Supplementary Table S2.3. *EGFR* mutation-positive patients: Histology by country

Country	Category	Number of samples *EGFR* mutation tested	*EGFR* mutation positive samples	%	95% CI*	
					Lower	Upper
Total	Adenocarcinoma	7698	3578	46.5	45.4	47.6
	Other morphological subtypes	1686	224	13.3	11.7	15
	Squamous cell carcinoma	902	69	7.6	6.1	9.6
China	Adenocarcinoma	1917	911	47.5	45.3	49.8
	Other morphological subtypes	752	112	14.9	12.5	17.6
	Squamous cell carcinoma	368	37	10.1	7.4	13.6
Hong Kong	Adenocarcinoma	292	148	50.7	45	56.4
	Other morphological subtypes	12	7	58.3	32	80.7
	Squamous cell carcinoma	7	1	14.3	2.6	51.3
Indonesia	Adenocarcinoma	76	21	27.6	18.8	38.6
	Other morphological subtypes	25	8	32	17.2	51.6
	Squamous cell carcinoma	4	1	25	4.6	69.9
Japan	Adenocarcinoma	1128	443	39.3	36.5	42.2
	Other morphological subtypes	412	23	5.6	3.7	8.2
	Squamous cell carcinoma	269	8	3	1.5	5.8
Korea	Adenocarcinoma	1414	608	43	40.4	45.6
	Other morphological subtypes	343	38	11.1	8.2	14.8
	Squamous cell carcinoma	209	12	5.7	3.3	9.8
Malaysia	Adenocarcinoma	352	161	45.7	40.6	51

	Other morphological subtypes	0	0			
	Squamous cell carcinoma	0	0			
Philippines	Adenocarcinoma	65	27	41.5	30.4	53.7
	Other morphological subtypes	5	0	0	0	43.4
	Squamous cell carcinoma	3	0	0	0	56.1
Singapore	Adenocarcinoma	528	240	45.5	41.3	49.7
	Other morphological subtypes	1	1	100	20.7	100
	Squamous cell carcinoma	1	1	100	20.7	100
Taiwan	Adenocarcinoma	1444	803	55.6	53	58.2
	Other morphological subtypes	125	33	26.4	19.5	34.7
	Squamous cell carcinoma	31	7	22.6	11.4	39.8
Thailand	Adenocarcinoma	432	198	45.8	41.2	50.5
	Other morphological subtypes	11	2	18.2	5.1	47.7
	Squamous cell carcinoma	10	2	20	5.7	51
Vietnam	Adenocarcinoma	50	18	36	24.1	49.9
	Other morphological subtypes	0	0			
	Squamous cell carcinoma	0	0			

*: Wilson score confidence interval.

This table is based on sites providing both "Number of samples *EGFR* mutation tested" and "*EGFR* mutation positive samples" for each category.

"Adenocarcinoma" includes adenocarcinoma and other characteristics in adenocarcinoma category.

"Other morphological subtypes" includes adenosquamous and histologies with other non-adenosquamous characteristics.

"Squamous cell carcinoma" is a subset of "other morphological subtypes".

Blank indicates no data are available for this table, hence the proportion is not calculable.

Any discrepancy between "Number of samples *EGFR* mutation tested" in Table S2.3 and "*EGFR* mutation positive samples" in Table S1.3 is due to difference in subsets of sites used for constructing these tables.

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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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See accompanying article on page 1874

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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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

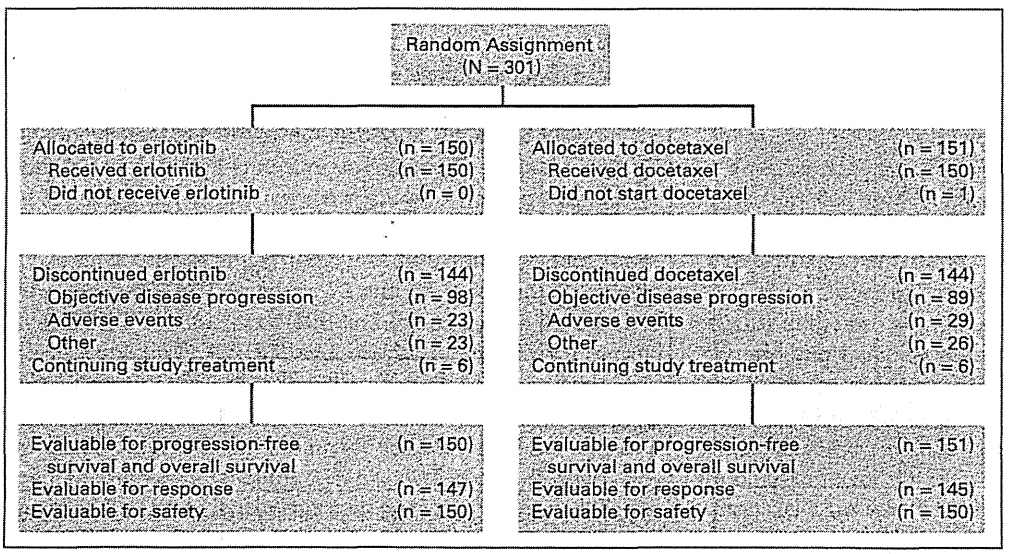

Fig 1. CONSORT diagram.

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

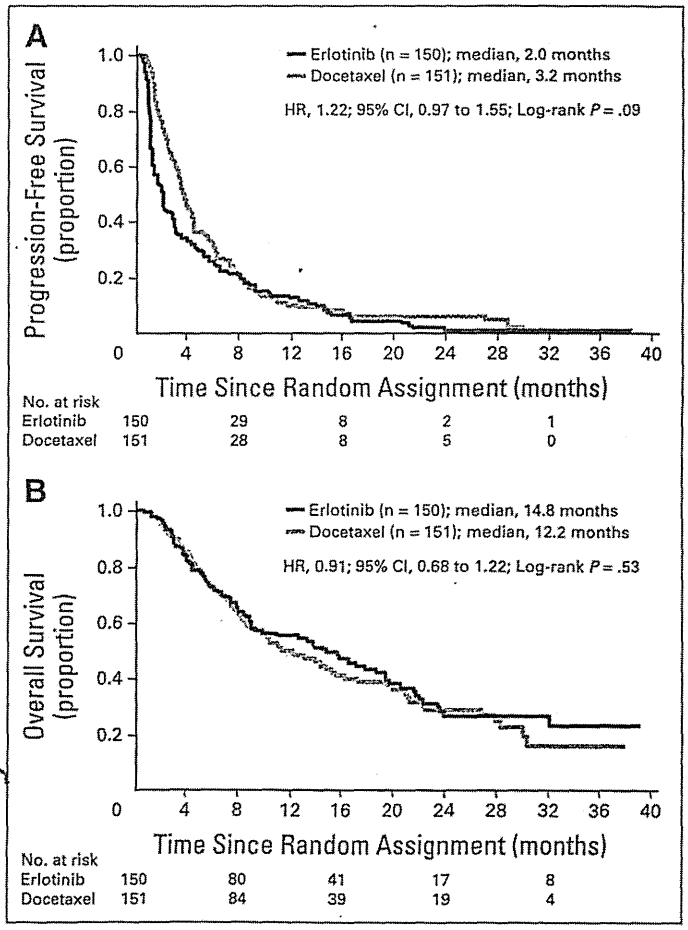

Fig 2. (A) Progression-free survival (all patients). (B) Overall survival (all patients). HR, hazard ratio.

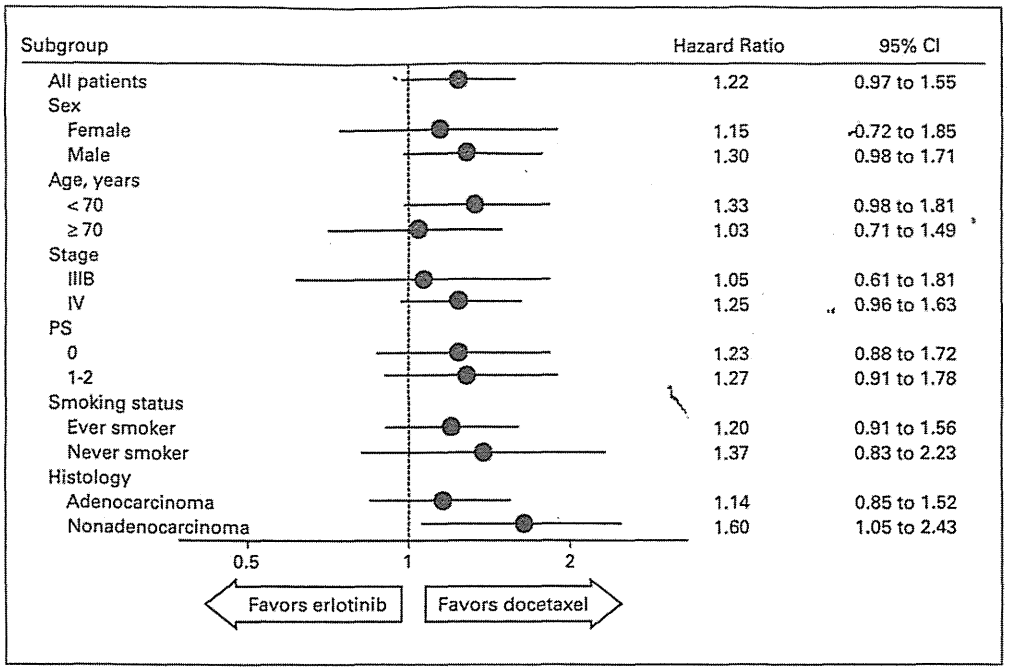

Fig 3. Progression-free survival in clinical subgroups (all patients). PS, performance status.

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; $P = .84$).

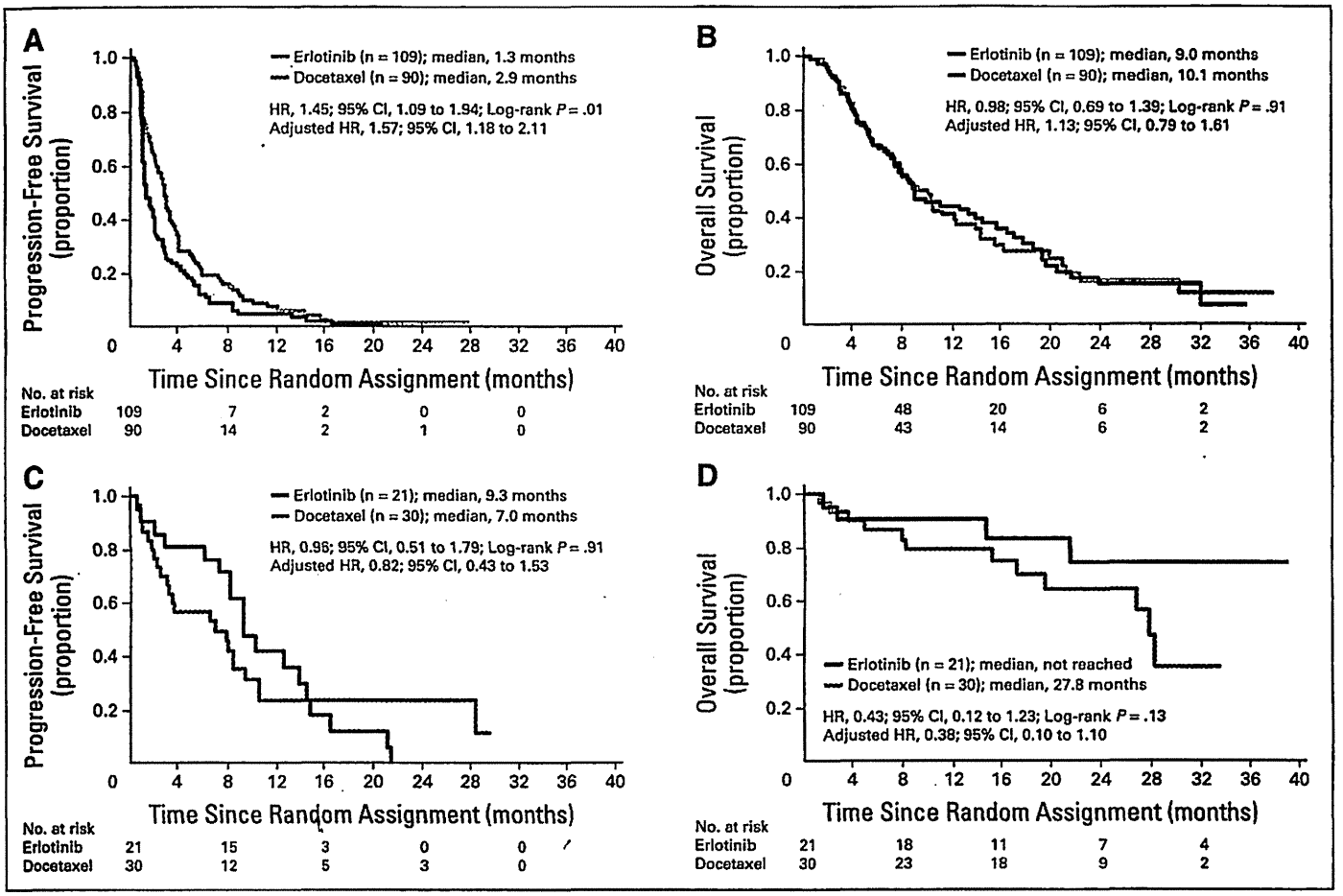

Fig 4. (A) Progression-free survival (PFS) in epidermal growth factor receptor (*EGFR*) wild-type tumors. (B) Overall survival (OS) in *EGFR* wild-type tumors. (C) PFS in *EGFR* mutant tumors (exon 19 deletion or L858R). (D) OS in *EGFR* mutant tumors (exon 19 deletion or L858R). HR, hazard ratio.

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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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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Review

Current status and future perspectives of cooperative study groups for lung cancer in Japan

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ABSTRACT

The performance of scientifically and ethically valid prospective clinical trials is the only means by which to obtain reliable clinical evidence that can improve clinical practice and thus the outcome of patients with lung cancer. The efficacy of treatment for advanced lung cancer remains limited; many cooperative study groups for lung cancer have been established in Japan since 1990s, and they have completed several landmark investigator-initiated clinical trials. This review highlights eight active Japanese cooperative study groups for lung cancer and summarizes their achievements made through clinical trials. In addition to their benefits, the existence of multiple study groups for a single disease such as lung cancer presents several challenges including the provision of infrastructure to ensure the scientific integrity of trial results, the unnecessary duplication of effort and the wasting of limited resources, and the accrual and completion of large-scale phase III trials in the shortest possible time. Collaboration among Japanese cooperative groups has recently increased in order to overcome these challenges. Although institutional barriers to the performance of such large intergroup trials remain, further harmonization and collaboration among cooperative groups will be vital in allowing Japanese investigators to make further important contributions for the development of new lung cancer therapies.

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Abbreviations: JCOG, Japan Clinical Oncology Group; SCLC, small cell lung cancer; ED, extensive disease; OS, overall survival; WJOG, West Japan Oncology Group; NSCLC, non-small-cell lung cancer; EGFR, epidermal growth factor receptor; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; OLCSG, Okayama Lung Cancer Study Group; TCOG, Tokyo Cooperative Oncology Group; NPO, nonprofit organization; NEJSG, North East Japan Study Group; CJLSG, Central Japan Lung Study Group; TORG, Thoracic Oncology Research Group; LOGiK, Lung Oncology Group in Kyushu

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1. Introduction

Lung cancer is the most common cause of death from cancer in Japan, being responsible for more than 70,000 deaths annually. Most individuals with lung cancer are already at an advanced stage of the disease at the time of diagnosis. Chemotherapy is the mainstay of treatment for such patients, but their median survival time is limited to ~15 months [1,2]. The development of new treatment strategies to improve the clinical outcome of individuals with this challenging disease is thus a priority.

The establishment of more effective treatments for advanced lung cancer requires the performance of scientifically and ethically valid prospective multicenter clinical trials. The first professional cooperative study group for lung cancer research in Japan was the Japan Clinical Oncology Group (JCOG), which was formed in 1990. Several other cooperative study groups for lung cancer were subsequently established to promote and support multicenter clinical trials of new treatments for this disease. Recently, the "Study for Enhancement of Quality and Efficiency of Cancer Therapeutic Development Research via Collaboration among Cooperative Groups and Designated Cancer Care Hospitals" was established to enhance collaboration of eight selected Japanese cooperative groups for lung cancer. It is supported by the National and Cancer Research Development Fund (26-A-22) and is chaired by Haruhiko Fukuda and Nobuyuki Yamamoto. For this review, we collected information about eight cooperative study groups by direct interviews. This review describes the current status and future challenges of investigator-initiated clinical trials for lung cancer.

2. Clinical Trial Groups in Japan

2.1. *Japan Clinical Oncology Group*

The Japan Clinical Oncology Group (JCOG) was launched in 1990 as a cooperative study group to perform multicenter clinical trials for cancer in Japan (Fig. 1, Table 1). It remains the only Japanese cooperative group supported primarily by a governmental research fund. Staff at the headquarters of JCOG, which includes a Data Center (director, Haruhiko Fukuda) and an Operations Office (director, Kenichi Nakamura), work closely with individual investigators to support the operational aspects of clinical trials. They thus provide help with protocol development, patient registration, reporting of adverse events, data management, and statistical analysis as well as perform regular (twice a year) central monitoring and site visit audits.

The individual study groups of JCOG are currently divided into 16 categories on the basis of specific tumor type or treatment modality. Among them, the Lung Cancer Study Group (LCSG) consists of 38 institutions distributed throughout the country and has conducted several practice-changing clinical trials, in particular for small cell lung cancer (SCLC). The first chair of LCSG was Nagahiro Saijo (1982–2002), who was succeeded by Tomohide Tamura (2002–2014) and then by Yuichiro Ohe (elected in 2014). One of the landmark trials performed by LCSG was a randomized phase III trial comparing cisplatin plus irinotecan with cisplatin plus etoposide (the standard treatment at the time) in chemotherapy-naïve patients with extensive disease (ED)-stage SCLC (JCOG9511) [3]. The trial was terminated early because the planned interim analysis showed a highly significant improvement in overall survival (OS) for patients treated with cisplatin plus irinotecan compared with those who received cisplatin plus etoposide. Although two subsequent large phase III trials in the United States failed to show a significant difference in OS between these two regimens, cisplatin plus irinotecan is now considered the standard regimen for previously untreated patients with ED-SCLC in Japan.

The number of elderly SCLC patients continues to rise with the growing geriatric population, with ~50% of individuals with SCLC now 70 years of age or older. JCOG performed a phase III trial comparing split doses of cisplatin (25 mg/m^2, days 1–3) plus etoposide (80 mg/m^2, days 1–3) (SPE regimen) with carboplatin (area under the curve=5, day 1) plus etoposide (80 mg/m^2, days 1–3) (CE regimen) in elderly (>70 years of age) or high-risk patients with ED-SCLC (JCOG9702) [4]. Although thrombocytopenia of grade 3 or 4 occurred more frequently in the CE arm than in the SPE arm (56% versus 14%, $P<0.01$), both regimens were found to be feasible and active, yielding a median OS of ~10 months. On the basis of the results of this phase III study, the CE regimen is now commonly used for elderly untreated patients with ED-SCLC. JCOG has recently initiated a randomized phase III trial comparing carboplatin plus irinotecan with the CE regimen for elderly (≥70 years) chemotherapy-naïve patients with ED-SCLC (JCOG1201) (Fig. 2A).

2.2. *West Japan Oncology Group*

The West Japan Thoracic Oncology Group (WJTOG) was established in 1992 as an expert group specific for lung cancer (Table 1). It was initially named the West Japan Lung Cancer Study Group, and it subsequently became the West Japan Oncology Group (WJOG) after joining gastrointestinal and breast

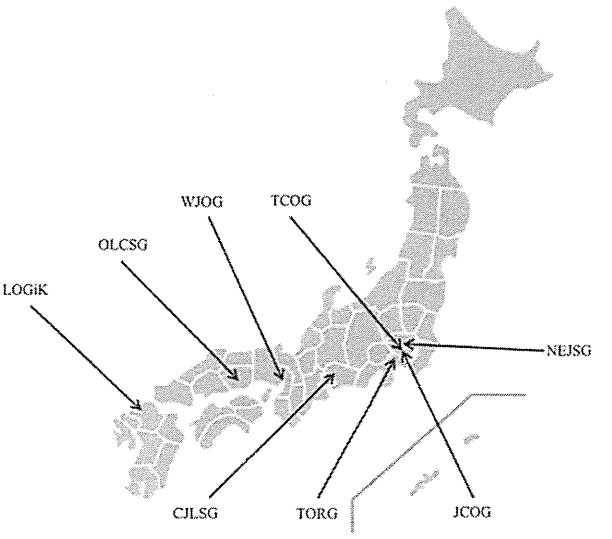

Fig. 1 – Cooperative study groups for lung cancer in Japan.

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Table 1 - Characteristics of the clinical study groups for lung cancer in Japan.

Group	Year established	Chairman	Number of facilities	Allowance for personal membership	Number of members	Data center	Financial resource	Phase III studies	References
JCOG	1990	Yuichiro Ohe	38	+	4600	+	A	+	[3,4]
WJOG	1992	Yoichi Nakanishi	187	+	1000	+	A, C, D, E	+	[1,5,6]
OLCSG	1995	Katsuyuki Kiura	20	+	110	–	D	+	[7]
TCOG	2001	Minoru Kurihara	37	+	77	–	C, D, E	+	[8,9]
CJLSG	2003	Hiroshi Saito	30	+	100	–	A, B, C, D	–	[10–12]
TORG	2004	Koshiro Watanabe	52	+	90	+	C, D	–	[13–16]
LOGiK	2004	Hiroshi Semba	89	+	322	–	F	–	[17,18]
NEJSG	2006	Toshihiro Nukiwa	108	+	20	–	A, C, D	+	[19–21]

A: National grant, B: Other grant, C: Donation, D: Membership fee, E: Consigned research fund, F: Clinical Research Support Center Kyushu.
Japan Clinical Oncology Group, JCOG; West Japan Oncology Group, WJOG; Okayama Lung Cancer Study Group, OLCSG; Tokyo Cooperative Oncology Group, TCOG; Central Japan Lung Study Group, CJLSG; Thoracic Oncology Research Group, TORG; Lung Oncology Group in Kyushu, LOGiK; North East Japan Study Group, NEJSG.

cancer groups in the late 2000s. Hiroshi Ariyoshi, the original chair of WJTOG, was succeeded in 2004 by Masahiro Fukuoka, who in turn was succeeded in 2009 by Yoichi Nakanishi. The missions of WJOG are to carry out clinical trials and to educate oncologists and patients with regard to appropriate cancer treatments and clinical studies. The data center was initially set up in 1998 at Kinki University Faculty of Medicine under the direction of Kazuhiko Nakagawa, and it subsequently relocated to Namba, Osaka, in 2004 (Fig. 1). At present, the WJOG Data Center is staffed by eight data managers led by Shinichiro Nakamura and ensures the adequacy, integrity, and quality of the data for patients enrolled in clinical trials. A total of 187 institutions across the country participate in clinical lung cancer research performed by WJOG.

WJTOG performed a multicenter, randomized, open-label, phase III trial (WJTOG3405) of first-line treatment with gefitinib versus cisplatin plus docetaxel in patients with advanced non-small-cell lung cancer (NSCLC) positive for activating mutations of the epidermal growth factor receptor (EGFR) gene [5]. The study demonstrated the superiority of gefitinib over cisplatin plus docetaxel in terms of its primary end point of progression-free survival (PFS). This was the first published report establishing the proof of concept that molecularly targeted agents are far more effective than conventional chemotherapy when administered to the appropriate genetically defined patient population. WJOG is currently conducting a phase III trial for patients with completely resected *EGFR* mutation-positive NSCLC of p-stage II or III. In this trial (WJOG6410L), patients are randomized to receive gefitinib (250 mg/day, 2 years) or cisplatin plus vinorelbine (four cycles), and the primary end point is disease-free survival.

WJOG also has two ongoing phase III trials of continuation maintenance therapy for advanced NSCLC. In WJOG5610L, patients with advanced nonsquamous NSCLC negative for *EGFR* mutations are initially treated with the combination of pemetrexed, carboplatin, and bevacizumab (Fig. 2B). Those individuals who complete four cycles of this treatment without disease progression are then randomized to receive bevacizumab alone or bevacizumab plus pemetrexed, with the goal of identifying an optimal maintenance regimen that improves OS. WJOG recently completed a multicenter randomized phase III study comparing carboplatin plus S-1 with carboplatin plus paclitaxel as a first-line treatment in patients with advanced NSCLC [1]. The primary objective of this Lung Cancer Evaluation of TS-1 (LETS) study—determination of the non-inferiority of carboplatin and S-1 compared with carboplatin and paclitaxel in terms of OS—was met. On the basis of the trial results, the Japanese guidelines for lung cancer treatment were updated to include carboplatin plus S-1 as one of the standard platinum-based regimens for first-line treatment of advanced NSCLC. Subsequent survival analysis according to histological subtype of NSCLC revealed that carboplatin plus S-1 showed a tendency to improve OS, with a 3.4-month increase in median OS compared with carboplatin plus paclitaxel (14.0 months versus 10.6 months; hazard ratio of 0.713 and 95% confidence interval of 0.476–1.068), for patients with squamous NSCLC [6]. This outcome is of particular interest because of the limited therapeutic options available for this patient population compared with patients with nonsquamous cell carcinoma. On the basis of

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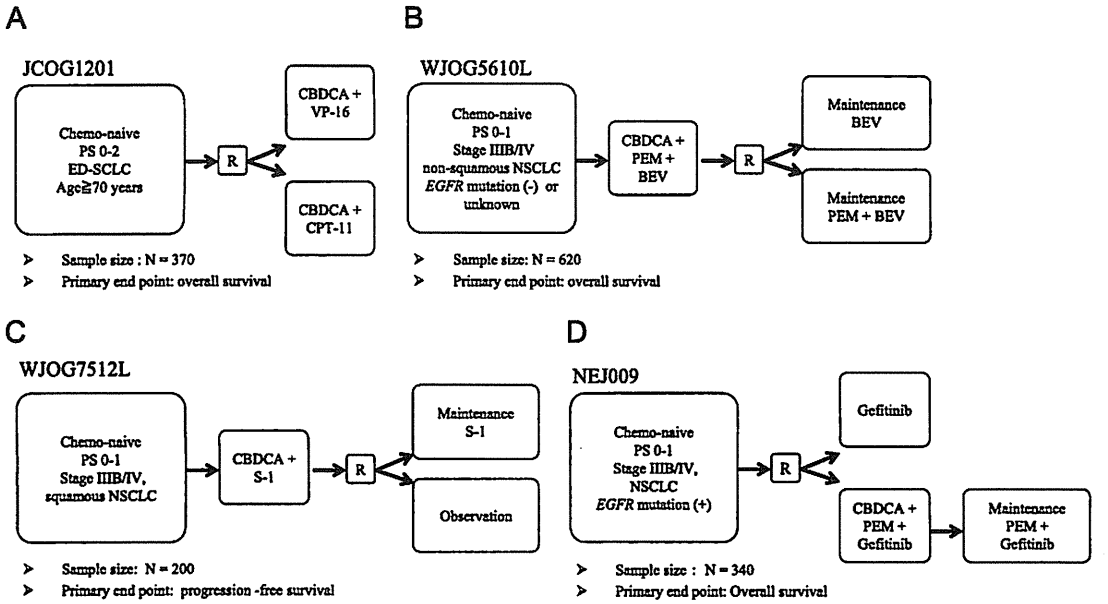

Fig. 2 – Ongoing phase III trials for advanced lung cancer in Japan. (A) JCOG1201. (B) WJOG5610L. (C) WJOG7512L. (D) NEJ009. Abbreviations: PS, performance status; R, randomization; CBDCA, carboplatin; VP-16, etoposide; CPT-11, irinotecan; PEM, pemetrexed; BEV, bevacizumab.

these results, WJOG is now conducting a randomized phase III trial for squamous NSCLC (WJOG7512L) (Fig. 2C), in which patients treated with four cycles of carboplatin plus S-1 are randomized to receive single-agent S-1 maintenance therapy or observation. Depending on the outcome, this would be the first study to establish the benefit of maintenance therapy for patients with squamous NSCLC.

Collaboration with JCOG is also an important activity of WJOG. JCOG1210/WJOG7813L, a randomized phase III trial comparing single-agent docetaxel with pemetrexed plus carboplatin followed by pemetrexed maintenance for elderly (≥75 years) individuals with nonsquamous NSCLC, is ongoing (Fig. 3A).

2.3. *Okayama Lung Cancer Study Group*

The Okayama Lung Cancer Study Group (OLCSG) was founded in 1995 to conduct multi-institutional clinical trials and now consists of 20 institutions in the Chugoku and Shikoku districts affiliated with the former Second Department of Internal Medicine at Okayama University Medical School (Table 1). During the last two decades, the group has published more than 20 research studies, some of which have been included in meta-analyses of prophylactic cranial irradiation in patients with SCLC and of thoracic irradiation and chemotherapy in those with limited disease SCLC. More recently, OLCSG performed a phase III trial of cisplatin, docetaxel, and concurrent thoracic irradiation in patients with locally advanced NSCLC (OLCSG 0007), the results of which informed the Japanese guidelines for the treatment of NSCLC [7]. The data for OLCSG 0007 were managed at Okayama University and Aichi Cancer Center Research Institute, whereas the statistical analysis was performed at the latter institution. OLCSG has not outsourced data management to an independent external data center, but it is now planning to do so for better quality assurance.

Over the last decade, substantial progress has been made in the development of genotype-based targeted therapies for advanced NSCLC. The discovery of somatic mutations in the tyrosine kinase domain of the EGFR and of the association of such mutations with a high response rate to EGFR tyrosine kinase inhibitors (EGFR-TKIs) such as gefitinib and erlotinib has had a profound impact on the treatment of metastatic NSCLC. This molecular basis for therapy selection may also be applicable to patients with locally advanced NSCLC, for whom targeted therapies remained to be established. OLCSG and LOGiK (see Section 2.7) are now conducting an intergroup trial to evaluate induction therapy with single-agent gefitinib followed by cisplatin, docetaxel, and concurrent thoracic irradiation for patients with EGFR mutation-positive locally advanced NSCLC (Fig. 3B).

2.4. *Tokyo Cooperative Oncology Group (TCOG)*

The Tokyo Cooperative Oncology Group (TCOG) was established in 1972 for the purpose of performing multi-institutional cooperative clinical trials of treatments for inoperable cancers of various organs, with Kiyoji Kimura (a former vice director of National Cancer Center Hospital) as its first organizer (Table 1). Its early research results with N1-(2-tetrahydrofuryl)-5-fluorouracil (FT-207) in 1974 and with 5-fluorouracil (5-FU) in 1975 led to the approval of these agents for clinical use in Japan. On the basis of its active clinical studies and continuing educational activities including monthly medical conferences and annual summer seminars, the group was certified as a nonprofit organization (NPO) by the Tokyo Metropolitan Government in 2001. The first leaders included Hisanobu Niitani as president and five other directors.

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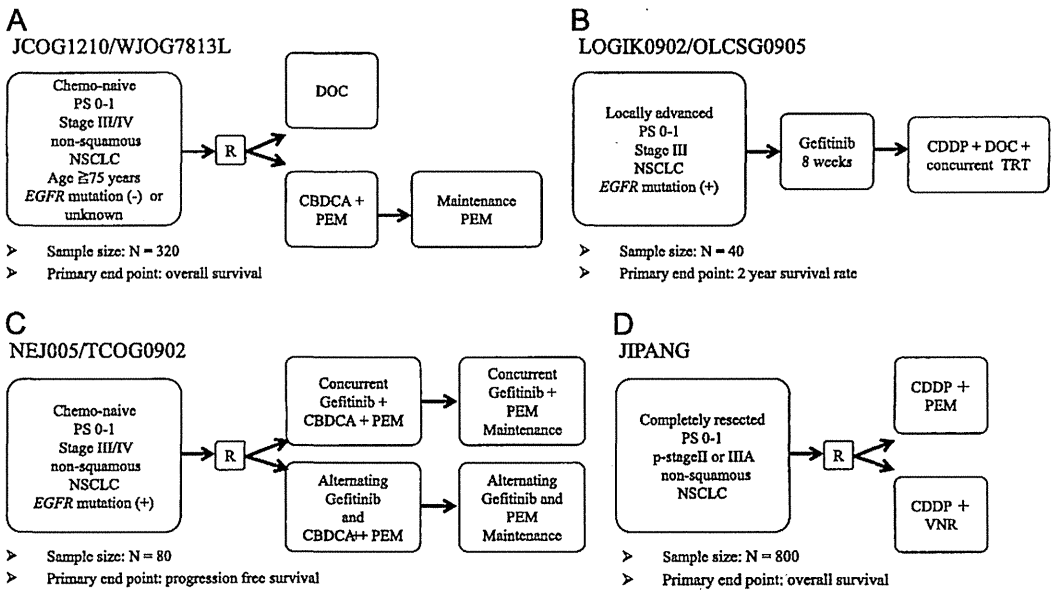

Fig. 3 – Recent intergroup trials for lung cancer in Japan. (A) JCOG1210/WJOG7813L. (B) LOGIK0902/OLCSG0905. (C) NEJ005/TCOG0902. (D) JIPANG. Abbreviations: PS, performance status; R, randomization; DOC, docetaxel; CBDCA, carboplatin; PEM, pemetrexed; TRT, thoracic radiotherapy; p-stage, pathological stage; CDDP, cisplatin; VNR, vinorelbine.

TCOG now consists of 37 institutions and is currently conducting clinical trials mostly in thoracic and gastrointestinal oncology. It has a clinical trial registration center and six committees for academic planning, clinical trial planning, clinical trial evaluation, overall trial monitoring, data and safety monitoring, and statistical analysis. For phase I and II studies, data management is carried out by the clinical trial registration center, and statistical considerations and analysis are the responsibility of the principal investigators with voluntary consultation of the statistical analysis committee. Because of a shortage of human resources, however, data management and statistical analysis for phase III studies are largely outsourced. TCOG has held monthly conferences for the past 33 years with ~70 participants at each meeting and annual summer seminars for the past 14 years with ~500 multidisciplinary team professionals in attendance. It has published >30 research articles on clinical trials in Japanese or English, which were accompanied by presentations at various medical conferences including those of the Japan Society of Clinical Oncology, American Society of Clinical Oncology, and European Society for Medical Oncology [8,9]. Since 2006, TCOG has also cooperated with the North East Japan Study Group (NEJSG, see Section 2.8) on lung cancer trials, with more than seven trials to date (Fig. 3C).

2.5. *Central Japan Lung Study Group*

The Central Japan Lung Study Group (CJLSG) was established in 2003 as an NPO to promote the prevention and diagnosis of, the performance of clinical trials for, and education about respiratory diseases (Table 1). The first chairperson of the group was Kaoru Shimokata. CJLSG consists of 30 facilities located mainly in central Japan, and most of its members are medical doctors who work in regional or university hospitals. CJLSG is supported by member fees and donations, and it holds educational seminars on several aspects of respiratory medicine including clinical trials, bronchoscopy, and clinical statistics for young doctors.

CJLSG has published the results of several clinical trials in international scientific journals [10–12] and is currently conducting 14 trials related to pneumonia, molecular biology, supportive care, and chemotherapy in lung cancer patients. CJLSG is now planning PREDICT1, a prospective observational survey of predictors of responses based on the analysis of blood samples for chemotherapy with carboplatin plus pemetrexed in patients with nonsquamous NSCLC.

2.6. *Thoracic Oncology Research Group*

The Thoracic Oncology Research Group (TORG) was founded as an NPO in 2004 (Table 1). It currently consists of 52 collaborative institutions, and it is chaired by Koshiro Watanabe; the TORG has published four studies to date [13–16]. The TORG data center promotes quality control of clinical trials by contributing to patient registration, data collection and management, and central monitoring. The monitoring reports are submitted to and reviewed by an independent monitoring committee and study investigators on a semiannual basis. Interim analysis is performed when a preplanned number of patients have been enrolled during the study period. In addition, TORG has taken appropriate advice from several biostatisticians when conducting new clinical trials or analyzing trial data.

TORG has seven and 11 trials in accrual and follow-up phases, respectively. Although TORG has no experience in conducting large-scale randomized trials, three studies have registered 100 or more patients. The policies of TORG are to initiate

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well-designed and timely clinical trials as soon as feasible and to finish the trials adequately and as rapidly as possible.

2.7. *Lung Oncology Group in Kyushu*

The Lung Oncology Group in Kyushu (LOGiK) was established in 2004 as a voluntary cooperative group to perform multicenter clinical trials for thoracic malignant diseases, mainly lung cancer, and is headquartered at the Research Institute for Diseases of the Chest at Kyushu University (Fig. 1, Table 1). It comprises a large network of medical oncologists, thoracic surgeons and physicians, radiologists, pathologists, and biostatisticians at public and private institutions across the country, although most LOGiK member institutions are located in Kyushu districts. As of 10 January 2014, the group had 322 members affiliated with 89 medical institutions. The operational policy of the group is decided at regularly held board meetings. Plans for clinical trials can be proposed by any member of the group and are discussed in detail by the protocol committee and, as necessary, by the pathology committee or radiology committee. The activities of the group are funded and supported by the Clinical Research Support Center Kyushu (CReS Kyushu), whose services include various aspects of clinical trials such as registration and assignment of patients, trial monitoring, collection of case report forms, and data cleaning. The biostatistics committee at CReS Kyushu meets regularly with contact biostatisticians to analyze clinical trial data or provide advice for trial planning. LOGiK has conducted various phase II and feasibility trials for lung cancer [17,18] and currently has 13 active clinical trials.

2.8. *North East Japan Study Group*

In January 2006, 35 institutions belonging to four Japanese regional groups in Hokkaido, Tohoku, Saitama, and Tokyo joined together to conduct a phase II study (NEJ001) and a phase III study (NEJ002) of patients with EGFR mutation-positive NSCLC screened with the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method developed by Koichi Hagiwara (Table 1). This North East Japan Study Group (NEJSG) was established with the assistance of Hisanobu Niitani, who was the chairperson of TCOG. Together, NEJ001 and NEJ002 showed that EGFR-TKI treatment conferred long-term PFS and a better quality of life and thereby helped to open the door to personalized medicine in the field of lung cancer [19–21]. NEJSG became an NPO in December 2010 for the performance of clinical studies in which biological investigation is important. The aim of NEJSG is to develop, conduct, coordinate, and stimulate translational and clinical research to improve the management of lung cancer and related problems and to increase the survival and quality of life of affected individuals. At present, 108 institutions located in the original four regions as well as in two additional regions (Tochigi and Niigata) are active in NEJSG studies.

NEJSG is currently conducting a randomized phase III study comparing single-agent gefitinib with the combination of carboplatin-pemetrexed and gefitinib followed by continuation maintenance therapy with pemetrexed and gefitinib in patients with advanced nonsquamous NSCLC positive for activating mutations of EGFR (Fig. 2D). The primary end point of this study is the OS.

3. Conclusions and future perspectives

Although only eight cooperative study groups in Japan are reviewed here because of space limitations, several other Japanese groups are also conducting clinical trials for lung cancer. The establishment of multiple study groups to perform clinical trials for this single disease is indicative of the high priority given to the development of new treatment strategies for lung cancer through such trials in Japan, but it also presents several challenges. First, it may be difficult for all such groups to be associated with a data center that maintains data quality, ensures the scientific integrity of trial results, and minimizes the risk to enrolled patients. Second, the number of clinical trials that target small subsets of patients with specific driver oncogenes, specific histological subtypes of lung cancer, poor performance status, or advanced age is increasing. Overlap in such trials performed by different groups and institutional overlap among clinical trial groups do not represent optimal use of limited resources. Third, the number of groups that are able to complete phase III trials is limited to date, given the large sample size required and the complexity of data management for such trials. The division of roles in each cooperative study groups is essential to improve efficiency of clinical trials in Japan.

To overcome these challenges, Japanese cooperative groups have increased the extent of their collaboration. Indeed, several intergroup clinical trials for advanced NSCLC (including those performed by JCOG and WJOG, NEJSG and TCOG, and OLCSG and LOGiK) are now ongoing (Fig. 3A–C). In addition, seven Japanese cooperative groups are working together to conduct a large randomized phase III trial comparing cisplatin plus vinorelbine with cisplatin plus pemetrexed in patients with completely resected nonsquamous NSCLC of p-stage II or III (Fig. 3D). The primary end point of this study is the OS, and a total of 800 patients will be enrolled. The study, named JIPANG, was designed to test a new application of pemetrexed to adjuvant chemotherapy in Japan. Smooth implementation of such intergroup studies requires abundant funds; however, Japan does not seem to have an effective national funding system for cooperative study groups. In United State of America, the National Cancer Institute has provided enormous funds for the consolidation of several cooperative groups and the merging of groups focused on a single disease site or modality with multidisciplinary groups.

Although institutional barriers to the performance of such large intergroup trials remain, further harmonization and collaboration among cooperative groups will be important in allowing Japanese investigators to generate new data that can change clinical practice and improve the clinical outcome of lung cancer patients.

Conflict of interest

Isamu Okamoto received honoraria from Pfizer Co., Eli Lilly K.K., and Taiho Pharmaceutical Co. Ltd.; Yuichiro Ohe

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received honoraria from Chugai Pharmaceutical Co. Ltd., Eli Lilly K.K., and Daiichi Sankyo Co., Ltd. and research funding from Chugai Pharmaceutical Co. Ltd., Pfizer Co., AstraZeneca K.K., and Merck Serono, Eisai; Kazuhiko Nakagawa received honoraria from Abbott Japan Co. Ltd., Eli Lilly K.K., Takeda Bio Development Center Ltd., Daiichi Sankyo Co. Ltd., AstraZeneca K.K., Kyowa Hakko Kirin Co. Ltd., and Chugai Pharmaceutical Co. Ltd., and research funding from Chugai Pharmaceutical Co. Ltd., AstraZeneca K.K., Nippon Boehringer Ingelheim Co. Ltd., and Daiichi Sankyo Co. Ltd. and subsidies from Daiichi Sankyo Co. Ltd., Taiho Pharmaceutical Co. Ltd., and Ono Pharmaceutical Co. Ltd.; Katsuyuki Kiura received honoraria from Pfizer Co., Taiho Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd, and Eli Lilly K.K., and research funding from Phizer Co., Chugai Pharmaceutical Co. Ltd., Novartis Pharmaceutical K.K., and Daiichi Sankyo Co. Ltd. and subsidies from Sanofi K.K. and Chugai Pharmaceutical Co. Ltd.; Yuichi Takiguchi received honoraria from AstraZeneca K.K, Chugai Pharmaceutical Co. Ltd., Sanofi K.K., and Titan Ltd.; Koichi Takayama received honoraria from Chugai Pharmaceutical Co. Ltd., Eli Lilly K.K., Phizer Co., and AstraZeneca K.K. and research grants from Chugai Pharmaceutical Co. Ltd., Eli Lilly K.K., Kyowa Hakko Kirin Co. Ltd., and Phizer Co.; Masahiro Tsuboi received honoraria from AstraZeneca K.K., Eli Lilly K.K., Johnson and Johnson, Chugai Pharmaceutical Co. Ltd., and Taiho Pharmaceutical Co. Ltd.; Nobuyuki Yamanoto received honoraria from Taiho Pharmaceutical Co. Ltd., Pfizer Co., Chugai Pharmaceutical Co. Ltd., AstraZeneca K.K., and Ono Pharmaceutical Co. Ltd.; Toshihiro Nukiwa received honoraria from Shionogi Pharmaceuticals and Boehringer Ingelheim Co. Ltd., research funding from AstraZeneca K.K. and Chugai Pharmaceutical Co. Ltd., and other fees from Sekisui Diagnostics; Hideo Saka received research funding from Daiichi Sankyo Co. Ltd., Ono pharmaceutical Co., AstraZeneca K.K., Novartis Pharmaceutical K.K., Eisai Co., Kyowa Hakko Kirin Co. Ltd., and Eli Lilly K.K.; Hiroaki Okamoto received research funding from Eli Lilly K.K., Chugai Pharmaceutical Co. Ltd., and Dainippon Sumitomo Pharma; the other authors have no conflict of interest.

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ORIGINAL ARTICLE

Significance of the serum carcinoembryonic antigen level during the follow-up of patients with completely resected non-small-cell lung cancer[†]

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Abstract

OBJECTIVES: The purpose of this study was to elucidate the detectability of recurrence and the prognostic significance of the serum carcinoembryonic antigen (CEA) levels in patients with completely resected non-small-cell lung cancer (NSCLC).

METHODS: Five hundred and eighteen NSCLC patients who underwent complete resection at Aichi Cancer Center between April 2001 and March 2006 were enrolled in this study. The patient characteristics were as follows: the median age was 63 years; 331 tumours were classified as pathological stage I, 88 tumours were pathological stage II and 99 tumours were pathological stage III; 140 tumours were adenocarcinomas with epidermal growth factor receptor (EGFR) mutations, 268 tumours were adenocarcinomas with EGFR wild-type mutations and 110 tumours were other NSCLCs. The patients were divided into three groups: those with a normal CEA level before and 1–3 months after surgery (N group, $n = 380$), those with an elevated CEA level before surgery and a normal CEA level 1–3 months after surgery (HN group, $n = 105$) and those with an elevated CEA level 1–3 months after surgery regardless of the preoperative CEA level (H group, $n = 33$). The correlations between the changes in the serum CEA levels and the clinical outcomes were analysed.

RESULTS: Recurrence developed in 122 patients (32%) in the N group, 49 patients (47%) in the HN group and 19 patients (58%) in the H group ($P = 0.001$). The sensitivity and specificity of an elevated serum CEA level during the follow-up period for detecting recurrence were 30 and 98% in the N group and 82 and 73% in the HN group, respectively. Twenty-seven asymptomatic recurrent tumours combined with an elevated serum CEA level were detected in the HN group. In the multivariate Cox regression analysis, the serum CEA level 1–3 months after surgery had prognostic value for overall survival.

CONCLUSIONS: In completely resected NSCLC patients, measuring the serum CEA level during the follow-up period is useful in patients in whom an elevated level normalizes after surgery, and the serum CEA level 1–3 months after surgery is considered to have prognostic significance regarding survival.

Keywords: Lung cancer • Carcinoembryonic antigen • Follow-up • Surveillance

INTRODUCTION

Non-small-cell lung cancer (NSCLC) is now the leading cause of cancer-related death worldwide. Due to cancer recurrence, the clinical outcomes of patients with NSCLC are not satisfactory, even when complete resection is performed. The purpose of surveillance following surgical resection is to detect recurrence and/or new primary lung cancer in order to apply appropriate treatment. The prognostic significance of intensive follow-up for detecting recurrence is debatable [1–3].

A certain population of NSCLC patients, first described in those with adenocarcinoma, produce carcinoembryonic antigens (CEAs) and have a high serum level at presentation. Among colon cancer patients, the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines recommend that the serum CEA level be measured during the follow-up period following surgery [4, 5]. Among NSCLC patients who undergo surgical treatment, there are currently no guidelines recommending the measurement of serum tumour markers, such as CEA, during the follow-up period to detect recurrence. Although

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