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ORIGINAL REPORT

Randomized Phase III Trial of Erlotinib Versus Docetaxel As Second- or Third-Line Therapy in Patients With Advanced Non–Small-Cell Lung Cancer: Docetaxel and Erlotinib Lung Cancer Trial (DELTA)

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ABSTRACT

Purpose

To investigate the efficacy of erlotinib versus docetaxel in previously treated patients with advanced non–small-cell lung cancer (NSCLC) in an epidermal growth factor receptor (EGFR) –unselected patient population.

Patients and Methods

The primary end point was progression-free survival (PFS). Secondary end points included overall survival (OS), response rate, safety, and analyses on *EGFR* wild-type tumors. Patients with stage IIIB or IV NSCLC, previous treatment with one or two chemotherapy regimens, evaluable or measurable disease, and performance status of 0 to 2 were eligible.

Results

From August 2009 to July 2012, 150 and 151 patients were randomly assigned to erlotinib (150 mg daily) and docetaxel (60 mg/m^2 every 3 weeks), respectively. *EGFR* wild-type NSCLC was present in 109 and 90 patients in the erlotinib and docetaxel groups, respectively. Median PFS for erlotinib versus docetaxel was 2.0 *v* 3.2 months (hazard ratio [HR], 1.22; 95% CI, 0.97 to 1.55; $P = .09$), and median OS was 14.8 *v* 12.2 months (HR, 0.91; 95% CI, 0.68 to 1.22; $P = .53$), respectively. In a subset analysis of *EGFR* wild-type tumors, PFS for erlotinib versus docetaxel was 1.3 *v* 2.9 months (HR, 1.45; 95% CI, 1.09 to 1.94; $P = .01$), and OS was 9.0 *v* 10.1 months (HR, 0.98; 95% CI, 0.69 to 1.39; $P = .91$), respectively.

Conclusion

Erlotinib failed to show an improvement in PFS or OS compared with docetaxel in an EGFR-unselected patient population.

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INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide. Non–small-cell lung cancer (NSCLC) comprises more than 80% of all lung tumors. Approximately two thirds of NSCLCs are diagnosed at advanced stages. The standard first-line treatment for NSCLC, platinum-based doublet chemotherapy, has a response rate of approximately 30%, and the response usually lasts only 4 to 5 months.[1] Second- and third-line chemotherapy has been used to further improve survival. A standard regimen of docetaxel has been established based on results from randomized phase III studies of patients with previously treated advanced NSCLC,[2,3] in whom the median progression-free survival (PFS) in response to docetaxel was 2.0 to 2.5 months.

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are active against previously treated NSCLC. Erlotinib, an EGFR-TKI, showed a significant survival benefit in a placebo-controlled phase III trial (BR21), with a median PFS of 2.2 months and hazard ratio (HR) of 0.61.[4] The noninferiority of gefitinib, another EGFR-TKI, to docetaxel in patients with previously treated NSCLC was shown in terms of survival in a global phase III study (Iressa NSCLC Trial Evaluating Response and Survival Versus Taxotere [INTEREST], n = 1,433)[5]

but not in a smaller phase III study in Japan (V15-32, n = 489).[6] A global phase IV study of erlotinib (Tarceva Lung Cancer Survival Treatment [TRUST], n = 6,580) showed a PFS of 3.3 months[7] and a much longer PFS (5.6 months) in an Asian subset.[8] Although both erlotinib and docetaxel are considered standard therapies for previously treated NSCLC, given the favorable survival in erlotinib-treated Asian patients, erlotinib might produce longer PFS than docetaxel in Asian patients with previously treated NSCLC in an EGFR-unselected population.

The Docetaxel and Erlotinib Lung Cancer Trial (DELTA) is a multicenter, open-label, phase III study from Japan. Because gefitinib failed to show noninferiority to docetaxel in the V15-32 trial, we investigated the efficacy and tolerability of erlotinib versus docetaxel as second- or third-line treatment for *EGFR*-unselected patients with NSCLC.

When this study was initiated, EGFR-TKIs were usually used without testing for EGFR mutational status in clinical practice. Then, the pivotal Iressa Pan-Asia Study (IPASS) study showed that gefitinib was superior to carboplatin and paclitaxel in terms of PFS in patients with *EGFR* mutant tumors (HR, 0.48; 95% CI, 0.36 to 0.64), whereas the opposite results were observed in patients with *EGFR* wild-type tumors (HR, 2.85; 95% CI, 2.05 to 3.98) in the first-line setting.[9] Given the advancement of molecular knowledge, we preplanned an analysis to examine the treatment effect in *EGFR* wild-type and *EGFR* mutant disease.

PATIENTS AND METHODS

Patients

This multicenter, open-label, randomized phase III study was sponsored by the National Hospital Organization, an independent administrative agency in Japan. Patients age 20 years or older were eligible if they met the following criteria: pathologically or histologically proven NSCLC with stage IIIB or IV disease (International Union Against Cancer, version 6); previous treatment with one or two chemotherapy regimens, including at least one platinum agent; evaluable or measurable disease by computed tomography (CT) or magnetic resonance imaging; and Eastern Cooperative Oncology Group performance status (PS) of 0 to 2. The main exclusion criteria were previous exposure to EGFR-TKI or docetaxel, symptomatic brain metastasis, and a second active cancer. Patients were also excluded from the study if they had interstitial pneumonia or pulmonary fibrosis detected by chest CT. All enrolled patients provided written informed consent before entering the study. The protocol was approved by the institutional review boards and ethics committees of the National Hospital Organization.

Treatment

Erlotinib (150 mg per day) was administered orally. Docetaxel was administered every 3 weeks as a 1-hour intravenous infusion of 60 mg/m^2 (ie, the approved dose in Japan). Adverse events were monitored and graded according to the Common Terminology Criteria for Adverse Events (version 3.0). Patients received the study treatment until disease progression or intolerable toxicities. Poststudy treatment was given at the discretion of the physician and patient, and cross-over treatment was allowed in this trial.

Assessments

Tumors assessments were performed via CT, spiral CT, or magnetic resonance imaging, and the same methods of measurement were used throughout the study for each patient. PFS was defined as the time from random assignment to the earliest occurrence of disease progression or death from any cause; patients who had not experienced progression or died at data cutoff were censored at the last tumor assessment. Overall survival (OS) was assessed from the date of random assignment to the date of death as the result of any cause, or data were censored at the last date the patient was confirmed to be alive. Tumor response according to RECIST was assessed at baseline, every month for the first 4 months, and every 2 months thereafter. Investigator assessment of best overall tumor response was used for the analysis. Routine laboratory assessments were performed at baseline, every week for the first month, and every 2 to 4 weeks thereafter. *EGFR* mutations were examined in exons 18 to 21 by a highly sensitive polymerase chain reaction (PCR) –based method (ie, the PCR-invader method, peptide nucleic acid–locked nucleic acid PCR clamp method, or cycleave method). These assays were performed in commercial laboratories to which each institute sent the diagnostic tumor samples.[10]

Statistical Analysis

Eligible patients were randomly assigned 1:1 to erlotinib or docetaxel by the minimization method according to sex, performance status, histology, and institution. Efficacy analyses were completed for the intent-to-treat population. Safety analyses were performed for the population who received at least one dose of the trial medication after random assignment. The primary end point was PFS. Secondary end points were OS, response, safety, and analyses on *EGFR* wild-type and mutant tumors. Median PFS was assumed to be 3.5 months and 2.5 months in patients receiving erlotinib and docetaxel, respectively, based on data from previous clinical trials.[2,7,8] The present study was

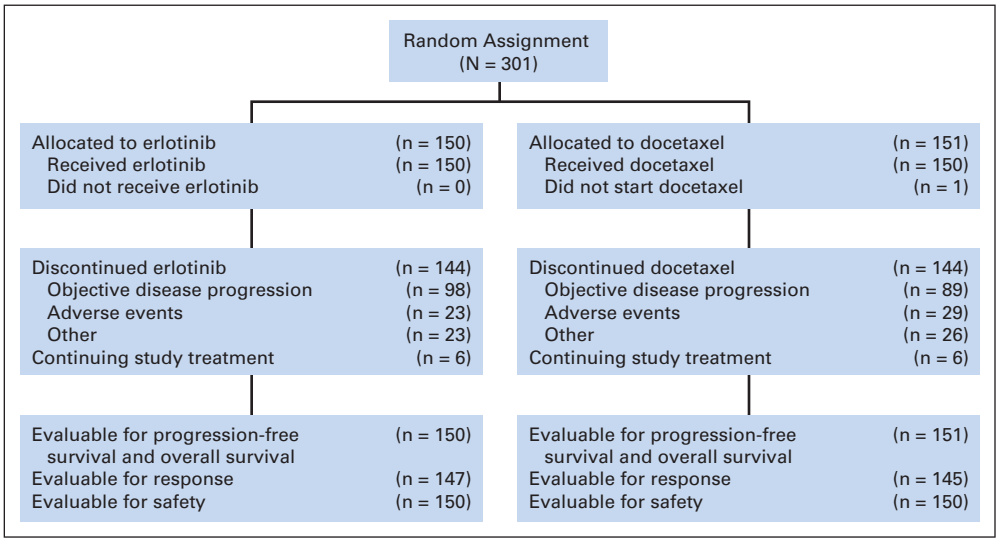

Fig 1. CONSORT diagram.

designed to assess the efficacy of erlotinib versus docetaxel in *EGFR*-unselected patients and to have 80% power to detect a 1-month difference at a two-sided significance level of $P = .05$. A sample size of 300 patients was planned based on these assumptions. Final analysis was planned after 278 events. Survival curves were calculated using the Kaplan-Meier method, and a log-rank test was used to compare treatment groups. The 95% CI of the median survival time was calculated by the method of Brookmeyer and Crowly.[11] Estimates of the treatment effect were expressed as HRs and two-sided 95% CIs from a Cox regression model for erlotinib versus docetaxel.

Subgroup analyses for PFS were performed to explore the potential interaction effect of the treatment groups with sex (male *v* female), PS (0 *v* 1 or 2), stage (IIIB *v* IV), histology (adenocarcinoma *v* other), and smoking status (ever *v* never). Response, toxicity, and patient characteristics were compared between the treatment groups using Fisher's exact test, and age was compared using the Wilcoxon rank sum test. As secondary end points, we performed similar analyses for PFS and OS in patients with *EGFR* wild-type and *EGFR* mutant tumors. To assess the homogeneity of the treatment effect on PFS and OS, an interaction term of treatment and *EGFR* mutation status (wild-type, exon 19 deletion or L858R, or other) was evaluated in the Cox model using the likelihood ratio test. To correct for potential confounding of patient characteristics other than the *EGFR* mutation status in these subgroup analyses, adjusted HRs were also calculated using the Cox regression model, including stratification factors with the exception of institution. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

Table 1. Patient Demographics and Clinical Characteristics for All Study Patients

Demographic or Clinical Characteristic	Erlotinib (n = 150) No. of Patients	%	Docetaxel (n = 151) No. of Patients	%
Sex				
Female	42	28.0	44	29.1
Male	108	72.0	107	70.9
Age, years				
Median	68		67	
Range	37-82		31-85	
Stage				
IIIB	30	20.0	29	19.2
IV	120	80.0	122	80.8
Performance status				
0	77	51.3	78	51.7
1	67	44.7	67	44.4
2	6	4.0	6	4.0
Smoking status				
Ever-smoker	111	74.0	114	75.8
Never-smoker	39	26.0	37	24.5
Histology				
Adenocarcinoma	104	69.3	103	68.2
Squamous cell carcinoma	29	19.3	32	21.2
Others	17	11.3	16	10.6
First-line treatment	150	100	151	100
Platinum doublet	141	94.0	140	92.7
Platinum doublet + bevacizumab	6	4.0	10	6.6
Other	3	2.0	1	0.7
Second-line treatment	29	19.3	21	13.9
Platinum doublet	19	12.7	9	6.0
Platinum doublet + bevacizumab	3	2.0	3	2.0
Other	7	4.7	9	6.0
EGFR status				
Wild-type	109	72.7	90	59.6
Exon 19 deletion or L858R	21	14.0	30	19.9
Other mutations	2	1.3	3	2.0
Insufficient/not examined	18	12.0	28	18.6

Abbreviation: EGFR, epidermal growth factor receptor.

RESULTS

Patients

From August 2009 to July 2012, 301 patients were enrolled from 41 institutions belonging to the National Hospital Organization. In the intent-to-treat population, 150 and 151 patients were randomly assigned to erlotinib and docetaxel, respectively (Fig 1). The baseline characteristics were well balanced between the treatment groups in terms of age, sex, PS, smoking status, histology, first- and second-line chemotherapy regimens, and *EGFR* status (Table 1).

PFS, OS, and Response Rate in EGFR-Unselected Population

Median PFS time was 2.0 months (95% CI, 1.3 to 2.8 months) for erlotinib and 3.2 months (95% CI, 2.8 to 4.0 months) for docetaxel (Fig 2A), but this difference was not significant (HR, 1.22; 95% CI, 0.97 to 1.55; $P = .09$). At data cutoff (January 17, 2013) with median follow-up of 8.9 months, 141 patients (94.0%) in the erlotinib group and 138 patients (91.4%) in the docetaxel group experienced disease

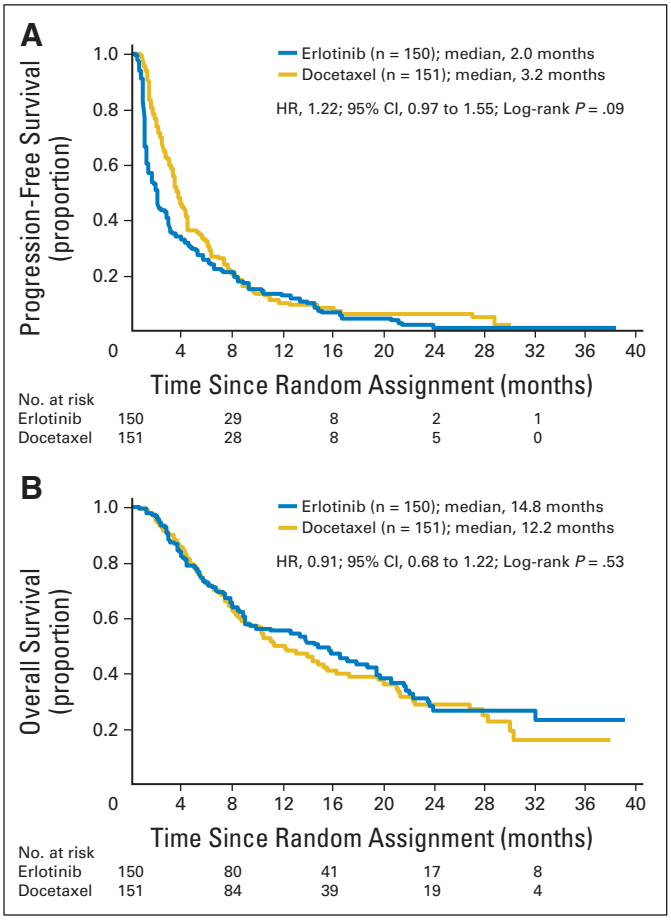

Fig 2. (A) Progression-free survival (all patients). (B) Overall survival (all patients). HR, hazard ratio.

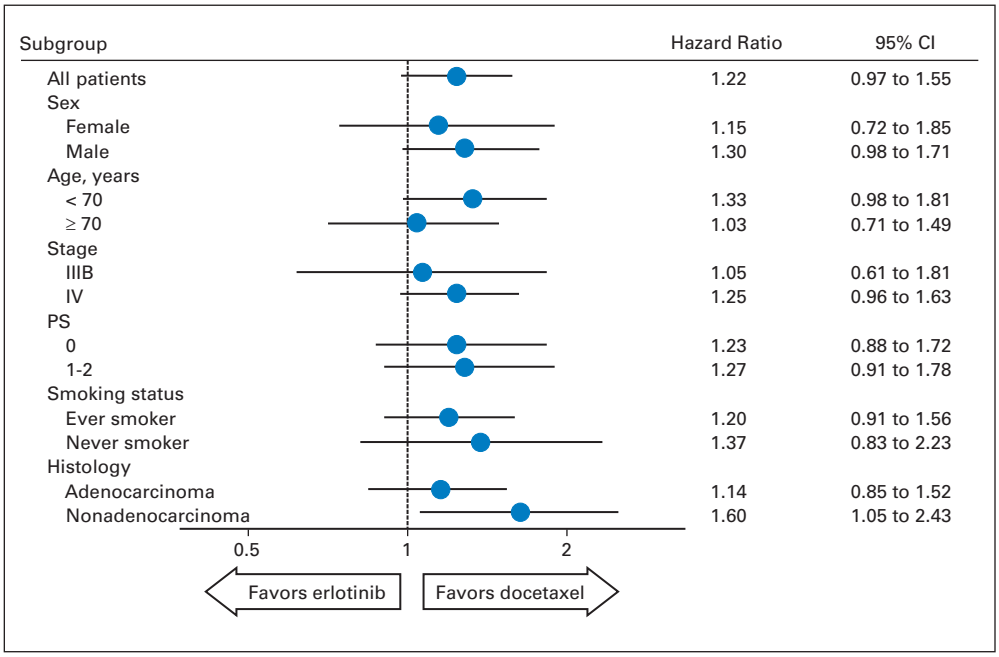

Fig 3. Progression-free survival in clinical subgroups (all patients). PS, performance status.

progression or death. The median OS time was 14.8 months (95% CI, 9.0 to 19.4 months) for erlotinib and 12.2 months (95% CI, 9.0 to 15.5 months) for docetaxel (HR, 0.91; 95% CI, 0.68 to 1.22; $P = .53$; Fig 2B). The number of patients with tumor response was similar in both groups; 25 patients (17.0%; 95% CI, 11.3% to 24.1%) responded in the erlotinib group, and 26 patients (17.9%; 95% CI, 12.1% to 25.2%) responded in the docetaxel group ($P = .88$). A complete response was reported in the erlotinib group in one patient with unknown *EGFR* status. As shown in Figure 3, subgroup analyses for PFS revealed that there was no significant difference between the two drugs, with the exception of nonadenocarcinoma histology (HR, 1.60; 95% CI, 1.05 to 2.43; $P = .03$). All factors numerically favored docetaxel.

PFS, OS, and Response Rate in EGFR *Wild-Type and Mutant Tumors*

EGFR status was determined in 255 (84.7%) of 301 patients, including 199 patients with wild-type *EGFR* NSCLC and 51 patients with active mutant *EGFR* NSCLC. The interaction term between treatment and *EGFR* mutation status was significant for PFS but not for OS ($P = .03$ and $P = .20$, respectively). In patients with *EGFR* wild-type disease, there was no significant difference between the erlotinib and docetaxel groups regarding sex (men and women: 85 and 24 *v* 68 and 22 patients, respectively; $P = .74$), age (median age, 68 *v* 67 years, respectively; $P = .96$), PS (0, 1, and 2: 52, 52, and five *v* 38, 49, and three patients, respectively; $P = .66$), histology (adenocarcinoma and nonadenocarcinoma: 72 and 37 *v* 58 and 32 patients, respectively; $P = .88$), stage (IIIB and IV: 26 and 83 *v* 20 and 70 patients, respectively; $P = .87$), and smoking status (ever-smoker and never-smoker: 87 and 22 *v* 76 and 14 patients, respectively; $P = .46$). In patients with *EGFR* wild-type tumors, the docetaxel group had a significantly longer PFS (2.9 months; 95% CI, 2.1 to 3.3 months) than the erlotinib group (1.3 months; 95% CI, 1.1 to 2.0 months; Fig 4A). A supportive Cox analysis with stratification factors confirmed the significant difference (adjusted HR, 1.57; 95% CI, 1.18 to 2.11; $P < .01$). However, the difference in OS was not statistically significant. The median OS was 9.0 months (95% CI, 7.8 to 14.5 months) in the erlotinib group compared with 10.1 months (95% CI, 7.3 to 12.4 months) in the docetaxel group ($P = .91$; Fig 4B). In terms of tumor response, six patients (5.6%; 95% CI, 2.1% to 11.9%) responded to erlotinib, and 17 patients (20.0%; 95% CI, 12.1% to 30.1%) responded to docetaxel ($P < .01$).

In patients with *EGFR* mutations, median PFS and median OS were longer in the erlotinib group than in the docetaxel group (PFS: 9.3 *v* 7.0 months, respectively; OS: not reached *v* 27.8 months, respectively). However, these differences in PFS (Fig 4C) and OS (Fig 4D) were not statistically significant.

Safety

The safety population included 300 patients: 150 in each group (Table 2). The most common adverse event with erlotinib was rash (92.7%), whereas docetaxel was associated with fatigue (71.3%), nausea (50.0%), and hematologic toxicities. Grade 3 to 4 leukopenia, neutropenia, and febrile neutropenia were significantly more frequent with docetaxel compared with erlotinib (0.7% *v* 64.0%, 0.7% *v* 80.0%, and none *v* 15.3%, respectively; Table 2). Two patients in the erlotinib group died of interstitial lung disease, and one patient in the docetaxel group died as a result of infection.

Poststudy Treatment

The number of patients who received further treatment was similar in the two groups ($P = .22$). Sixty-one patients (42.3%) in the erlotinib group received docetaxel, and 55 patients (37.9%) in the docetaxel group received EGFR-TKIs. Other drugs were administered to 45 patients (31.3%) in the erlotinib group and 41 patients (28.3%) in the docetaxel group. In the unselected population, no difference in OS was observed between the erlotinib and docetaxel arms when comparing patients who went on to receive subsequent chemotherapy (HR, 0.96; 95% CI, 0.62 to 1.49; $P = .84$).

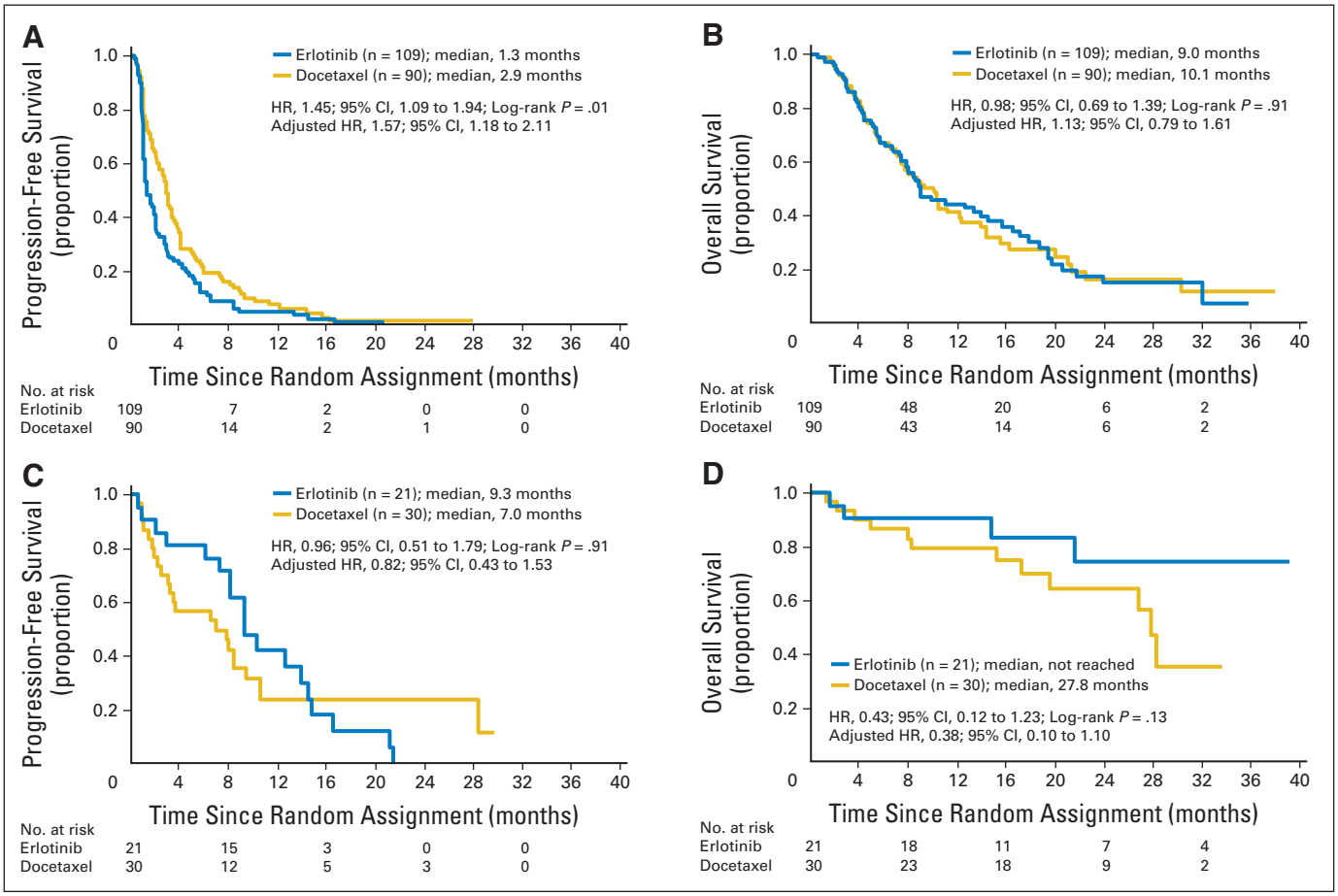

Fig 4. (A) Progression-free survival (PFS) in epidermal growth factor receptor (*EGFR*) wild-type tumors. (B) Overall survival (OS) in *EGFR* wild-type tumors. (C) PFS in *EGFR* mutant tumors (exon 19 deletion or L858R). (D) OS in *EGFR* mutant tumors (exon 19 deletion or L858R). HR, hazard ratio.

Similarly, no difference was observed in the unselected population between the two arms when comparing patients who did not go on to receive subsequent chemotherapy (HR, 1.28; 95% CI, 0.77 to 2.12; $P = .34$). However, patients with *EGFR* wild-type tumors who were treated with docetaxel and did not receive subsequent therapy had a trend toward longer OS when compared with patients treated with erlotinib (HR, 1.79; 95% CI, 0.95 to 3.35; $P = .06$). However, no significant difference in OS was seen between the

Table 2. Common Adverse Events

	All Grades					Grade 3 or 4				
	Erlotinib (n = 150)		Docetaxel (n = 150)			Erlotinib (n = 150)		Docetaxel (n = 150)		
Toxicity	No. of Patients	%	No. of Patients	%	*P*	No. of Patients	%	No. of Patients	%	*P*
Rash	139	92.7	22	14.7	< .01	20	13.3	1	0.7	< .01
Nausea	46	30.7	75	50.0	< .01	3	2.0	5	3.3	.72
Vomiting	13	8.7	25	16.7	.06	1	0.7	0		1.00
Diarrhea	57	38.0	31	20.7	< .01	2	1.3	2	1.3	1.00
Fatigue	80	53.3	107	71.3	< .01	8	5.3	7	4.7	1.00
Anemia	120	80.0	141	94.0	< .01	6	4.0	12	8.0	.22
Thrombocytopenia	31	20.7	48	32.0	.04	0		3	2.0	.245
Leukopenia	19	12.7	140	93.3	< .01	1	0.7	96	64.0	< .01
Neutropenia	15	10.0	136	90.7	< .01	1	0.7	120	80.0	< .01
Neutropenic fever						0		23	15.3	< .01
AST	43	28.7	36	24.0	.43	3	2.0	0		.25
ALT	39	26.0	35	23.3	.69	5	3.3	1	0.7	.21
Pneumonitis	10	6.7	8	5.3	.81	2	1.3	3	2.0	1.00

erlotinib and docetaxel arms in patients who received any subsequent treatment (HR, 0.91; 95% CI, 0.63 to 1.32; $P = .62$).

DISCUSSION

This study showed that there was no significant difference in PFS when comparing erlotinib versus docetaxel as second- or third-line treatment for an *EGFR*-unselected population with NSCLC. In the preplanned subgroup analysis, PFS and response rate were significantly better with docetaxel than erlotinib in *EGFR* wild-type tumors. In contrast, patients with *EGFR* mutant tumors showed longer PFS and OS in the erlotinib group than in the docetaxel group, although these differences did not reach statistical significance, possibly because of the small sample size.

To date, five phase III trials have compared EGFR-TKI and chemotherapy in patients with previously treated and EGFR-unselected NSCLC.[5,6,12-14] INTEREST was the largest study and examined gefitinib versus docetaxel, but there was no significant difference between these two agents in terms of median PFS (2.2 *v* 2.7 months, respectively) and median OS (7.6 *v* 8.0 months, respectively).[5] This trend was also confirmed for Japanese patients in the V15-32 trial.[6] Other drugs examined included erlotinib versus pemetrexed by the Hellenic Oncology Research Group[13] and erlotinib versus docetaxel/pemetrexed in the Tarceva in Treatment of Advanced NSCLC (TITAN) study,[14] and similar results were obtained; there was no difference in PFS and OS between EGFR-TKI and chemotherapy. The findings of DELTA are consistent with the results from these phase III trials in *EGFR*-unselected patients with NSCLC.

Therapy can now be individualized based on the molecular profile of the tumor. Convincing evidence that EGFR-TKIs have marked antitumor activity in patients with activating mutations of exons 19 and 21 of the *EGFR* gene has accumulated.[15,16] This genotyping-guided treatment has been effective in clinical practice. Along with these achievements, the role of EGFR-TKIs in patients with *EGFR* wild-type NSCLC has been discussed.[17] Our prospectively defined analyses included an examination of *EGFR* wild-type NSCLC, revealing 199 patients with wild-type *EGFR* disease (66.1%) among the 255 patients (84.7%) who were assessed for *EGFR* mutations, which is a higher proportion than that assessed in previous studies.[13,14,18] The present analysis showed that docetaxel was superior to erlotinib in terms of PFS in the subset analysis for *EGFR* wild-type NSCLC. To date, three randomized studies have compared EGFR-TKIs and chemotherapy focusing on wild-type *EGFR* tumors.[14,18] However, our data are inconsistent with the subset analyses of the INTEREST[18] and TITAN trials,[14] both of which showed no significant difference in PFS when comparing EGFR-TKIs and chemotherapy. Another recent phase III study, the Tarceva Italian Lung Optimization Trial (TAILOR),[19] in which all the patients had *EGFR* wild-type disease, reported the same results as ours. Because the sample size of the four studies is approximately 200 patients, the discrepancy in PFS among studies might partly be attributable to the methods used for *EGFR* analysis. For example, INTEREST and TITAN used direct sequencing, whereas the TAILOR study used restriction fragment length polymorphism and Sanger sequencing. DELTA adopted highly sensitive PCR-based assays. The TAILOR and DELTA studies used likely more sensitive methods to detect mutations than direct sequencing, particularly for diagnostic tumor samples.[20] The response rates for EGFR-TKI versus docetaxel were 6.6% *v* 9.8%, respectively, in INTEREST; 3.0% *v* 15.5%, respectively, in TAILOR; and 5.6% *v*. 20.0%, respectively, in DELTA (no data available for TITAN). These data support our observations regarding the PFS benefit in the docetaxel group of DELTA.

In contrast to PFS and response rate, there were no differences in OS when comparing EGFR-TKI and chemotherapy in our study as well as in the subset analysis of INTEREST and TITAN. Only the TAILOR study, which did not allow cross-over therapy, showed that docetaxel was better than erlotinib in terms of PFS and OS. In the DELTA study, approximately 40% of patients received cross-over treatments, and other subsequent therapies were similarly delivered in both groups. Therefore, unlike PFS, OS may not be affected by subsequent therapies. In fact, we found a trend toward better OS in the docetaxel group than in the erlotinib group in *EGFR* wild-type patients who received no subsequent chemotherapy in our subset analysis. Given the active drugs available for poststudy chemotherapy that might confer prolonged survival after progression, PFS can be a clinically relevant end point, and further research and discussion are required.[21,22]

The response rate of 20% in the docetaxel arm was higher and hematologic toxicities were more severe compared with the response rate and hematologic toxicities seen in phase III trials in Western countries. There might be some ethnic differences in efficacy and toxicity between white and Asian patients.[23,24] For example, in the Common Arm Trial, which compared clinical outcomes between US and Japanese patients treated with carboplatin and paclitaxel according to identical study design, eligibility criteria, and staging system,[25] the PFS and OS were longer and adverse effects of neutropenia and anemia were more severe in Japanese patients. Although 75 mg/m^2 of docetaxel is more commonly used in Western populations, the absolute response rate and survival in DELTA do not suggest underdosing.

This study has several limitations. First, we failed to detect a significant difference in PFS in the unselected population, which may have been a result of the small sample size. Second, the trial was nonblinded, and the primary end point of PFS was assessed by the individual investigator at each institution. Therefore, caution should be used when comparing our results with those of other studies in which PFS was centrally assessed.

In summary, the present study showed no significant difference in PFS and OS when comparing docetaxel and erlotinib in EGFR-unselected patients with NSCLC. However, docetaxel was superior to erlotinib in terms of PFS and response rate (but not OS) in patients with *EGFR* wild-type disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Favaretto AG, Pasello G, Magro C: Second and third line treatment in advanced non-small cell lung cancer. Discov Med 8:204-209, 2009
2. Shepherd FA, Dancey J, Ramlau R, et al: Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 18:2095-2103, 2000
3. Fossella FV, DeVore R, Kerr RN, et al: Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens: The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 18:2354-2362, 2000
4. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al: Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 353:123-132, 2005
5. Kim ES, Hirsh V, Mok T, et al: Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): A randomised phase III trial. Lancet 372:1809-1818, 2008
6. Maruyama R, Nishiwaki Y, Tamura T, et al: Phase III study, V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. J Clin Oncol 26:4244-4252, 2008
7. Reck M, van Zandwijk N, Gridelli C, et al: Erlotinib in advanced non-small cell lung cancer: Efficacy and safety findings of the global phase IV Tarceva Lung Cancer Survival Treatment study. J Thorac Oncol 5:1616-1622, 2010
8. Perng RP, Yang CH, Chen YM, et al: High efficacy of erlotinib in Taiwanese NSCLC patients in an expanded access program study previously treated with chemotherapy. Lung Cancer 62:78-84, 2008
9. Mok TS, Wu YL, Thongprasert S, et al: Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361:947-957, 2009
10. Goto K, Satouchi M, Ishii G, et al: An evaluation study of EGFR mutation tests utilized for non-small-cell lung cancer in the diagnostic setting. Ann Oncol 23:2914-2919, 2012
11. Brookmeyer R, Crowly J: A confidence interval for the median survival time. Biometrics 38:29-41, 1982
12. Lee DH, Park K, Kim JH, et al: Randomized phase III trial of gefitinib versus docetaxel in non-small cell lung cancer patients who have previously received platinum-based chemotherapy. Clin Cancer Res 16:1307-1314, 2010
13. Karampeazis A, Voutsina A, Souglakos J, et al: Pemetrexed versus erlotinib in pretreated patients with advanced non-small cell lung cancer: A Hellenic Oncology Research Group (HORG) randomized phase 3 study. Cancer 119:2754-2764, 2013
14. Ciuleanu T, Stelmakh L, Cicenas S, et al: Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): A randomised multicentre, open-label, phase 3 study. Lancet Oncol 13:300-308, 2012
15. Maemondo M, Inoue A, Kobayashi K, et al: Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 362:2380-2388, 2010
16. Mitsudomi T, Morita S, Yatabe Y, et al: Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): An open label, randomised phase 3 trial. Lancet Oncol 11:121-128, 2010
17. Laurie SA, Goss GD: Role of epidermal growth factor receptor inhibitors in epidermal growth factor receptor wild-type non-small-cell lung cancer. J Clin Oncol 31:1061-1069, 2013
18. Douillard JY, Shepherd FA, Hirsh V, et al: Molecular predictors of outcome with gefitinib and docetaxel in previously treated non-small-cell lung cancer: Data from the randomized phase III INTEREST trial. J Clin Oncol 28:744-752, 2010
19. Garassino MC, Martelli O, Broggini M, et al: Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): A randomised controlled trial. Lancet Oncol 14:981-988, 2013
20. Pao W, Ladanyi M: Epidermal growth factor receptor mutation testing in lung cancer: Searching for the ideal method. Clin Cancer Res 13:4954-4955, 2007
21. Broglio KR, Berry DA: Detecting an overall survival benefit that is derived from progression-free survival. J Natl Cancer Inst 101:1642-1649, 2009
22. Booth CM, Eisenhauer EA: Progression-free survival: Meaningful or simply measurable? J Clin Oncol 30:1030-1033, 2012
23. Soo RA, Loh M, Mok TS, et al: Ethnic differences in survival outcome in patients with advanced stage non-small cell lung cancer: Results of a meta-analysis of randomized controlled trials. J Thorac Oncol 6:1030-1038, 2011
24. Hasegawa Y, Kawaguchi T, Kubo A, et al: Ethnic difference in hematological toxicity in patients with non-small cell lung cancer treated with chemotherapy: A pooled analysis on Asian versus non-Asian in phase II and III clinical trials. J Thorac Oncol 6:1881-1888, 2011
25. Gandara DR, Kawaguchi T, Crowley J, et al: Japanese-US common-arm analysis of paclitaxel plus carboplatin in advanced non-small-cell lung cancer: A model for assessing population-related pharmacogenomics. J Clin Oncol 27:3540-3546, 2009

GLOSSARY TERMS

epidermal growth factor receptor (EGFR): also known as HER1. Belongs to a family of receptors (HER2, HER3, HER4 are other members of the family) and binds to the EGF, TGF-α, and other related proteins, leading to the generation of proliferative and survival signals within the cell. It also belongs to the larger family of tyrosine kinase receptors and is generally overexpressed in several solid tumors of epithelial origin.

erlotinib: also known as Tarceva (Genentech, South San Francisco, CA). Erlotinib is a small molecule that inhibits the tyrosine kinase activity of epidermal growth factor receptor/HER1 and has been evaluated extensively in clinical trials in patients with non–small-cell lung cancer, pancreatic cancer, and glioblastoma multiforme.

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