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Erlotinib versus gemcitabine/cisplatin in Chinese patients with *EGFR* mutation-positive advanced non-small-cell lung cancer: Crossover extension and post-hoc analysis of the ENSURE study

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ABSTRACT

Objectives: Sequential combination of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) and chemotherapy has shown greater benefits than either treatment alone in non-small-cell lung cancer (NSCLC). In this follow-up of the ENSURE study, we evaluated progression-free survival (PFS) with first-line erlotinib followed by chemotherapy at progression versus the inverse treatment sequence in 175 Chinese patients with *EGFR* mutation-positive NSCLC.

Materials and methods: Forty-five of the 175 patients included in the follow-up analysis experienced progressive disease (PD). Those with PD on first-line erlotinib (n = 24) received gemcitabine/cisplatin while those who failed first-line chemotherapy (n = 21) received erlotinib until second-line PD. The primary endpoint was PFS in the crossover subpopulation. Post-hoc analysis of survival outcomes was also measured for the overall population of 175 Chinese patients.

Results: Among patients who crossed over at progression, PFS was comparable between those who received second-line erlotinib and those who received second-line chemotherapy (median, 26.3 months and 23.4 months, respectively; $P = 0.529$). Regardless of the sequence in which the therapies were administered, patients in the crossover treatment subgroup benefited from either second-line therapy after progression with a median overall survival of 51.6 months versus 23.0 months achieved among patients in the non-crossover treatment subgroup. Post-hoc biomarker analyses of Kaplan–Meier survival curves and Cox regression showed that survival benefits with either treatment sequence were similar between patients with circulating free DNA *EGFR* mutations in exons 19 and 21; however, those with undetectable mutations achieved significantly greater survival benefits.

Conclusion: In advanced *EGFR* mutation-positive NSCLC, first-line erlotinib followed by chemotherapy at

Abbreviations: cfDNA, circulating free DNA; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small-cell lung cancer; OS, overall survival; PD, progressive disease; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; TTF, time to treatment failure

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progression demonstrated comparable PFS benefit with the inverse treatment sequence, irrespective of mutation subtype. Utilizing both EGFR-TKIs and chemotherapy, irrespective of the sequence, maximizes survival benefits for patients.

1. Introduction

Epidermal growth factor receptor (*EGFR*) mutations are present in almost half of all Asian patients with non-small-cell lung cancer (NSCLC) of adenocarcinoma histology [1,2]. Survival benefits of erlotinib over chemotherapy in the first-line setting were subsequently demonstrated in the EURTAC study in Caucasians [3] and in the OPTIMAL study in Chinese patients [4]. The final analysis from the OPTIMAL study in Chinese patients confirmed that sequential combination of erlotinib and chemotherapy is more beneficial than either treatment alone [5].

The phase III ENSURE study evaluated first-line erlotinib versus chemotherapy (gemcitabine/cisplatin) in patients with *EGFR* mutation-positive NSCLC from China, Malaysia, and the Philippines [6]. We reported that treatment with first-line erlotinib significantly improved progression-free survival (PFS) by 5.5 months compared with chemotherapy, but OS was not significantly different between treatment arms. Post-study treatments received by the patients after progression, which were not documented, may have confounded the true effect of the initial treatment on OS. This subpopulation extension of the ENSURE study aimed to evaluate PFS in Chinese patients with *EGFR* mutation-positive NSCLC enrolled in the parent ENSURE study receiving first-line erlotinib followed by second-line chemotherapy at progression, or the inverse treatment sequence. Additionally, post-hoc analyses were conducted in this patient subpopulation to assess OS and efficacy according to EGFR biomarker status.

2. Materials and methods

2.1. Study design and participants

Full details of the parent ENSURE study have been published previously [6]. All Chinese patients enrolled in the ENSURE study were included in this follow-up analysis. Those who failed first-line treatment were included in this open-label, phase IV crossover extension sub-study. Patients in the follow-up analysis who were lost to follow-up, died, withdrew from the study, or did not provide written informed consent were excluded from the crossover extension sub-study.

Patients who failed first-line treatment received crossover second-line treatment upon disease progression. Those treated with first-line erlotinib in the parent ENSURE study received second-line chemotherapy (intravenous gemcitabine 1250 mg/m^2 on days 1 and 8, and intravenous cisplatin 75 mg/m^2 on day 1 of a 3-week cycle for up to four cycles), while patients who were treated with first-line chemotherapy in the ENSURE study received second-line oral erlotinib 150 mg once daily until progressive disease (PD).

For patients who failed first-line treatment, tumor assessment was carried out according to the following status at enrollment: (1) for patients who had already experienced second-line PD, previous tumor assessment information and investigator-determined PD date were retrospectively recorded at screening; (2) for patients who were receiving second-line treatment and had not experienced second-line PD, tumor assessment was carried out every 6 weeks from the date of first-line PD until second-line PD, study withdrawal, death, or 28 days after the last administration of second-line treatment; and (3) patients who were still receiving first-line treatment from the parent ENSURE study were enrolled in the extension study upon first-line PD, with subsequent tumor assessment carried out every 6 weeks until second-line PD, study withdrawal, death, or 28 days after the last administration of second-line treatment had passed.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice principles. The protocol was approved by local institution review boards and ethics committees at each participating center and all patients provided written informed consent for participation in the study and provision of tumor samples.

2.2. Study objectives and endpoints

The primary endpoint was investigator-assessed median PFS of patients in the crossover extension sub-study, defined as time from

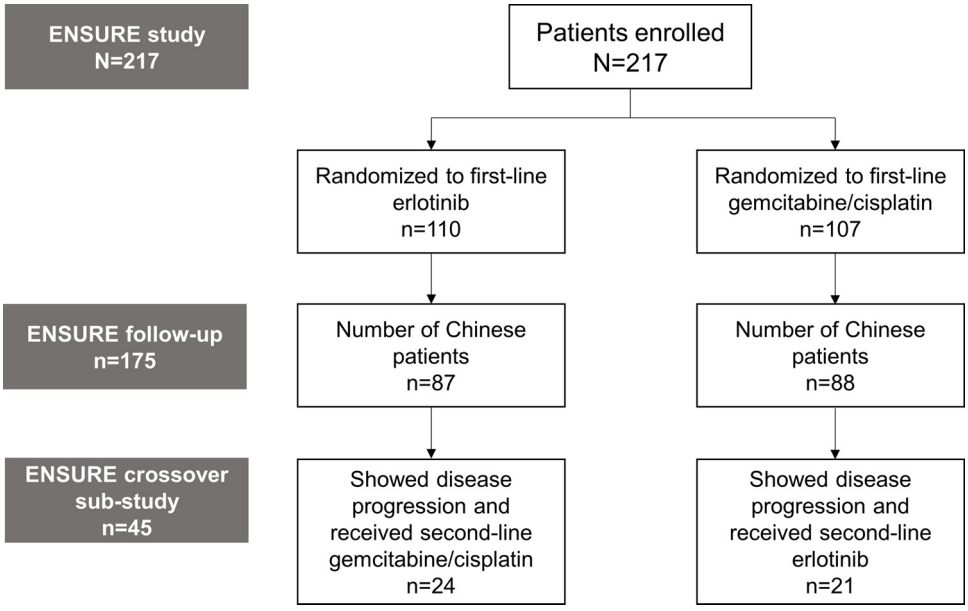

Fig. 1. Populations included in the ENSURE follow-up analysis and crossover extension sub-study. [Orientation: landscape].

Table 1
Patient demographics and baseline characteristics.

Characteristic	ENSURE extension analysis		ENSURE follow-up analysis	
	First-line erlotinib / second-line chemotherapy (n = 24)	First-line chemotherapy / second-line erlotinib (n = 21)	First-line erlotinib (n = 87)	First-line chemotherapy (n = 88)
Median age, years (range)	61.0 (34–67)	55.5 (30–75)	57.0 (33–77)	55.0 (30–75)
Sex, n (%)				
Female	12 (57.1)	10 (41.7)	55 (63.2)	49 (55.7)
Male	9 (42.9)	14 (58.3)	32 (36.8)	39 (44.3)
ECOG PS, %				
0	2 (9.5)	2 (8.3)	13 (14.9)	11 (12.5)
1	19 (90.5)	21 (87.5)	71 (81.6)	75 (85.2)
2	0	1 (4.2)	3 (3.4)	2 (2.3)
Smoking history, n (%)				
Never smoked	14 (66.7)	13 (54.2)	61 (70.1)	58 (65.9)
Former smoker	1 (4.8)	1 (4.2)	2 (2.3)	1 (1.1)
Current smoker	6 (28.6)	10 (41.7)	24 (27.6)	29 (33.0)
Tumor*EGFR*mutation status, n (%)				
Exon 19 deletion	11 (52.4)	9 (37.5)	44 (50.6)	49 (55.7)
Exon 21 L858R substitution	10 (47.6)	15 (62.5)	43 (49.4)	39 (44.3)
cfDNA*EGFR*mutation status, n (%)*				
Exon 19 deletion	–	–	29 (34.1)	39 (46.4)
Exon 21 L858R substitution			26 (30.6)	21 (25.0)
Undetectable			30 (35.3)	24 (28.6)

cfDNA, circulating free DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor.
* Sufficient (≥2.0 mL) plasma samples were available for 169 patients.

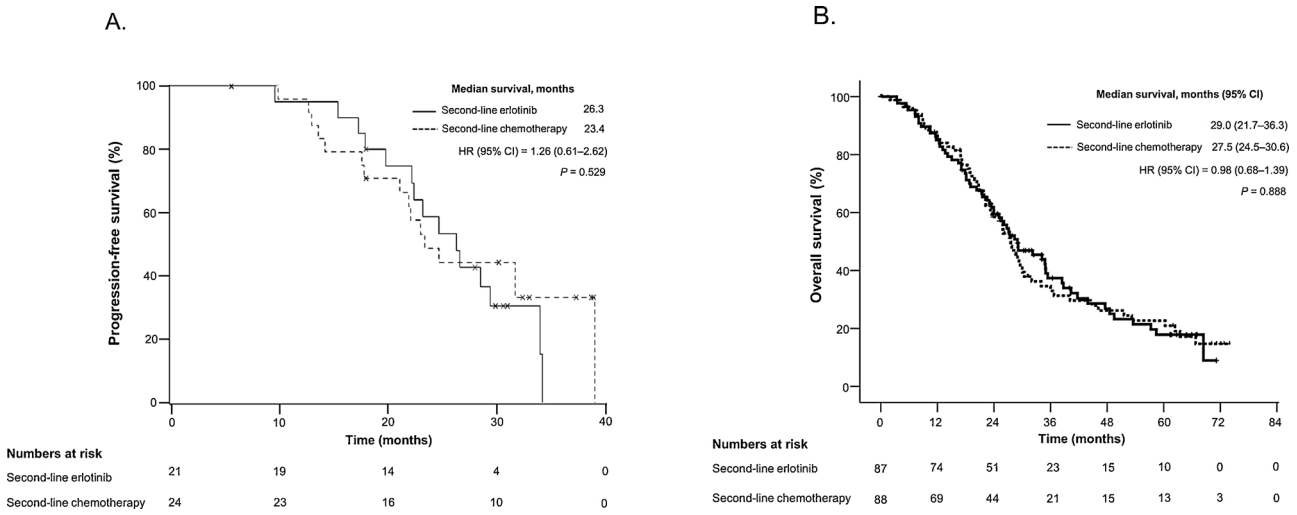

Fig. 2. Kaplan–Meier curves of patients in the extension crossover sub-study for progression-free survival from randomization in the ENSURE study to disease progression or death on second-line treatment (**A**). Kaplan–Meier curves of patients in the ENSURE follow-up analysis for overall survival (**B**). [Orientation: landscape].

randomization in the ENSURE study to the time of second-line PD (as determined by means of the Response Evaluation Criteria in Solid Tumors; PFS was not centralized) [7], or death on second-line treatment of Chinese patients who experienced first-line treatment failure in the ENSURE study. The safety data of patients in the crossover extension study were also collected. Time to treatment failure (TTF) was determined for all Chinese patients enrolled in the ENSURE study, including those who did not experience first-line PD, and was defined as time from randomization in the ENSURE study to discontinuation of second-line treatment for any reason including toxicity, PD, and death.

A post-hoc analysis of OS was performed for all Chinese patients enrolled in ENSURE and those in the crossover extension sub-study. Patients who did not experience PD or in whom second-line treatment did not fail were censored at the date of last tumor assessment and last second-line treatment, respectively.

2.3. Biomarker analysis

Post-hoc exploratory *EGFR* mutation biomarker analysis was performed retrospectively on available plasma samples from Chinese patients enrolled in the ENSURE study. Blood for plasma and serum isolation, along with formalin-fixed paraffin-embedded tissue, was collected at individual sites during screening, transported to a central laboratory (Quintiles Medical Research and Development, Beijing, China), and stored according to standard procedures. Manual circulating free DNA (cfDNA) extraction and analyses were carried out at the central laboratory using the cobas® EGFR Mutation Test v2 (Roche Molecular Systems, Inc., Pleasanton, CA, USA), which was provided by the study sponsor. Automated amplification, detection, and interpretation of results were performed using the cobas® 4800 System. Only plasma samples with a volume of 2.0 mL available for testing were included in the efficacy analysis.

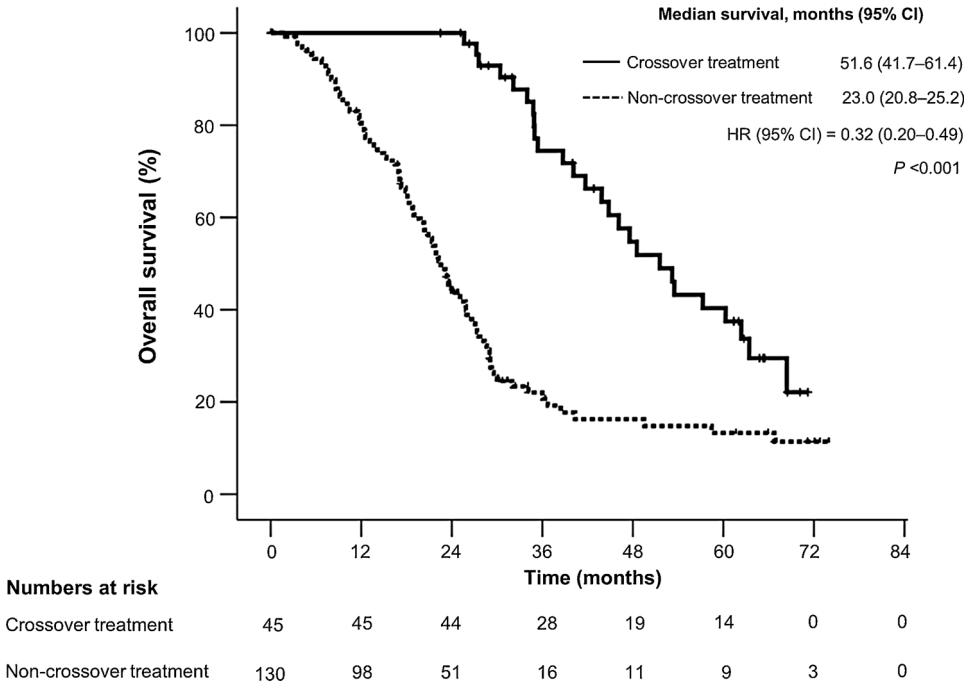

Fig. 3. Kaplan–Meier curves of overall survival for patients in crossover treatment subgroup who received further treatment upon progression on first-line therapy vs non-crossover treatment subgroup.[Orientation: landscape].

2.4. Statistical analyses

Because of the retrospective nature of the analysis, the study was not powered to detect statistically significant differences in survival outcomes. Instead, the sample size reflected the maximum number of Chinese patients from the ENSURE study who could be enrolled in the follow-up analysis and extension study. Study completion was defined as the date of the last patient's last visit.

Survival outcomes were estimated by treatment group using the Kaplan–Meier methodology and summarized as a median value. For the biomarker analysis, patients were classified as those whose cfDNA harbored an exon 19 deletion, exon 21 L858R substitution, or undetectable aberration (absence of exon 19 and exon 21 mutations). PFS and OS were estimated for each of these groups. Cox regression analysis was used to estimate treatment effects expressed as hazard ratio (HR) and its confidence interval (CI). All analyses were compared using a two-sided log rank test and were evaluated based on a two-sided 5% significance level and 95% CI. All patients who received at least one dose of study drug were included in the safety analysis. Adverse events were summarized according to the Medical Dictionary for Regulatory Activities version 17.1 coding system and the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03 grading system. All analyses were carried out using SAS software version 9.2 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patient disposition, baseline characteristics, and demographics

A total of 175 Chinese patients from the parent ENSURE study were included in this follow-up analysis (Fig. 1). Between January 2013 and August 2014, 45 Chinese patients from the ENSURE study experienced PD with first-line treatment and were enrolled in the crossover extension sub-study. Twenty-four of these patients received erlotinib as first-line therapy and were treated with second-line gemcitabine/cisplatin chemotherapy at crossover, while 21 patients received first-line gemcitabine/cisplatin chemotherapy and were switched to second-line erlotinib upon PD. The percentages of ENSURE study patients treated with first-line erlotinib or first-line gemcitabine/cisplatin who were enrolled in the crossover extension sub-study were similar (27.6% [24/87] and 23.9% [21/88], respectively).

Demographic and baseline characteristics were well balanced across the two treatment groups (Table 1). In the crossover subpopulation, the median (range) duration of treatment was 361 (280–429) days with second-line erlotinib and 88.5 (81–112) days with second-line chemotherapy. Most patients were never-smokers and had an Eastern Cooperative Oncology Group (ECOG) performance status of 1. Demographics and baseline characteristics were also similar for the population included in the ENSURE follow-up analysis (Table 1).

3.2. Efficacy outcomes

Among patients who experienced disease progression on first-line treatment and who received crossover second-line therapy in the crossover extension sub-study, PFS (from the time of randomization in the ENSURE study to the time of second-line PD) was comparable between those who received second-line erlotinib and those who received second-line chemotherapy (median 26.3 months and 23.4 months, respectively; HR 1.26; 95% CI 0.61–2.62; $P = 0.529$) (Fig. 2A and Supplementary Table 1). Median PFS1 (from the time of randomization in the ENSURE study to the time of first-line PD) and median PFS2 (from the time of first-line PD to the time of second-line PD) were 16.8 and 8.3 months, respectively, for first-line erlotinib patients who received second-line gemcitabine/cisplatin, and 5.7 and 18.0 months, respectively, for first-line gemcitabine/cisplatin patients who received second-line erlotinib (Supplementary Table 1). OS was comparable between the groups in the follow-up analysis (Fig. 2B). The median OS among the entire subgroup of 45 patients who received crossover treatment upon PD on first-line therapy was 51.6 months (95% CI 41.7–61.4), and the median OS for non-crossover patients was 23.0 months (95% CI 20.8–25.2) (Fig. 3).

The objective response rate was 33.3% with second-line chemotherapy and 66.7% with second-line erlotinib ($P = 0.038$).

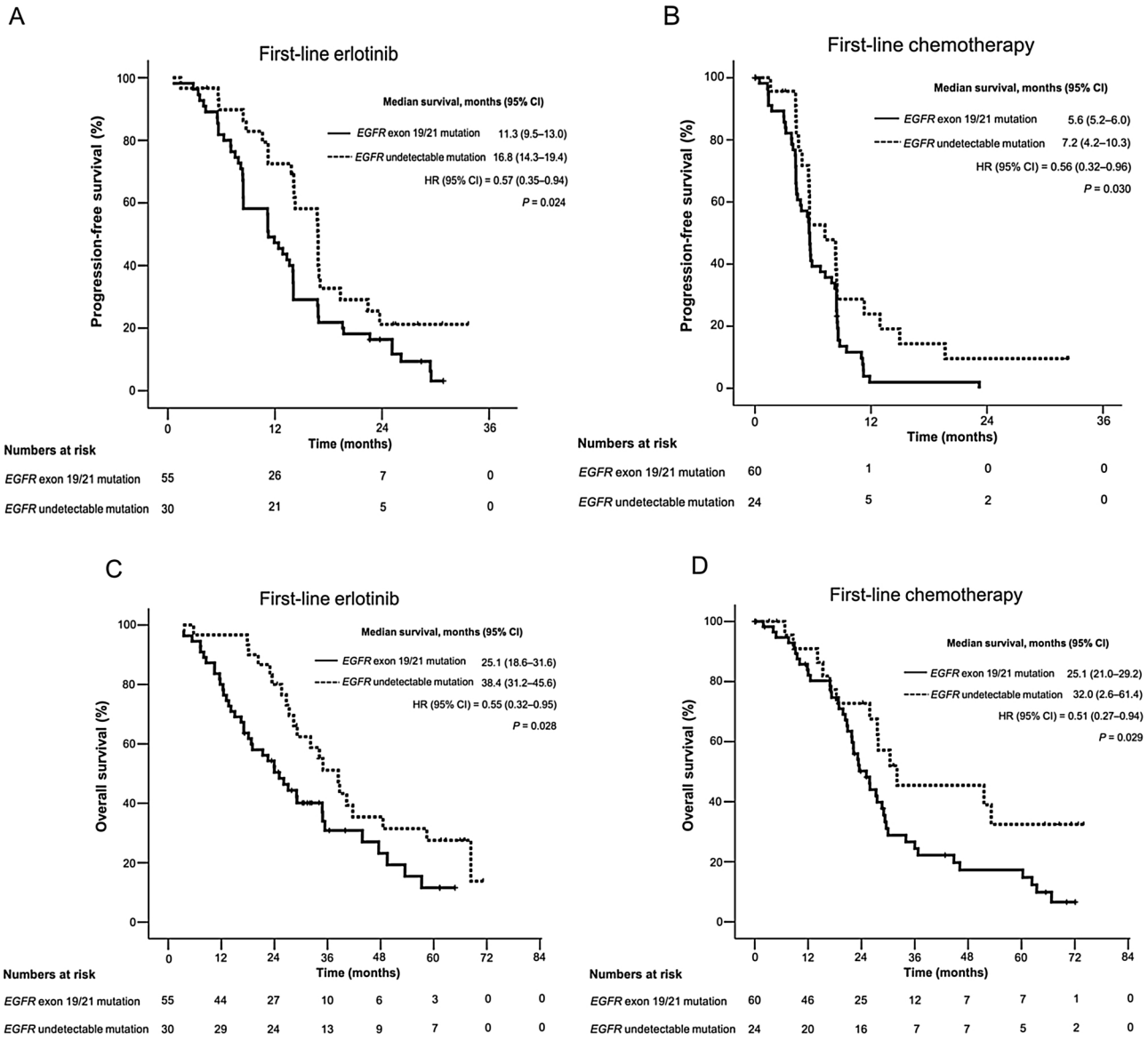

Fig. 4. Kaplan–Meier survival curves according to cfDNA *EGFR* mutation status among Chinese patients with available plasma samples enrolled in the ENSURE study. (**A**) PFS in the first-line erlotinib arm, (**B**) PFS in the first-line chemotherapy arm, (**C**) OS in the first-line erlotinib arm, and (**D**) OS in the first-line chemotherapy arm. [Orientation: landscape].

3.3. Biomarker analysis

Of the 175 Chinese patients enrolled in the ENSURE study, 172 had plasma samples available, three of which were invalid. In total, 169 samples were included in the biomarker analysis. Overall, 68% (115/169) of the plasma samples tested positive for *EGFR* exon 19 deletion or exon 21 L858R substitution.

Treatment with first-line erlotinib resulted in longer median PFS in patients with undetectable *EGFR* mutations (16.8 months, 95% CI 14.3–19.4) compared with those who had an *EGFR* mutation in exon 19 or 21 (11.3 months, 95% CI 9.5–13.0) (Fig. 4A). Among patients who received first-line chemotherapy, median PFS was slightly longer among those with undetectable *EGFR* mutations in their cfDNA (7.2 months, 95% CI 4.2–10.3) than patients with exon 19 deletion (4.8 months, 95% CI 3.3–6.3) and those with exon 21 L858R substitution (6.8 months, 4.6–8.9; $P = 0.049$) (Fig. 4B). There was no differential treatment effect for OS by cfDNA *EGFR* mutation subtype with both first-line chemotherapy and first-line erlotinib (Fig. 4C and 4D). However, when compared with all patients with detectable *EGFR* mutations (in either exon 19 or 21), those with undetectable mutations in their cfDNA had significantly improved survival outcomes with both treatment regimens.

3.4. Safety

There were no adverse events leading to treatment discontinuation or death, nor drug-related serious adverse events during the study. The most common adverse event with second-line chemotherapy was nausea (28.6%) and the most common adverse event with second-line erlotinib was rash (33.3%) (Table 2).

4. Discussion

This phase IV crossover extension of the ENSURE study aimed to provide physicians with the evidence necessary to formulate a rational approach to the sequential and combined use of erlotinib and chemotherapy. While the ENSURE study demonstrated a statistically significant PFS improvement when treatment was initiated with erlotinib

Table 2
Safety outcomes of patients in the ENSURE crossover sub-study.

Variable, n (%)	First-line erlotinib / second-line chemotherapy (n = 24)	First-line chemotherapy / second-line erlotinib (n = 21)
≥1 adverse event	14 (66.7)	12 (50.0)
≥1 serious adverse event	0	1 (4.2)
Adverse event leading to death	0	0
Adverse event leading to discontinuation	0	0
Treatment-related adverse event, all grades	10 (47.6)	9 (37.5)
Treatment-related adverse event, grade ≥3	5 (23.8)	2 (8.3)
Adverse events*		
Rash	0	8 (33.3)
Nausea	6 (28.6)	0
Leukopenia	4 (19.0)	0
Diarrhea	1 (4.8)	4 (16.7)
Vomiting	3 (14.3)	1 (4.2)
Alanine aminotransferase increased	3 (14.3)	1 (4.2)
Anemia	3 (14.3)	0
Neutropenia	3 (14.3)	0
Thrombocytopenia	3 (14.3)	0
White blood cell count decreased	3 (14.3)	0
Dry skin	0	3 (12.5)
Platelet count decreased	2 (9.5)	1 (4.2)
Musculoskeletal and connective tissue disorders	2 (9.5)	1 (4.2)
Aspartate aminotransferase increased	2 (9.5)	0
Neutrophil count decreased	2 (9.5)	0
Nervous system disorders	1 (4.8)	2 (8.3)
Infections and infestations	0	2 (8.3)
Paronychia	0	2 (8.3)
Chest discomfort	0	2 (8.3)

* Patients may have had more than one adverse event. Listed adverse events are those reported by > 5% of patients in either treatment group.

rather than chemotherapy [6], we found that the sequential combination of first-line erlotinib and second-line chemotherapy conferred comparable survival benefits with the same combination in an inverse sequence, suggesting that survival benefits are not affected by the sequence order of these therapies. Our findings are consistent with those of the OPTIMAL and EURTAC studies and confirm the role of erlotinib in prolonging survival in patients with *EGFR* mutation-positive NSCLC when used as either first- or second-line treatment [3–5]. Our study also demonstrated that the objective response rates of erlotinib and chemotherapy as second-line treatment were similar to their use in the first-line setting, as reported in the ENSURE study [6]. Thus, using chemotherapy in the second-line setting does not compromise response and OS benefit.

Furthermore, patients benefited from crossover treatment at progression, achieving a median OS of 51.6 months compared with 23.0 months among patients in the non-crossover treatment subgroup. This highlights the importance of utilizing both therapies during treatment, irrespective of sequence, to extend survival benefits obtained from first-line treatment, which is important particularly for patients with advanced disease. A systematic review was performed by Zhang et al. to quantify OS benefits of sequential therapy of EGFR-TKIs and chemotherapy in patients with *EGFR* mutation-positive advanced NSCLC and revealed no significant differences between the two treatment sequences [8].

The feasibility of assessing *EGFR* mutation status in cfDNA has been confirmed in retrospective and prospective studies. We evaluated the correlation of *EGFR* mutations between matched tumor and plasma samples in a post-hoc analysis and assessed the clinical utility of the cobas® EGFR Mutation Test v2, the first FDA-approved liquid biopsy test [9]. The sensitivity of plasma assay was 68.6% with a false-negative rate of approximately 30%, consistent with previous reports [10,11]. Reasons for the relatively limited sensitivity are unclear. However, a correlation between sensitivity and disease burden has been postulated, with higher numbers of metastatic sites predicting increased sensitivity, possibly because of the increased likelihood of cfDNA shed into plasma [12,13].

Our post-hoc biomarker analysis demonstrated similar survival benefits between patients with cfDNA *EGFR* mutations in exon 19 and exon 21; however, those with undetectable *EGFR* mutations by plasma assessment achieved greater benefits with both treatment regimens. This was particularly pronounced in patients receiving first-line erlotinib for whom OS was longer by 13 months in those with undetectable mutations compared with those with *EGFR* mutations, suggesting the potential value of cfDNA assessment in predicting benefit with TKI therapy. In contrast to our findings, a retrospective study that analyzed plasma samples using a denaturing high-performance liquid chromatography method demonstrated superior PFS benefits with EGFR-TKIs in patients with co-existing mutations in tissue and plasma samples over those with mutations detected only in either tumor tissue or plasma [14]. Compared with this report, which included both first-line and second-line patients, our analysis was focused on first-line treatment only. Furthermore, an analysis of the LUX Lung 3 and 6 trial suggested that patients with *EGFR* positive cfDNA had more advanced disease, including a greater tumor burden, higher ECOG performance status, more metastatic sites, and metastases to liver and bone [15]. All these characteristics are likely to contribute to poorer prognosis irrespective of treatment agents. Possible assumption of the association may be the increased escape of tumor cells and DNA into the blood. We look forward to more evidence from larger prospective trials to inform the utility of plasma-based assays in clinical practice.

A limitation of our study was that the extension phase was initiated 2 years after the parent ENSURE study and excluded patients from the original trial who died or withdrew, thereby introducing potential selection bias for patients with better prognosis and survival. Additionally, our analysis was not sufficiently powered to detect differences in PFS between treatment arms as it was initiated after the parent ENSURE study had enrolled patients. Instead, this study subpopulation reflected the maximum number of Chinese patients from the ENSURE study. Furthermore, first-line osimertinib is now considered one of the treatment options for NSCLC patients who have tumors with EGFR sensitizing mutations [16,17]. Our study was initiated early before third-generation TKIs had received approval, so chemotherapy was used as the standard treatment after PD following TKI treatment. Thus, further studies to evaluate the best sequencing strategy for *EGFR*

mutation-positive NSCLC including new-generation TKIs is of interest.

Our study aimed to provide physicians with the evidence necessary to formulate a rational approach to the sequential and combined use of these medications. In patients with advanced *EGFR* mutation-positive NSCLC, first-line erlotinib followed by chemotherapy upon progression demonstrated comparable PFS benefit with the inverse sequence, irrespective of *EGFR* mutation subtype. Findings from our study confirmed the benefits of erlotinib as first-line treatment for patients with *EGFR* mutation-positive advanced NSCLC, and highlight the importance of a sequential combination strategy with an EGFR-TKI and chemotherapy, irrespective of the sequence, in maximizing PFS benefits for these patients. Furthermore, our post-hoc biomarker analysis demonstrated that patients with undetectable *EGFR* mutations by plasma assessment achieved greater benefits with both treatment regimens, which might suggest the potential value of cfDNA assessment in predicting benefit with TKI therapy. However, large and prospective trials are needed to increase confidence in the clinical utilization of blood-based *EGFR* mutation testing to select patients for EGFR-targeted therapy.

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Conflict of interest

Yi-Long Wu reports honoraria from AstraZeneca, Eli Lilly, Roche, Pierre Fabre, Pfizer, and Sanofi; consulting or advisory roles for AstraZeneca, Roche, Merck, and Boehringer Ingelheim; and research funding from Boehringer Ingelheim (Inst) and Roche (Inst). Other authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.01.016.

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