, and suggest that EGFR tyrosine kinase inhibitors (TKIs) have greater first-line efficacy than does chemotherapy in *EGFR* mutation-positive NSCLC. We recommend that EGFR TKIs be regarded as the first-line treatment of choice for this subgroup of patients and chemonaive patients should undergo *EGFR* mutation testing wherever possible.

chemotherapy in patients with advanced NSCLC whose tumours harbour activating mutations in *EGFR* (exons 19 or 21; panel). Platinum doublet chemotherapy consisting of a platinum agent plus a third-generation cytotoxic agent such as gemcitabine, paclitaxel, or docetaxel is the standard first-line treatment for advanced NSCLC[15] and typically achieves response rates in the region of 20% and 1-year survival of 30–36%.[16] The gemcitabine plus carboplatin combination is a standard regimen in China, and four cycles of chemotherapy have been shown to have similar efficacy to six cycles, with reduced toxic effects.[17] By comparison with this conventional chemotherapy approach, the results of the OPTIMAL study conclusively show that erlotinib provides significantly longer progression-free survival in the first-line setting in a preselected population of patients with activating *EGFR* mutations, prolonging median progression-free survival by 8·5 months.

Nine patients refused chemotherapy after being assigned to gemcitabine plus carboplatin, because their preference was to receive TKI treatment. Additionally, one patient discontinued treatment on the basis of the decision of the investigator because rapid progression of malignant pleural effusion left them unsuitable for chemotherapy. These ten patients were excluded from all efficacy and safety analyses because analysis of the primary endpoint included only patients who received at least one dose of study drug. The baseline characteristics of these ten patients were similar to those of the overall study population, so the effect on the overall result was not significant. Sensitivity analyses were done for progression-free survival with all patients randomly assigned to treatment groups and the results were consistent with those of the primary endpoint analysis (data not shown).

The results of the efficacy analysis showed that first-line treatment with erlotinib conferred longer progression-free survival compared with chemotherapy in patients with *EGFR* mutation-positive advanced NSCLC. These results were consistent with those of other randomised studies in patients with NSCLC using TKIs in the first-line setting.[6,7,9,10] In the IPASS study of patients with lung adenocarcinoma with none or former light smoking history,[6] the benefit of gefitinib was limited to patients with *EGFR* mutations (HR 0·48, 95% CI 0·36–0·64) and gefitinib treatment was detrimental for those without mutations (HR 2·85, 95% CI 2·05–3·98). In the WJTOG3405 study,[9] gefitinib alone was superior to cisplatin plus docetaxel in patients selected by *EGFR* mutation (median progression-free survival 9·2 *vs* 6·3 months, HR 0·48, 95% CI 0·34–0·71). The NEJ002 study (first-line gefitinib versus first-line carboplatin plus paclitaxel in NSCLC patients with *EGFR* mutation-positive disease)[10] identified similar progression-free survival benefits (median 10·4 *vs* 5·5 months, HR 0·36, 95% CI 0·24–0·44). In the SLCG study[7] of erlotinib in patients with advanced NSCLC prospectively screened for *EGFR* mutations, median progression-free survival for the 217 patients who received erlotinib was 14 months, which is quite similar to the OPTIMAL results.

With respect to response rates, the results for the chemotherapy group of this study (36%) were consistent with those of the WJTOG3405 study (32%)[9] and NEJ002 (31%),[10] although a higher response rate was reported for patients on chemotherapy in IPASS (47%).[6] For the TKI groups in these studies—all of which used the TKI gefitinib—the response rates were also similar: 83% in our study compared with 62% in WJTOG3405,[9] 74% in NEJ002,[10] and 71% in IPASS.[6]

Although this study included Asian patients only, evidence suggests that the results seen with erlotinib in *EGFR* mutation-positive NSCLC are consistent irrespective of ethnic origin, with similar findings reported in white patients.[7,11,18] The clinical advantage of large-scale screening for *EGFR* mutations in patients with NSCLC was emphasised in a recent prospective Spanish study of erlotinib therapy.[7] In this trial, 113 patients received erlotinib as first-line therapy and 104 patients received erlotinib as second-line or third-line therapy. Median progression-free survival for all 217 patients was 14 months and overall survival was 27 months, and there was an association between reduced

progression-free survival and presence of the L858R mutation as compared with a deletion at exon 19 (HR 1·92, 1·19–3·10; p=0·02).[7] Further confirmation of these findings is expected shortly, when the results of the EURTAC study (NCT00446225) become available. EURTAC, a phase 3 trial initiated by the SLCG, is evaluating the efficacy and safety of first-line erlotinib versus chemotherapy in European patients with confirmed *EGFR* mutation-positive NSCLC. The trial has met its primary endpoint of improved progression-free survival for erlotinib versus chemotherapy and has been halted after a planned interim analysis by the data safety monitoring board.[19]

Although subgroup analyses according to other clinical characteristics in the OPTIMAL study were not powered to detect any significant difference in treatment outcome, they did suggest that, first, *EGFR* mutations occur in all clinical subgroups (including present smokers and non-adenocarcinoma histology) and, second, these clinical characteristics do not seem to affect the extent of benefit obtained from erlotinib in patients with *EGFR* mutation-positive disease. These findings therefore suggest that all Asian patients with advanced NSCLC should be screened for *EGFR* mutations at diagnosis, irrespective of their histological subtype, to inform decisions about optimum first-line treatment. Patients whose tumours have confirmed *EGFR* activating mutations should receive erlotinib as first-line therapy on the basis of this study.

In addition to improved efficacy versus chemotherapy in patients with advanced *EGFR* mutation-positive NSCLC, erlotinib is also associated with reduced toxic effects, allowing patients to achieve longer progression-free survival without the frequent haematological side-effects of chemotherapy. Of those erlotinib-treated patients with skin toxic effects or diarrhoea in the OPTIMAL study, most could be managed on the basis of available guidelines[20,21] and by use of dose reductions when needed. Discontinuation of erlotinib treatment was seldom necessary. The tolerability profile of erlotinib in this study also compares favourably with that of the TKI inhibitor gefitinib reported in two recent phase 3 studies.[6,10] When compared with carboplatin or paclitaxel as first-line therapy for advanced NSCLC, gefitinib was associated with a lower incidence of severe adverse events (grade ≥3) and a lower incidence of haematological adverse events; however, the incidence of skin toxic effects, diarrhoea, and raised aminotransferase concentrations was substantially higher with gefitinib. We do not believe that there is a need to a head-to-head clinical trial between gefinitib and erlotinib; rather, further investigation is needed into why responding patients develop resistance and how to treat them.

The OPTIMAL study provides the first conclusive evidence that erlotinib provides superior overall response rate and progression-free survival versus platinum doublet chemotherapy as first-line treatment in Asian patients whose tumours harbour activating mutations of *EGFR*. The results of this study have practice-changing implications and provide justification for widespread implementation of routine *EGFR* mutation testing in advanced NSCLC.

Contributors

Gongyan Chen, Jifeng Feng, Xiao-Qing Liu, Changli Wang, Shucai Zhang, Jie Wang, Shun Lu, Li Zhang†, Chengping Hu, Chunhong Hu, Yi Luo, Lei Chen, Ming Ye, Jianan Huang, Xiuyi Zhi, Yiping Zhang, Qingyu Xiu, Jun Ma, Li Zhang‡, and Changxuan You acted as study investigators and contributed to enrolment and management of patients. Caicun Zhou was responsible for conception, design, and financial support of the study and for collection and interpretation of data. Yi-Long Wu contributed to protocol discussion, data review, reviewing all previous presentations of trial data, and enrolment and management of patients. Songwen Zhou and Shengxiang Ren were involved in collection of clinical data. All authors participated in writing and review of the Article and accept full responsibility for its overall content.

Conflicts of interest

Caicun Zhou has received a grant and fees for participation in review activities, for his institution, from Roche. He has also received payment for lectures from Roche China and Eli Lilly China. Yi-Long Wu has received a consulting fee or honorarium from Roche and payment for lectures from Eli Lilly, Pfizer, and AstraZeneca. Jie Wang has received payment for lectures from AstraZeneca, Eli Lilly, and Roche. Li Zhang† has received payment for board membership from Eli Lilly and AstraZeneca. He has also received research grants for his institution from Roche. All other authors declare that they have no conflicts of interest.

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