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First-line erlotinib versus gemcitabine/cisplatin in patients with advanced *EGFR* mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study†

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Background: The phase III, randomized, open-label ENSURE study (NCT01342965) evaluated first-line erlotinib versus gemcitabine/cisplatin (GP) in patients from China, Malaysia and the Philippines with epidermal growth factor receptor (*EGFR*) mutation-positive non-small-cell lung cancer (NSCLC).

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Patients and methods: Patients ≥18 years old with histologically/cytologically confirmed stage IIIB/IV *EGFR* mutation-positive NSCLC and Eastern Cooperative Oncology Group performance status 0–2 were randomized 1:1 to receive erlotinib (oral; 150 mg once daily until progression/unacceptable toxicity) or GP [G 1250 mg/m^2 i.v. days 1 and 8 (3-weekly cycle); P 75 mg/m^2 i.v. day 1, (3-weekly cycle) for up to four cycles]. Primary end point: investigator-assessed progression-free survival (PFS). Other end points include objective response rate (ORR), overall survival (OS), and safety.

Results: A total of 217 patients were randomized: 110 to erlotinib and 107 to GP. Investigator-assessed median PFS was 11.0 months versus 5.5 months, erlotinib versus GP, respectively [hazard ratio (HR), 0.34, 95% confidence interval (CI) 0.22–0.51; log-rank $P < 0.0001$]. Independent Review Committee-assessed median PFS was consistent (HR, 0.42). Median OS was 26.3 versus 25.5 months, erlotinib versus GP, respectively (HR, 0.91, 95% CI 0.63–1.31; log-rank $P = .607$). ORR was 62.7% for erlotinib and 33.6% for GP. Treatment-related serious adverse events (AEs) occurred in 2.7% versus 10.6% of erlotinib and GP patients, respectively. The most common grade ≥3 AEs were rash (6.4%) with erlotinib, and neutropenia (25.0%), leukopenia (14.4%), and anemia (12.5%) with GP.

Conclusion: These analyses demonstrate that first-line erlotinib provides a statistically significant improvement in PFS versus GP in Asian patients with *EGFR* mutation-positive NSCLC (NCT01342965).

Key words: NSCLC, erlotinib, first-line, EGFR mutation-positive, Asian

introduction

Non-small-cell lung cancer (NSCLC) is the most common cause of cancer deaths worldwide [1]. Epidermal growth factor receptor (EGFR) is critical in proliferation and survival pathways, and activating mutations are often seen in NSCLC [2]. *EGFR* mutations occur more frequently in Asian patients compared with Caucasian patients (30% and ~16%, respectively) [3–5]. However, studies have shown that EGFR tyrosine kinase inhibitors (TKIs) including erlotinib are effective in both populations [6].

Erlotinib has proven efficacy as second-/third-line treatment of advanced NSCLC [7], and superior first-line efficacy versus chemotherapy in *EGFR* mutation-positive disease [8–11]. The phase III EURTAC study demonstrated a significant progression-free survival (PFS) benefit for first-line erlotinib versus chemotherapy in European patients with *EGFR* mutation-positive NSCLC [8, 9]. Significant PFS benefit with erlotinib was also reported in the Chinese, phase III, first-line OPTIMAL study [10]. Additionally, the single-arm, first-line, Japanese, phase II JO22903 reported a PFS of 11.8 months with erlotinib [11]. Afatinib and gefitinib have also demonstrated efficacy in the first-line treatment of patients with *EGFR* mutation-positive NSCLC [12–15].

The phase III, randomized, open-label ENSURE study (NCT01342965) evaluated first-line erlotinib versus gemcitabine/cisplatin (GP) in patients with *EGFR* mutation-positive NSCLC from China, Malaysia, and the Philippines. The rationale was to provide further evidence of the efficacy of this regimen in a broader Asian population, following the positive outcomes from the Chinese phase III OPTIMAL study [10].

patients and methods

patient eligibility

Patients ≥18 years old with histologically or cytologically confirmed stage IIIB/IV *EGFR* mutation-positive NSCLC (exon 19 deletion or exon 21 L858R mutation from tissue assessed centrally by the cobas® EGFR Mutation Test, Roche Molecular Systems, Inc., Pleasanton, CA) and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2 were eligible. Exclusion criteria included: patients with prior exposure to chemotherapy or agents targeting HER receptors; inability to take oral medication; ≥grade 2 peripheral neuropathy; brain metastases; history of any malignancies within 5 years; or surgery within 4 weeks of the study.

study design

Eligible patients from 30 centers across China, Malaysia, and the Philippines were randomized 1:1 to receive erlotinib (oral; 150 mg once daily until progression/unacceptable toxicity) or GP (gemcitabine 1250 mg/m^2 i.v. days 1 and 8 plus cisplatin 75 mg/m^2 i.v. day 1, every 3 weeks, for up to four cycles). Patients were stratified by *EGFR* mutation type, ECOG PS, gender, and country. Following disease progression, erlotinib patients could crossover to receive GP and GP patients could crossover to receive erlotinib. All patients provided informed consent to participate in the trial. The trial was approved by local independent ethics committees, including an independent review board, and complied with the Declaration of Helsinki and Good Clinical Practice principles.

assessments

The primary end point was investigator-assessed PFS [time from randomization until disease progression, assessed by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, or death], with Independent Review Committee (IRC) blinded assessment used for sensitivity analyses. Other end points included objective response rate (ORR; complete or partial response as assessed every 6 weeks by RECIST 1.1), disease control rate (DCR: complete response, partial response or stable disease), overall survival (OS), and safety (assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0). Tumor tissue was obtained at baseline to assess *EGFR* mutation status.

statistical methods

All efficacy analyses were conducted on the intent-to-treat population (all randomized patients). The safety analyses population comprised all patients who received at least one dose of study medication, analyzed according to actual therapy received. Kaplan–Meier methodology was used to calculate median PFS/OS. PFS was assessed using a two-sided unstratified log-rank test at significance level 5%. Cox regression analysis was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Stratified log-rank test and Cox regression analysis was also carried out with mutation type, ECOG PS, gender, and country as the stratification factors. A sample size of 139 events was calculated to provide 85% power

(significant P value set at 0.05) based on a median PFS of 6 months (GP) or 10 months (erlotinib). An interim analysis was planned after 67% of events had occurred (93 events) using O'Brien–Fleming-like sequential boundary function.

results

The preplanned interim analysis was conducted after 73% of PFS events had occurred (cutoff 20 July 2012). An Independent Data Monitoring Committee recommended stopping the trial due to the positive treatment benefit of erlotinib versus GP and, therefore, the interim analysis became the final analysis. The data cutoff for the PFS analysis was 20 July 2012; the OS data cutoff was 25 April 2014.

Between March 2011 and June 2012, 217 patients were randomized: 110 to receive erlotinib and 107 to receive GP (Figure 1). Median duration of follow-up calculated as reverse survival time was 28.9 and 27.1 months for the erlotinib and GP arms, respectively, by 25 April 2014. Baseline characteristics were similar in both arms (Table 1).

efficacy

Investigator-assessed median PFS was 11.0 versus 5.5 months, for erlotinib versus GP, respectively (HR, 0.34, 95% CI 0.22–0.51; log-rank $P < 0.0001$) (Figure 2A). In the IRC assessment, the benefit of erlotinib compared with GP was further confirmed; median PFS was 11.0 months with erlotinib versus 5.6 months with GP (HR, 0.42, 95% CI 0.27–0.66; log-rank $P = 0.0001$) (Figure 2B). PFS across subgroups was generally similar to that observed in the overall population (Figure 2C).

At the data cutoff for the OS analysis (25 April 2014), median OS was 26.3 versus 25.5 months, for erlotinib versus GP, respectively (HR, 0.91, 95% CI 0.63–1.31; log-rank $P = 0.607$) (Figure 3A). Results were generally similar in the subgroup analysis (Figure 3B). Differences seen between mutation types (exon 19 deletion versus exon 21 L858R mutations) are presented in the biomarker section. OS stratified by treatment relating to crossover or further-line therapy [erlotinib only, GP only or erlotinib plus GP (i.e. crossover erlotinib then GP or GP then erlotinib)] is shown in supplementary Figure S1.

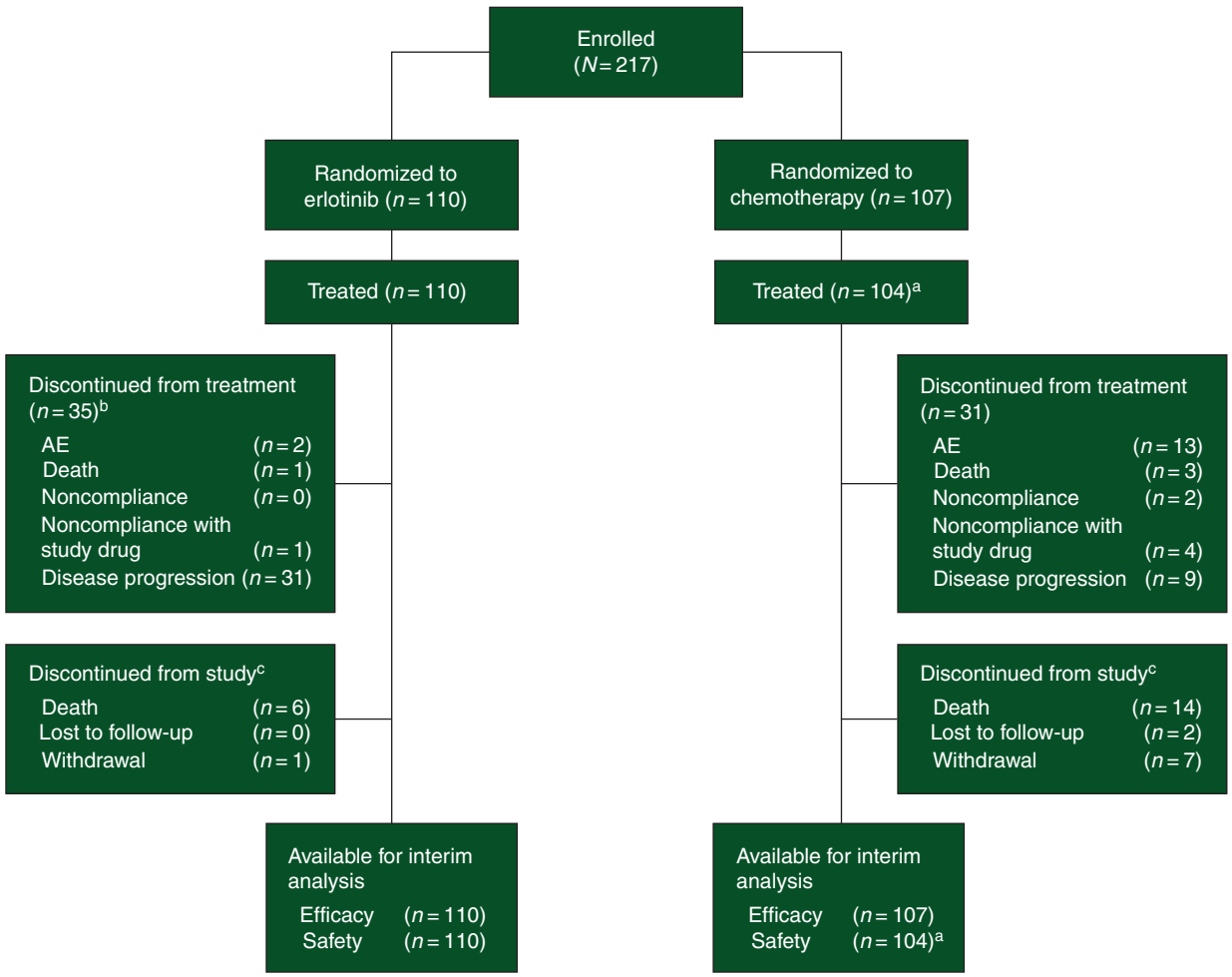

Figure 1. CONSORT diagram. [a]Three patients were randomized but did not receive any study medication and therefore were excluded from the safety analysis. [b]At 25 April 2014 cutoff, $n = 100$ from the erlotinib arm had discontinued treatment (AE $n = 4$, death $n = 0$, noncompliance $n = 0$, noncompliance with study drug $n = 1$, other $n = 1$, physician decision $n = 2$, disease progression $n = 92$. [c]At 25 April 2014 cutoff, $n = 109$ (death $n = 58$, lost to follow-up $n = 5$, other $n = 44$, withdrawal by subject $n = 2$) had discontinued from the study in the erlotinib arm, $n = 107$ had discontinued the GP arm (death $n = 57$, lost to follow-up $n = 3$, other $n = 38$, withdrawal by subject $n = 9$). These patients were censored at the time of discontinuation for OS analysis. AE, adverse event.

Table 1. Baseline demographics and disease characteristics of the ENSURE patient population (intent-to-treat population)

Characteristic	Erlotinib ($N = 110$[a])	GP ($N = 107$[a])
Age		
Median, years (range)	57.5 (33–79)	56.0 (30–78)
<65 years, %	79.1	79.4
≥65 years, %	20.9	20.6
Gender, %		
Male	38.2	39.3
Female	61.8	60.7
Country, %		
China	79.1	82.2
Non-China	20.9	17.8
ECOG PS, %	$n = 109$	$n = 104$
0	14.7	14.4
1	78.9	79.8
2	6.4	5.8
Smoking status, %		
Current smoker	24.5	29.0
Former smoker	3.6	1.9
Never smoker	71.8	69.2
Stage of disease, %		
IIIB	9.1	6.5
IV	90.9	93.5
Histology,%		
Adenocarcinoma	94.5	94.4
Squamous-cell carcinoma	1.8	1.9
Other	3.6	3.6
Tissue-assessed *EGFR* mutation type, %	($n = 109$)	($n = 107$)
Exon 19 deletion	52.3	57.0
Exon 21 L858R mutation	47.7	43.0

[a]Unless otherwise specified.
ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; GP, gemcitabine/cisplatin.

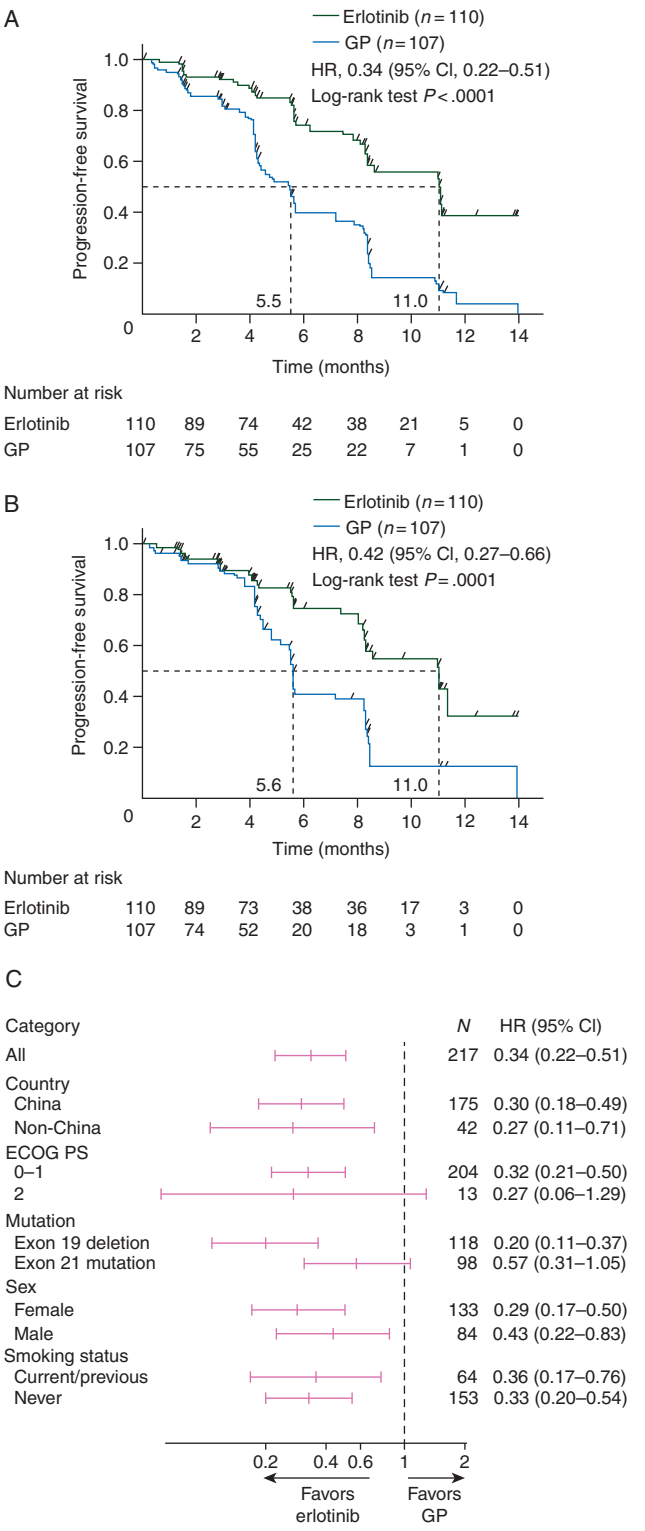

Figure 2. Kaplan–Meier curves for progression-free survival assessed by (A) investigator and (B) Independent Review Committee at the interim analysis and (C) progression-free survival in subgroups stratified by country, ECOG PS, *EGFR* mutation type and gender. HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; GP, gemcitabine/cisplatin.

In total, 65.5% of the erlotinib arm and 85.6% of the GP arm received second- or further-line treatment. In the erlotinib arm, the most common post-study therapies were platinum compounds (59.1% receiving ≥1 treatment; the most common including cisplatin in 37.3% and carboplatin in 20.9%) and antimetabolites (54.5% receiving ≥1 treatment; gemcitabine in 25.5% and pemetrexed in 10.0%). In the GP arm, 85.6% received EGFR TKIs, including erlotinib (33.7%), erlotinib hydrochloride (51.9%), and gefitinib (2.9%). In the GP arm, 12.5% received further treatment with platinum compounds, 10.6% with antimetabolites, and 7.7% with taxanes.

ORR was 62.7% and 33.6% for erlotinib and GP, respectively, and there were no complete responses. DCR was 89.1% with erlotinib and 76.6% with GP.

biomarker assessment

PFS was improved with erlotinib versus GP regardless of *EGFR* tumor tissue mutation type. In patients whose tumors had an exon 19 deletion, the HR for PFS was 0.20 (95% CI 0.11–0.37) and in patients whose tumors had an exon 21 L858R mutation, the HR for PFS was 0.57 (95% CI 0.31–1.05; Figure 2C). In the

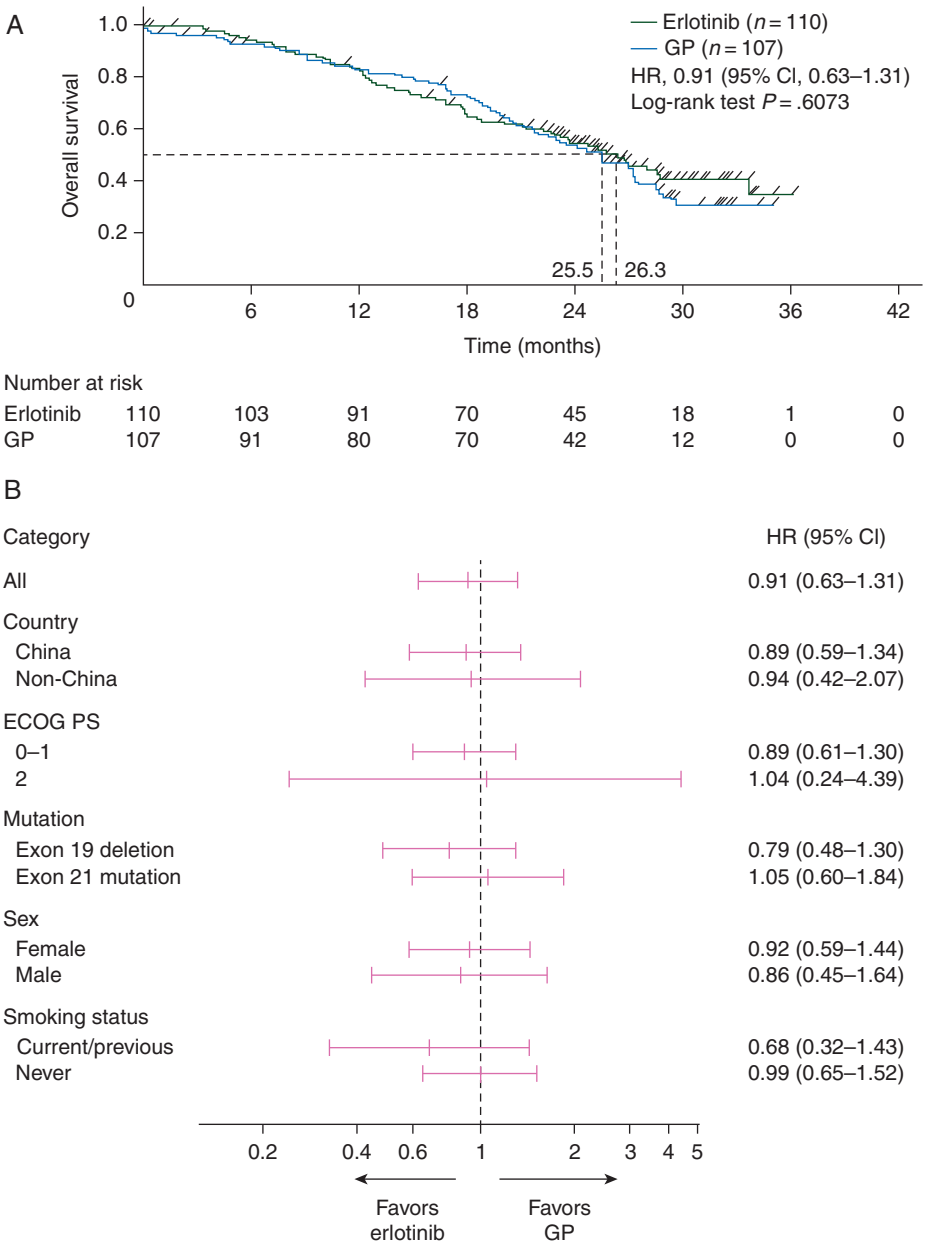

Figure 3. Kaplan–Meier curves for (A) overall survival (data cutoff 25 April 2014) and (B) overall survival by subgroup. HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; GP, gemcitabine/cisplatin.

exon 19 deletion subgroup, the HR for OS was 0.79 (95% CI 0.48–1.30) and, in the exon 21 L858R mutation subgroup, the HR for OS was 1.05 (95% CI 0.60–1.84; Figure 3B). Kaplan–Meier curves for these subgroups are shown in supplementary Figure S2.

safety

The safety population included 110 patients for the erlotinib arm and 104 for the GP arm. Treatment-related serious adverse events (AEs) occurred in 2.7% versus 10.6% of patients, respectively (Table 2). AEs leading to death were reported for one erlotinib patient (caused by pulmonary embolism) and three GP patients (one case from anemia, two cases from respiratory failure). The most common grade ≥3 AEs in the GP arm were neutropenia (25.0%), leukopenia (14.4%) and anemia (12.5%). Rash was the most common grade ≥3 AE in the erlotinib arm (6.4%) (Table 3). Grade ≥3 AEs of special interest (defined using erlotinib-specific umbrella terms) were rash (6.4% for erlotinib, 1.0% for GP), interstitial lung disease (0% in the erlotinib arm, 1.0% for GP), and diarrhea (1.8% for the erlotinib arm, 0% for GP).

At the OS data cutoff (25 April 2014), a further 57 patients had died in the erlotinib group (56 from disease progression, 1 from an unknown cause) and a further 54 had died in the GP arm compared with the initial analysis (52 from disease progression, 1 case of respiratory failure, and 1 unknown cause). The overall safety analysis at this cutoff was similar to the safety analysis at the PFS data cutoff. At the 25 April 2014 data cutoff,

Table 2. Summary of AEs, withdrawals and deaths (safety population)

N (%)	Erlotinib (*N* = 110)	GP (*N* = 104[a])
Total patients with ≥1 AE	101 (91.8)	100 (96.2)
Serious AE	15 (13.6)	15 (14.4)
Severe AE (grade ≥3)	44 (40.0)	59 (56.7)
AE leading to death	1 (0.9)	3 (2.9)
AE leading to withdrawal from treatment	3 (2.7)	13 (12.5)
AE leading to dose modification/ interruption	21 (19.1)	53 (51.0)
Treatment-related AE	96 (87.3)	97 (93.3)
Treatment-related serious AE	3 (2.7)	11 (10.6)

[a]Three patients were randomized but did not receive any study medication and were therefore excluded from the safety analysis.
AE, adverse event; GP, gemcitabine/cisplatin.

grade ≥3 AEs had been experienced by 35.5% of erlotinib patients and 57.7% of GP patients.

discussion

ENSURE was the first and largest trial to our knowledge to prospectively investigate erlotinib versus chemotherapy in a broad Asian population, following the positive results in Chinese patients in the OPTIMAL trial. These analyses demonstrate that erlotinib provides a statistically significant improvement in PFS compared with GP in Asian patients with *EGFR* mutation-positive NSCLC. Subgroup PFS analyses were consistent with data from the overall population. These data further confirm that the erlotinib regimen would be suitable for a wide range of Asian patients, including those from outside China with *EGFR* mutation-positive NSCLC. Primary efficacy results were supported by secondary end points including ORR and DCR.

OS was not significantly different between the two arms. This may be due to the effect of post-study therapy as 85.6% of patients randomized to the GP arm received further treatment with EGFR TKIs compared with 59.1% of the erlotinib arm receiving post-study platinum chemotherapy. Post-study crossover means it is challenging to determine the true OS benefit derived from first-line randomized regimens. A limitation of our study was that specific combinations of post-study therapy were not documented, e.g. maintenance erlotinib plus chemotherapy; therefore, this limits the ability to fully interpret the OS data. In a pooled analysis of two afatinib studies, Yang et al. reported for the first time that first-line irreversible second-generation EGFR TKIs significantly extended OS in *EGFR* mutation-positive NSCLC [16].

No new safety concerns were reported. The frequency of erlotinib treatment-related AEs seen in ENSURE (87.3%) was similar to that observed in the OPTIMAL trial (87.0%) [10].

The ENSURE results corroborate the data from other first-line studies in both Caucasian and Asian populations, showing that erlotinib provides a PFS benefit over chemotherapy in a broad population of patients with *EGFR* mutation-positive NSCLC [8, 9, 10]. The ENSURE efficacy data are also consistent with those from second-generation TKIs such as afatinib [12]. However, afatinib has been associated with a higher incidence of serious treatment-related AEs in Asian patients (6.3% in LUX-Lung 6) [13] than were seen with erlotinib in the ENSURE study (2.7%). LUX-Lung 6 also reported a higher incidence of grade ≥3 rash (14.6% in the afatinib arm), than was reported in the erlotinib arm of ENSURE (6.4%).

Table 3. Summary of all grade and grade ≥3 AEs experienced by ≥5% of patients in either arm (safety population)

N (%)	Erlotinib (*N* = 110)	GP (*N* = 104[a])
All grade AEs		
Nausea	5 (4.5)	60 (57.7)
Vomiting	7 (6.4)	56 (53.8)
Diarrhea	50 (45.5)	9 (8.7)
Constipation	2 (1.8)	19 (18.3)
Mouth ulcers	6 (5.5)	3 (2.9)
Rash	78 (70.9)	11 (10.6)
Pruritus	11 (10.0)	7 (6.7)
Alopecia	6 (5.5)	10 (9.6)
Dry skin	10 (9.1)	2 (1.9)
Dermatitis acneiform	9 (8.2)	0 (0.0)
Leukopenia	7 (6.4)	51 (49.0)
Neutropenia	5 (4.5)	53 (51.0)
Anemia	8 (7.3)	48 (46.2)
Thrombocytopenia	2 (1.8)	20 (19.2)
White blood cell count decreased	3 (2.7)	16 (15.4)
Platelets decreased	1 (0.9)	15 (14.4)
Alanine aminotransferase increased	13 (11.8)	2 (1.9)
Neutrophils decreased	2 (1.8)	10 (9.6)
Bilirubin increased	11 (10.0)	0 (0.0)
Fatigue	6 (5.5)	20 (19.2)
Pyrexia	8 (7.3)	13 (12.5)
Chest discomfort	6 (5.5)	3 (2.9)
Cough	19 (17.3)	9 (8.7)
Dyspnea	6 (5.5)	3 (2.9)
Decreased appetite	14 (12.7)	30 (28.8)
Hypokalemia	6 (5.5)	7 (6.7)
Paronychia	17 (15.5)	0 (0.0)
Dizziness	7 (6.4)	14 (13.5)
Headache	5 (4.5)	7 (6.7)
Backpain	8 (7.3)	6 (5.8)
Insomnia	5 (4.5)	8 (7.7)
Grade ≥3 AEs		
Neutropenia	1 (0.9)	26 (25.0)
Leukopenia	1 (0.9)	15 (14.4)
Anemia	1 (0.9)	13 (12.5)
Thrombocytopenia	0 (0.0)	7 (6.7)
Decreased white blood cell count	0 (0.0)	7 (6.7)
Decreased neutrophil count	0 (0.0)	6 (5.8)
Rash	7 (6.4)	1 (1.0)

[a]Three patients were randomized but did not receive any study medication and were therefore excluded from the safety analysis.
AEs, adverse events; GP, gemcitabine/cisplatin.

In ENSURE, efficacy was analyzed according to type of *EGFR* mutation. The interaction term for *EGFR* mutation type and treatment demonstrated statistical significance ($P = 0.0187$) for PFS. The PFS benefit seen in the erlotinib arm versus the GP arm was greater in the exon 19 deletion subgroup (HR, 0.20) than in the exon 21 L858R subgroup (HR, 0.57), this trend was also seen in the OS analysis. This is consistent with observations in other studies [4, 11]. In the OPTIMAL study, the HR for median PFS was 0.13 in the exon 19 subgroup and 0.26 in the exon 21 subgroup [10]. A pooled analysis of afatinib studies showed that OS benefit with afatinib was greater in the exon 19 deletion subgroup (HR, 0.59) versus the L858R subgroup (HR, 1.25) [16]. It remains unclear why patients with exon 19 deletions may have improved outcomes compared with patients with L858R mutations. One hypothesis is that *EGFR* with exon 19 deletions are inhibited more efficiently by erlotinib than those with L858R mutations. Alternatively, T790M mutations, which are associated with acquired resistance, might occur more frequently with L858R mutations than with exon 19 deletions [17, 18].

One limitation of the ENSURE study is the use of the more traditional cisplatin/gemcitabine regimen as a comparator instead of more novel combinations such as cisplatin/pemetrexed. However, the use of the cisplatin/gemcitabine regimen allowed for comparison of the results of the ENSURE study with those from the OPTIMAL study in Chinese patients, and therefore was warranted.

conclusion

The results of the ENSURE study have confirmed that erlotinib provides a significant improvement in PFS compared with chemotherapy in Asian patients with *EGFR* mutation-positive NSCLC and should be considered a standard first-line treatment regimen for this population.

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disclosure

YLW received honoraria from Roche, Eli Lilly, and Astra Zeneca; YZh, YZu, and XF are employees of Roche (China) Holdings; SH received honoraria from Astra Zeneca, GSK, and Bayer, consulted for Novartis and Astra Zeneca, attended speaker bureaus for Astra Zeneca, GSK, Bayer, and Boehringer Ingelheim, received funding from Roche, Boehringer Ingelheim, and Nycomed, and received travel expenses from Novartis, Astra Zeneca, Bayer, and Boehringer Ingelheim. All remaining authors have declared no conflicts of interest.

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