33. Jones SM, Kazlauskas A. Growth-factor-dependent mitogenesis requires two distinct phases of signalling. Nat Cell Biol 2001;3:165–72.
34. Yamamoto T, Ebisuya M, Ashida F, Okamoto K, Yonehara S, Nishida E. Continuous ERK activation downregulates antiproliferative genes throughout G_1 phase to allow cell-cycle progression. Curr Biol 2006;16:1171–82.
35. Fassett JT, Tobolt D, Nelsen CJ, Albrecht JH, Hansen LK. The role of collagen structure in mitogen stimulation of ERK, cyclin D1 expression, and G_1-S progression in rat hepatocytes. J Biol Chem 2003;278: 31691–700.
36. Smalley KS, Lioni M, Dalla Palma M, et al. Increased cyclin D1 expression can mediate BRAF inhibitor resistance in BRAF V600E-mutated melanomas. Mol Cancer Ther 2008;7:2876–83.
37. King AJ, Patrick DR, Batorsky RS, et al. Demonstration of a genetic therapeutic index for tumors expressing oncogenic BRAF by the kinase inhibitor SB-590885. Cancer Res 2006;66:11100–5.
38. Huser M, Luckett J, Chiloeches A, et al. MEK kinase activity is not necessary for Raf-1 function. EMBO J 2001;20:1940–51.
39. Mikula M, Schreiber M, Husak Z, et al. Embryonic lethality and fetal liver apoptosis in mice lacking the c-raf-1 gene. EMBO J 2001;20:1952–62.
40. Salgia R, Skarin AT. Molecular abnormalities in lung cancer. J Clin Oncol 1998;16:1207–17.
41. Montagut C, Sharma SV, Shioda T, et al. Elevated CRAF as a potential mechanism of acquired resistance to BRAF inhibition in melanoma. Cancer Res 2008;68: 4853–61.
42. Baumann B, Weber CK, Troppmair J, et al. Raf induces NF-κB by membrane shuttle kinase MEKK1, a signaling pathway critical for transformation. Proc Natl Acad Sci U S A 2000;97:4615–20.
43. Galaktionov K, Jessus C, Beach D. Raf1 interaction with Cdc25 phosphatase ties mitogenic signal transduction to cell cycle activation. Genes Dev 1995;9:1046–58.
44. Kerkhoff E, Rapp UR. Cell cycle targets of Ras/Raf signalling. Oncogene 1998;17:1457–62.
45. Hindley A, Kolch W. Extracellular signal regulated kinase (ERK)/mitogen activated protein kinase (MAPK)-independent functions of Raf kinases. J Cell Sci 2002;115: 1575–81.
46. Liu L, Cao Y, Chen C, et al. Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. Cancer Res 2006;66: 11851–8.

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

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Summary

Background Patients with non-small-cell lung cancer harbouring mutations in the epidermal growth factor receptor (*EGFR*) gene respond well to the EGFR-specific tyrosine kinase inhibitor gefitinib. However, whether gefitinib is better than standard platinum doublet chemotherapy in patients selected by EGFR mutation is uncertain.

Methods We did an open label, phase 3 study (WJTOG3405) with recruitment between March 31, 2006, and June 22, 2009, at 36 centres in Japan. 177 chemotherapy-naive patients aged 75 years or younger and diagnosed with stage IIIB/IV non-small-cell lung cancer or postoperative recurrence harbouring *EGFR* mutations (either the exon 19 deletion or L858R point mutation) were randomly assigned, using a minimisation technique, to receive either gefitinib (250 mg/day orally; n=88) or cisplatin (80 mg/m², intravenously) plus docetaxel (60 mg/m², intravenously; n=89), administered every 21 days for three to six cycles. The primary endpoint was progression-free survival. Survival analysis was done with the modified intention-to-treat population. This study is registered with UMIN (University Hospital Medical Information Network in Japan), number 000000539.

Findings Five patients were excluded (two patients were found to have thyroid and colon cancer after randomisation, one patient had an exon 18 mutation, one patient had insufficient consent, and one patient showed acute allergic reaction to docetaxel). Thus, 172 patients (86 in each group) were included in the survival analyses. The gefitinib group had significantly longer progression-free survival compared with the cisplatin plus docetaxel goup, with a median progression-free survival time of 9·2 months (95% CI 8·0–13·9) versus 6·3 months (5·8–7·8; HR 0·489, 95% CI 0·336–0·710, log-rank p<0·0001). Myelosuppression, alopecia, and fatigue were more frequent in the cisplatin plus docetaxel group, but skin toxicity, liver dysfunction, and diarrhoea were more frequent in the gefitinib group. Two patients in the gefitinib group developed interstitial lung disease (incidence 2·3%), one of whom died.

Interpretation Patients with lung cancer who are selected by EGFR mutations have longer progression-free survival if they are treated with gefitinib than if they are treated with cisplatin plus docetaxel.

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Introduction

Lung cancer is a major cause of cancer-related mortality worldwide.[1] However, current standard platinum doublet therapy seems to have reached a therapeutic plateau,[2] although it has recently been shown that patients with non-squamous histology who are treated with pemetrexed disodium have better survival than if they are treated with older drugs.[3]

Targeted therapies are actively being developed to improve efficacy in selected patient populations.[4] Small-molecule tyrosine kinase inhibitors (TKIs) that target the epidermal growth factor receptor (EGFR), such as gefitinib and erlotinib, are the first targeted drugs to enter clinical use for the treatment of lung cancer. Subgroups of patients of east-Asian origin, female sex, adenocarcinoma, and no history of smoking have been shown to be significantly associated with a favourable response to EGFR TKIs.[5,6] In 2004, researchers noted that activating mutations of the *EGFR* gene present predominantly in patients with the above-mentioned clinical characteristics, and determine sensitivity to EGFR TKIs.[7,8] *EGFR* mutations are present in the first four exons of the tyrosine kinase domain of the *EGFR* gene, and about 90% of these *EGFR* mutations are either short in-frame deletions in exon 19, or point mutations that result in a substitution of arginine for leucine at aminoacid 858 (L858R).[7–9] Subsequent retrospective and prospective trials confirmed that the response rate to gefitinib or erlotinib in patients with *EGFR* mutations is about 70–80%.[10–13] Furthermore, patients with *EGFR* mutations have a significantly longer survival than those with wild-type *EGFR* when treated

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with EGFR TKIs.[14,15] We proposed that the absence of any survival advantage conferred by gefitinib monotherapy in previous studies[16–18] is due at least in part to a lack of patient selection, and that gefitinib would confer a survival advantage compared with platinum doublet chemotherapy in a first-line setting if eligible patients were selected on the basis of *EGFR* mutation status. To address this issue, we did a phase 3 trial that compared gefitinib with cisplatin plus docetaxel in patients with an *EGFR* mutation.

Methods

Patients

This study (WJTOG 3405) was a multicentre, randomised, open-label, phase 3, trial of first-line treatment with gefitinib versus cisplatin plus docetaxel for patients with advanced or recurrent non-small-cell lung cancer (NSCLC) harbouring an activating mutation of the *EGFR* gene. We recruited patients between March 31, 2006, and June 22, 2009, at 36 centres in Japan. All centres were members of the West Japan Oncology Group (WJOG), which is a Japanese non-profit organisation for oncological clinical trials (formerly the West Japan Thoracic Oncology Group, or WJTOG).

Initially, only patients with postoperative recurrence were eligible, because these surgical specimens were expected to ensure good sample quality. However, because of the initial slow accrual, the protocol was amended on July 10, 2006, to include patients with stage IIIB/IV disease. Patients were eligible if they had histologically or cytologically confirmed NSCLC, harbouring activating *EGFR* mutations (either exon 19 deletion or L858R in exon 21), were aged 75 years or younger, had WHO performance status 0–1, had measurable or non-measurable disease according to the Response Evaluation Criteria in Solid Tumours (RECIST), and had adequate organ function. Patients with postoperative recurrence, treated with adjuvant therapy other than cisplatin plus docetaxel, were included when the interval between the end of adjuvant chemotherapy and registration exceeded 6 months for platinum-doublet

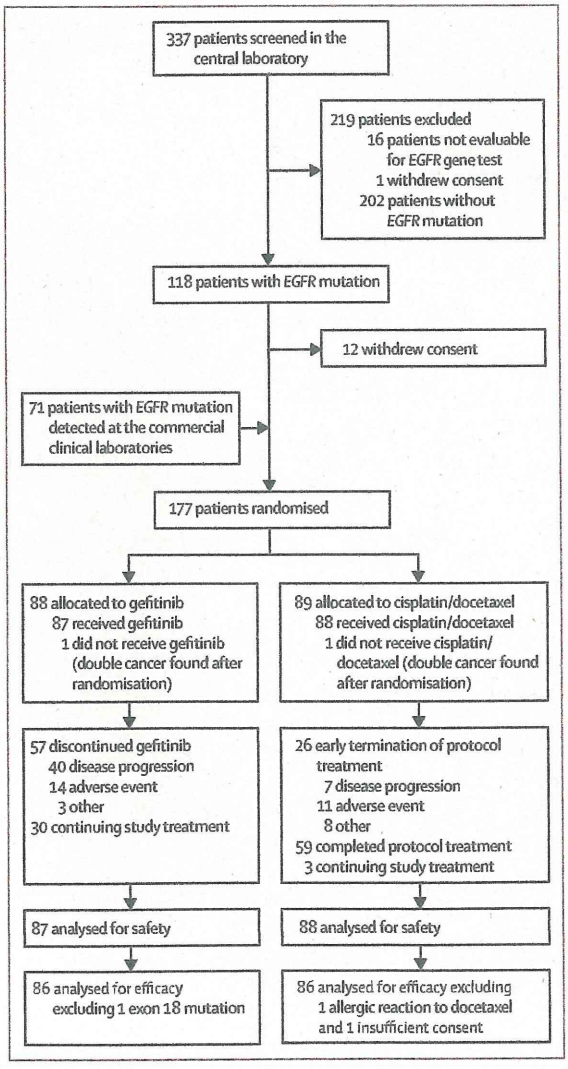

Figure 1: Trial profile

	Gefitinib (N=86)	Cisplatin plus docetaxel (N=86)
Sex		
Male	27	26
Female	59	60
Age (years; median; range)	64·0 (34–74)	64·0 (41–75)
Histological type		
Adenocarcinoma	83	84
Adenosquamous carcinoma	0	1
Squamous-cell carcinoma	1	0
Non-small-cell lung cancer; not otherwise specified	2	1
Smoking history		
Never	61	57
Former/current	25	29
Performance status		
0	56	52
1	30	34
Stage		
Postoperative recurrence	35	36
With postoperative adjuvant chemotherapy	19	23
Without postoperative adjuvant chemotherapy	16	13
IIIB	10	9
IV	41	41
EGFR mutation		
Exon 19 deletion	50	37
L858R	36	49

Table 1: Demographic and baseline characteristics of the modified intention-to-treat population

therapy and more than 1 month for oral tegafur plus uracil therapy. Patients were not eligible if they had received previous drug therapy that had targeted EGFR, had a history of interstitial lung disease, severe drug allergy, active infection or other serious disease condition, symptomatic brain metastases, poorly controlled pleural effusion, pericardial effusion or ascites necessitating drainage, active double cancer, or severe hypersensitivity to drugs containing polysolvate 80. Patients in pregnancy or lactation, or whose participation in the trial was judged to be inappropriate by the attending doctor, were not eligible. All patients provided written informed consent. Study approval was obtained from independent ethics committees at every institution. The study was undertaken in accordance with the Declaration of Helsinki.

Procedures

Patients were randomly assigned in a 1:1 ratio to receive gefitinib (250 mg/day, administered orally), or docetaxel (60 mg/m^2, administered intravenously over a 1 h period) followed by cisplatin (80 mg/m^2, administered intravenously over a 90-min period), with adequate hydration, in cycles of once every 21 days for three to six cycles.Treatment continued until progression of the disease, development of unacceptable toxic effects, a request by the patient to discontinue treatment, serious non-compliance with the protocol, or completion of three to six chemotherapy cycles. Further therapy after progression of the disease was at the physician's discretion. The primary endpoint was progression-free survival. Secondary endpoints included overall survival and response rate. Tertiary endpoints were disease control rate, safety, and mutation-type-specific survival.

Initially, patients were screened for *EGFR* mutation in a central laboratory at the Department of Molecular Diagnostics, Aichi Cancer Centre Hospital, Nagoya, Japan. The exon 19 deletion mutation was screened by fragment analysis and the L858R point mutation was screened by the Cycleave method, as described previously,[19] followed by confirmation by direct sequencing. On Feb 16, 2008, the protocol was amended to allow outsourcing of *EGFR* genetic testing from each institution to commercial clinical laboratories, either at SRL in Tokyo (direct sequencing), Mitsubishi Chemical Medience in Tokyo (peptide nucleic acid-locked nucleic acid PCR clamp[20]), or BML in Tokyo (PCR invader[21]), as this amendment would further facilitate patient accrual. The sensitivity of direct sequencing was anticipated to be less than that of other methods; however, false negativity was not a problem in this trial, since patients judged to lack EGFR mutations were not randomly allocated to a treatment.

Progression-free survival was assessed from the date of randomisation to the earliest sign of disease progression as determined by CT or MRI imaging using RECIST criteria, or death from any cause. Overall survival was assessed from the date of randomisation until death from any cause. Tumour response was assessed every 2 months

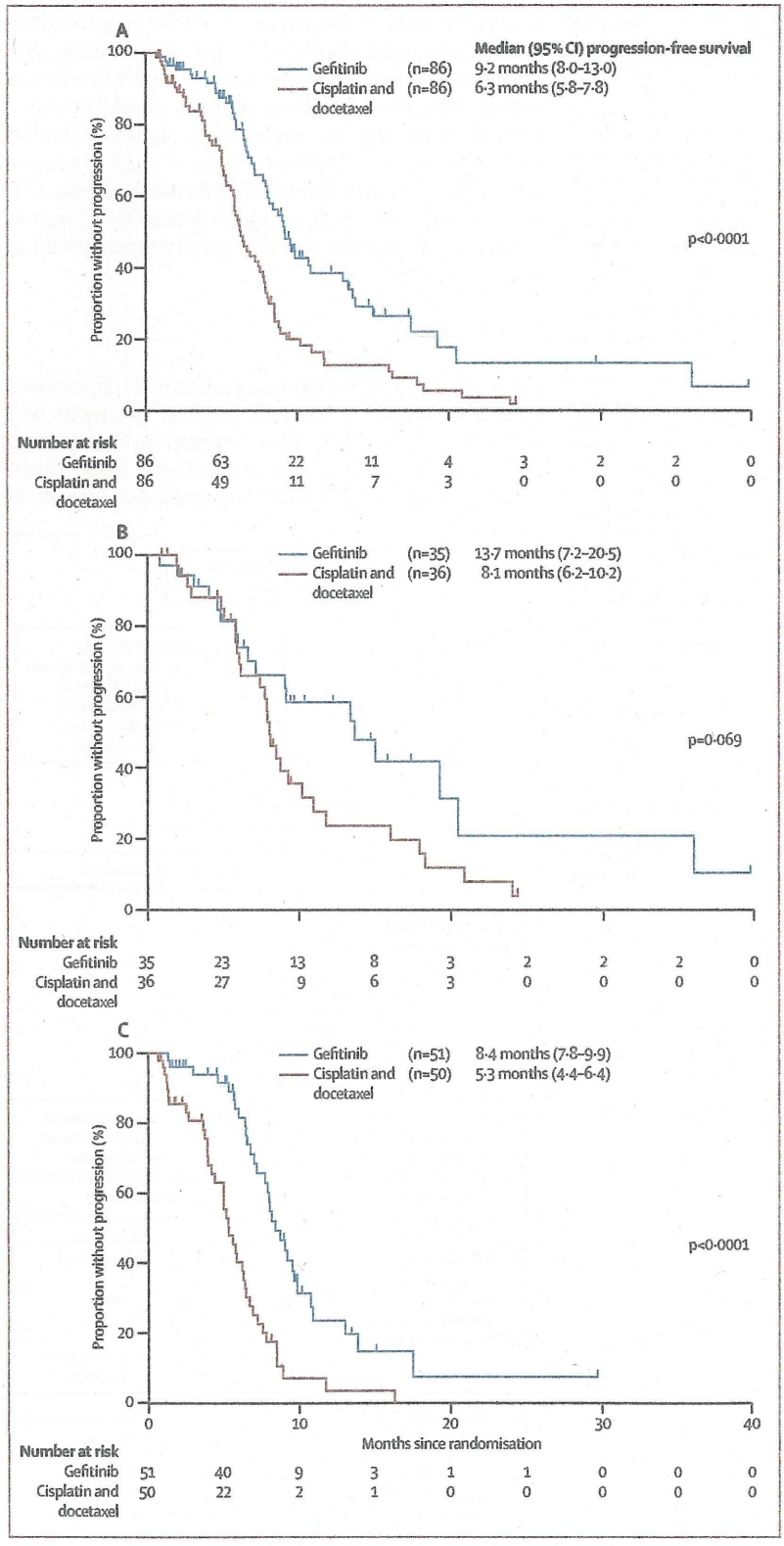

Figure 2: **Progression-free survival in the overall population (A), in patients with postoperative recurrence (B), and in patients with stage IIIB/IV disease (C)**

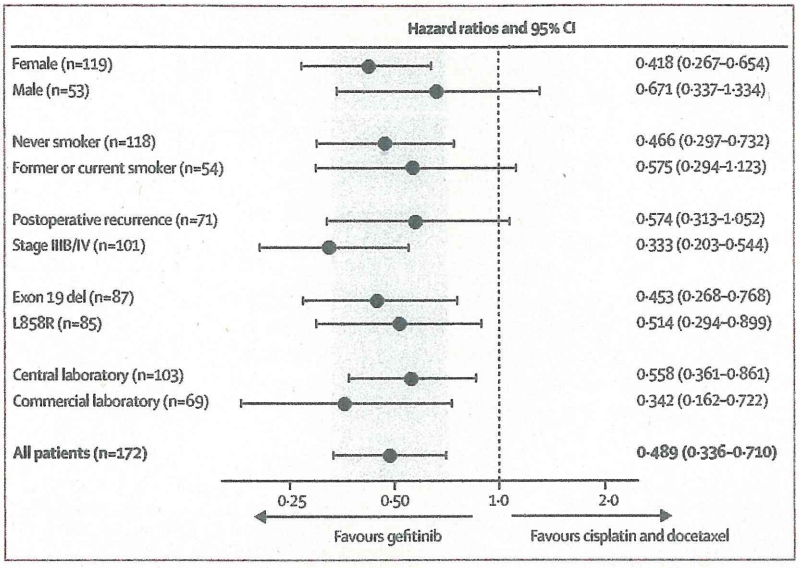

Figure 3: **Hazard ratios for progression-free survival using subgroup analysis in the overall population**
The shaded band represents the 95% CI of the hazard ratio for the overall population of patients.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Group (gefitinib/cisplatin plus docetaxel)	0·489 (0·336–0·710)	0·0002	0·258 (0·385–0·575)	<0·0001
Sex (male/female)	0·935 (0·625–1·398)	0·742	0·628 (0·361–1·092)	0·099
Age (<65 years /≥65 years)	1·091 (0·757–1·572)	0·641	1·183 (0·813–1·721)	0·380
Smoking history (never/former or current)	0·801 (0·541–1·186)	0·268	0·646 (0·378–1·105)	0·111
Stage (recurrence/IIIB–IV)	0·463 (0·220–0·976)	0·043	0·433 (0·290–0·649)	<0·0001
Mutation (exon 19 del/L858R)	1·001 (0·694–1·444)	0·996	1·135 (0·777–1·658)	0·514

Table 2: **Univariate and multivariate analysis of progression-free survival**

during the first year after randomisation, every 3 months between 12 and 18 months, and thereafter the interval of assessment was at the physician's discretion. Safety and tolerability were assessed according to National Cancer Institute Common Terminology Criteria (CTC) for Adverse Events, version 3.0. All events were confirmed via source-document verification at site visits to each participating institution by members of the WJOG data centre and the investigators.

Randomisation and masking

The investigator provided the necessary information to personnel at the WJOG data centre by fax. After an eligibility check, patients were allocated at the WJOG data centre to each treatment group using a desktop computer programmed for the minimisation method.[22] In this way, patient allocation was concealed from the investigator.

Because of the nature of treatment in each group, the study was open label. Stratification factors were: institution; postoperative adjuvant chemotherapy (presence *vs* absence); interval between surgery and recurrence (≥1 *vs* <1 year) for patients with postoperative recurrent disease; and institution; stage (IIIB *vs* IV); and sex (male *vs* female) for patients with stage IIIB/IV disease.

Statistical analysis

In previous studies the progression-free survival of patients harbouring EGFR mutations and treated with gefitinib was reported as 12·6 months,[15] compared with 6·6 months for patients harbouring EGFR mutations treated with carboplatin plus paclitaxel.[23] Assuming a progression-free survival for gefitinib and platinum doublet chemotherapy of 12·5 and 7 months, respectively, would yield a hazard ratio (HR) of 0·56. Taking this HR into consideration, 146 patients would be required to achieve 90% power to show superiority with α=0·05 (two-sided). Therefore, sample size was initially set at 200 patients. While this trial was ongoing, the results of the Iressa Pan-Asia Study (IPASS) were presented at the annual meeting of the European Society for Medical Oncology (Stockholm, Sweden, Sept 12–16, 2008), and were later published.[24] Subgroup analysis of patients with EGFR mutations using about a third of the patients showed that the HR of gefitinib compared with carboplatin plus paclitaxel for progression-free survival was 0·48. Similarly, the HR of gefitinib compared with carboplatin plus paclitaxel for progression-free survival in patients with EGFR mutations was 0·36 in the study done by the North East Japan (NEJ) 002 Gefitinib Study Group, which was presented at the annual meeting of the American Society of Clinical Oncology (Orlando, FL, USA, May 29–June 2, 2009).[25] NEJ 002 was a phase 3 trial that analysed 198 patients with EGFR mutation randomised either to gefitinib or carboplatin plus paclitaxel. 177 patients had been randomised in our trial as of June 13, 2009, and 79 events had been noted during the regular monitoring done in March, 2009. The number of events needed to detect a conservative HR of 0·48 was calculated to be 78, based on normal approximation of the logarithm of the hazard ratio under α=0·05 (two-sided) and 90% power. Therefore, further accrual of patients was considered to be futile and potentially unethical. Although interim analysis was originally planned to analyse progression-free survival, this analysis was not done. Instead, the steering committee held on June 13, 2009, proposed the amendment of the sample size and the final analyses be done using available data. This proposal was approved by the independent data and safety monitoring committee on Aug 28, 2009. The data were locked on June 30, 2009. Patient follow-up for safety and survival will continue until 1·5 years after the last patient entry, as originally described in the study protocol.

Progression-free and overall survival were analysed for the modified intention-to-treat population as defined previously.[26] They were analysed using the Kaplan-Meier method, and were compared using the log-rank test. Hazard ratios in the overall population and in patient

subsets were calculated using the Cox proportional hazards model. The χ^2 test was used to compare proportions. Differences were considered significant at a two-sided p value of 0·05 or less. All statistical analyses were done with SAS version 9.1. This study is registered with UMIN (University Hospital Medical Information Network in Japan), number 000000539.

Role of the funding source

There was no sole study sponsor for this trial. The WJOG designed and did the trial independently of any pharmaceutical company. The report was written by the corresponding author, who had unrestricted access to the study data and is responsible for the accuracy and completeness of the reported analyses. The corresponding author had final responsibility for the decision to submit for publication.

Results

118 patients were positive for EGFR mutation at the central laboratory, 106 of whom were randomly allocated a treatment together with 71 patients with EGFR mutations who were tested at the commercial laboratories, giving a modified intention-to-treat population of 172 patients (figure 1). Baseline characteristics were well balanced between the two treatment groups (table 1), with the exception that the gefitinib group had an excess of exon 19 deletion mutations (50 of 86; 58·1%) compared with the cisplatin plus docetaxel group (37 of 86; 43·0%). Most of the patients had adenocarcinoma. 71 of 172 (41·3%) patients had postoperative recurrent disease, and 54 of 172 (31·4%) of the patients had a history of smoking. At the data collection cut-off time, the median follow-up was 81 days (range 74–1253 days), the median exposure to gefitinib was 165 days (range 22–1100 days), and the median number of cycles of cisplatin plus docetaxel chemotherapy was four, or 64 days (range one to six cycles, or 1–106 days).

Median progression-free survival was 9·2 months (95% CI 8·0–13·9) in the gefitinib group and 6·3 months (5·8–7·8) in the cisplatin plus docetaxel group (p<0·0001; figure 2A). Gefitinib treatment resulted in significantly longer progression-free survival than cisplatin plus docetaxel (HR 0·489; 95% CI 0·336–0·710; p<0·0001). Progression-free survival can be affected by the schedule of clinic visits and the interpretation of evidence of disease progression. We were able to confirm that the time schedule for clinic visits was almost the same in the two treatment groups (data not shown). In our trial, 71 patients had postoperative recurrent disease, and the remaining 101 patients had stage IIIB/IV disease. In both patient subsets, progression-free survival in the gefitinib group was longer than that in the cisplatin plus docetaxel group (figure 2B, 2C), although this was not a pre-specified analysis and was non-significant for those patients with postoperative recurrence. We noted that curves for each treatment group in the postoperative recurrence subgroup (figure 2B) overlapped during the first 6 months, while the separation was clear during this time in the stage IIIB/IV group (figure 2C).

Patients treated with gefitinib had better progression-free survival than patients treated with cisplatin plus docetaxel in all subgroup analyses (figure 3). Additionally, gefitinib was better than cisplatin plus docetaxel, irrespective of where EGFR genetic testing was done. Exploratory analyses for progression-free survival showed that, in addition to the treatment group, patients with postoperative recurrent disease had a significantly better prognosis than those with stage IIIB/IV disease (table 2). We did a pre-planned comparison of exon 19 deletion with L858R in each treatment group. As shown in figure 4, mutation type was not prognostic. Therefore,

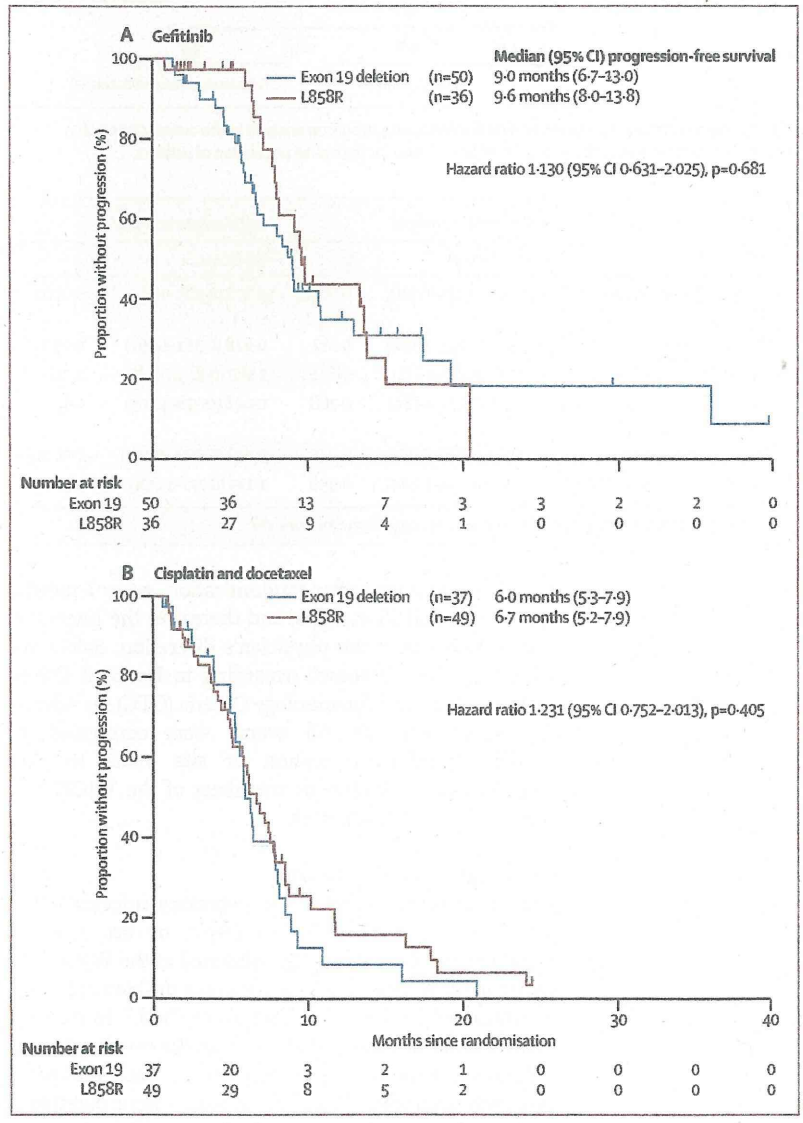

Figure 4: **Progression-free survival in (A) the gefitinib group and (B) the cisplatin plus docetaxel group according to type of the EGFR mutation**

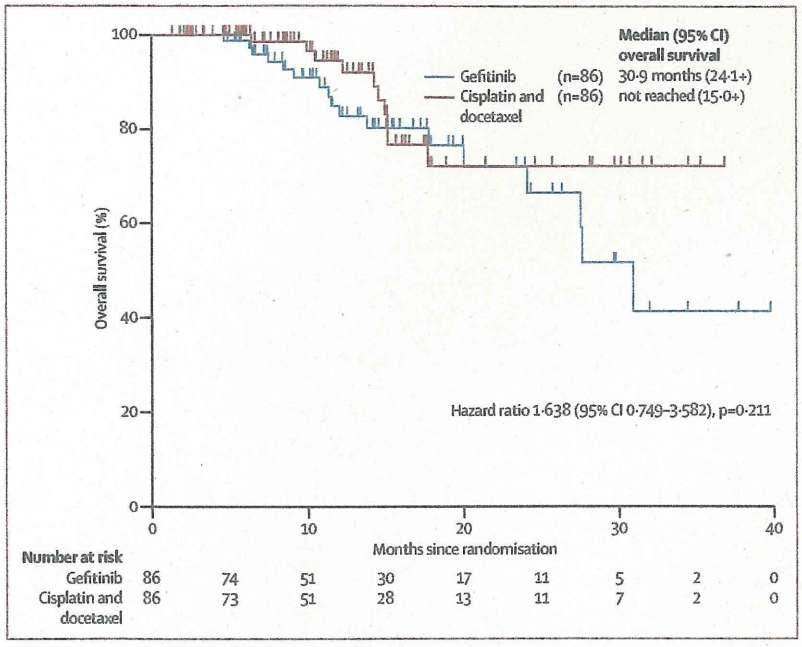

Figure 5: **Overall survival in the overall population**

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	Gefitinib (n=87)		Cisplatin plus docetaxel (n=88)	
	All	CTC grade ≥3	All	CTC grade ≥3
Non-haematological toxicity				
Rash*	74	2	7	0
AST*	61	14	17	1
ALT*	61	24	35	2
Dry skin*	47	0	3	0
Diarrhoea	47	1	35	0
Fatigue*	34	2	73	2
Paronychia*	28	1	1	0
Stomatitis	19	0	13	0
Nausea*	15	1	83	3
Constipation*	14	0	39	0
Alopecia*	8	0	67	0
Sensory disturbance*	7	1	23	0
Haematological toxicity				
Leucocytopenia*	13	0	82	43
Thrombocytopenia*	12	0	29	0
Neutropenia*	7	0	81	74
Anaemia*	33	0	79	15

ALT=alanine aminotransferase. AST=aspartate aminotransferase. CTC=National Cancer Institute Common Terminology Criteria. *p<0·001.

Table 3: **Adverse events occurring in more than 10% of either of the treatment groups listed according to incidence in the gefitinib group**

imbalance of mutation types was not likely to affect the interpretation of the overall results.

The objective response rate in the overall population with measurable disease (n=117) was 62·1% (36 of 58 patients) in the gefitinib group and 32·2% (19 of 59 patients) in the cisplatin plus docetaxel group (p<0·0001). The difference was significant (29·9%, 95% CI 12·6–47·1%; p<0·0001). The disease control rate was also higher in the gefitinib group (54/58, 93·1%) than in the cisplatin plus docetaxel group (46/59, 78·0%; difference in disease control rate 15·1%, 95% CI 2·7–27·6, p=0·020; webappendix). Because of frequent and detailed postoperative follow-up, which is standard practice in Japan, only 28 of 71 patients were found to have recurrent disease that met criteria for RECIST—ie, greater than 1 cm in the largest diameter. At the data cut-off, only 27 patients (15·7%) had died. Therefore, data for overall survival were immature, with follow-up still ongoing; 17 events (deaths) in the gefitinib group versus 10 events in the chemotherapy group—with an HR for gefitinib of 1·638 (95% CI, 0·75–3·58; figure 5). 51 patients in the chemotherapy group received an EGFR-TKI after they completed the study; 17 patients in the gefitinib group received post-protocol platinum doublet chemotherapy.

Adverse events occurring in more than 10% of either of the treatment groups are listed (table 3). The most common adverse event in the gefitinib group was skin rash followed by liver dysfunction, dry skin, and diarrhoea. However, adverse events with CTC grade 3 or more were infrequent, with the exception of liver dysfunction. By contrast, the most common adverse events in the cisplatin plus docetaxel group, which occurred in more than half of patients, were nausea, myelosuppression, fatigue, and alopecia.

Other potentially treatment-related toxicities included allergic reaction (one in gefitinib group, four in cisplatin plus docetaxel group) and oedema (one in gefitinib group, seven in the cisplatin plus docetaxel group). Two patients in the gefitinib group developed interstitial lung disease. There was one treatment-related death in the gefitinib group due to interstitial lung disease; there were no deaths in the cisplatin plus docetaxel group. There were no other serious adverse events.

Discussion

Our results show that first-line treatment with gefitinib conferred longer progression-free survival than treatment with cisplatin plus docetaxel in a molecularly defined (ie, EGFR mutation positive) group of patients with NSCLC.

In the IPASS study for patients with lung adenocarcinoma with no or former light smoking history, the progression-free survival of patients treated with gefitinib was significantly longer.[25] However, the curves crossed at the 6-month timepoint (initially chemotherapy was better, while gefitinib was better later). Molecular analysis for about a third of the patients suggested that the benefit of gefitinib was limited to patients with EGFR mutations with an HR of 0·48 (95% CI 0·36–0·64) and that gefitinib treatment was detrimental for patients without mutations (HR 2·85).[25] This result might seem similar to ours; however, the primary objective of the IPASS study was to assess gefitinib treatment in clinically selected patients,

Patient group		N	Median progression-free survival (months)			Median overall survival (months)	
			Gefitinib	Chemotherapy	HR (95% CI)	Gefitinib	Chemotherapy
Non-randomised pooled analysis							
I-CAMP[11]	Japanese, *EGFR* mutation	148	10·7	6·0	0·35 (0·23–0·52)	27·7	25·7
Subset analyses of the phase 3 trials for patients selected according to clinical backgrounds							
IPASS[25]	East Asian, light-non-smoker, adenocarcinoma	261	9·5	6·3	0·48 (0·36–0·64)	~20	~20
First SIGNAL[33]	Korean, non-smoker, adenocarcinoma	42	8·4	6·7	0·61 (0·31–1·22)	30·6	26·5
Phase 3 trials of patients selected according to *EGFR* mutation status							
NEJ 002[26]	Japanese, *EGFR* mutation	194	10·4	5·5	0·357(0·252–0·507)	28·0	23·6
WJTOG3405	Japanese, *EGFR* mutation	172	9·2	6·3	0·489 (0·336–0·710)	..	..

Table 4: Recent clinical trials assessing EGFR mutations as predictors of efficacy of gefitinib compared with chemotherapy

and not in molecularly selected patients, as was the case in our trial. In this context, a HR of 0·36 (95% CI 0·25–0·51)[26] for gefitinib compared with carboplatin plus paclitaxel in patients selected by EGFR mutation is highly relevant. Furthermore, our pooled analyses based on individual patient data from seven Japanese phase 2 studies that assessed prospectively the efficacy of gefitinib for patients with EGFR mutations (I-CAMP study)[11] and the pooled analysis of 1006 patients enrolled in a phase 3 trial of gefitinib[27] also showed similar progression-free survival of about 10 months for patients harbouring an EGFR mutation who were treated with gefitinb, while the median progression-free survival of patients treated with chemotherapy was 6·0 months (table 4).[11] These results strongly suggest that the presence of EGFR mutations, and not the clinical background of patients, determines clinical efficacy, and this knowledge should lead to molecularly based, personalised treatment of lung cancer.

Since the median duration of each treatment was quite different (165 days for gefitinib compared with 64 days for chemotherapy), one interpretation might be that a maintenance effect of gefitinib therapy contributed to the positive progression-free survival outcome, at least in part. Indeed, the progression-free survival curves of both groups in IPASS were initially similar, and then separate at about the time that chemotherapy stops. However, this was not the case in our trial, especially in patients with stage IIIB/IV disease. Furthermore, the SATURN[28] and the FAST-ACT[29] trials that tested maintenance erlotinib after chemotherapy showed that progression-free survival (both trials) and overall survival (SATURN) was prolonged. The benefit was much greater in patients with an *EGFR* mutation than in those without it in the SATURN trial.[28]

According to analyses of five US and European clinical trials that assessed first-line TKI treatment,[12] patients with the exon 19 deletion have a significantly longer progression-free and overall survival than patients with L858R (30·8 *vs* 14·8 months; p<0·0001). A similar trend was shown in a recent Spanish study.[13] In IPASS, the HR for progression-free survival for gefitinib versus chemotherapy was 0·38 (95% CI 0·25–0·56) in the subgroup of patients with exon 19 deletions, and 0·55 (95% CI 0·35–0·87) in the L858R mutation subgroup, although a direct comparison between exon 19 deletion and L858R in the gefitinib group was not done.[30] However, recent Japanese trials, including I-CAMP[11] and this study, did not detect any difference. The reason for this discrepancy is not clear, although it might be attributable to ethnic differences or difference of EGFR-TKI used between study populations.

Two patients in the gefitinib group (2·3%) developed interstitial lung disease, one of whom died. This incidence was low compared with previous Japanese reports of 4·0% (59/1482)[31] and 3·5% (70/1976).[32] Selecting patients according to EGFR mutation status is expected to reduce the risk of interstitial lung disease, because risk factors for interstitial lung disease include smoking, male sex, and squamous histology, all of which are negative predictors of the presence of EGFR mutations.[31,32]

Our study indicates that EGFR genetic testing is feasible and should be done when possible. Although patients without EGFR mutations were not included in our study, potential harm of first-line gefitinib therapy compared with chemotherapy for patients without EGFR mutation shown in the IPASS[25] and the First-SIGNAL[33] study indicate the necessity of patient selection by EGFR mutation.

Clinical background might help identify patients who have a higher chance of carrying EGFR mutations. However, it should be noted that in a previous study,[9] eight of 37 (22%) patients with lung adenocarcinoma with a history of heavy smoking (>50 pack-years) harboured EGFR mutations.[9]

In conclusion, gefitinib significantly prolonged the progression-free survival of patients with NSCLC who carry EGFR mutations compared with cisplatin plus docetaxel. It is not yet known whether the prolonged progression-free survival conferred by gefitinib will translate into prolonged overall survival; we will continue to carefully follow-up our patients to determine its long-term effects. Considering the efficacy and toxicity of gefitinib, it is a reasonable option for the first-line treatment of patients with activating EGFR mutations.

Contributors

TM, SM, SN, TS, MS, NK, and KN were involved in the conception and design of the study. KN and MF supervised the study. TM, IO, TS, MS, HT, TH, KA, NK, MT, HY, KS, SK, ES, HS, and ST were involved in the

provision of study material, patients, and data acquisition. TM, SM, YY, SN, IO, JT, TH, NK, MT, HY, KS, ES, HS, ST, and KN were involved in data analysis and interpretation. SM was in charge of the statistical design of the study. YY was in charge of *EGFR* gene testing at the central laboratory. All authors were involved in writing the report and approved the final version.

Conflicts of interest

TM has received lecture fees from AstraZeneca, Chugai, and Boehringer-Ingelheim. SN has received honoraria from AstraZeneca and Sanofi-Aventis. MS has received honoraria from AstraZeneca. HT has received honoraria from AstraZeneca and Sanofi-Aventis. ST has received honoraria from AstraZeneca and Chugai. KN has received lecture fees from AstraZeneca, Chugai, and Boehringer-Ingelheim. MF has received lecture fees from AstraZeneca, Chugai, and Boehringer-Ingelheim. All other authors declared that they have no conflicts of interest.

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References

1 Jemal A, Siegel R, Ward E, jet al. Cancer statistics, 2009. *CA Cancer J Clin* 2009; **59:** 225–49.

2 Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002; **346:** 92–98.

3 Scagliotti G, Hanna N, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two phase III studies. *Oncologist* 2009; **14:** 253–63.

4 Herbst RS, Heymach JV, Lippman SM. Lung cancer. *N Engl J Med* 2008; **359:** 1367–80.

5 Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2003; **21:** 2237–46.

6 Kris MG, Natale RB, Herbst RS, et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. *JAMA* 2003; **290:** 2149–58.

7 Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004; **350:** 2129–39.

8 Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004; **304:** 1497–500.

9 Kosaka T, Yatabe Y, Endoh H, Kuwano H, Takahashi T, Mitsudomi T. Mutations of the epidermal growth factor receptor gene in lung cancer: biological and clinical implications. *Cancer Res* 2004; **64:** 8919–23.

10 Tamura K, Okamoto I, Kashii T, et al. Multicentre prospective phase II trial of gefitinib for advanced non-small cell lung cancer with epidermal growth factor receptor mutations: results of the West Japan Thoracic Oncology Group trial (WJTOG0403). *Br J Cancer* 2008; **98:** 907–14.

11 Morita S, Okamoto I, Kobayashi K, et al. Combined survival analysis of prospective clinical trials of gefitinib for non-small cell lung cancer with EGFR mutations. *Clin Cancer Res* 2009; **15:** 4493–98.

12 Jackman DM, Miller VA, Cioffredi LA, et al. Impact of epidermal growth factor receptor and KRAS mutations on clinical outcomes in previously untreated non-small cell lung cancer patients: results of an online tumor registry of clinical trials. *Clin Cancer Res* 2009; **15:** 5267–73.

13 Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. *N Engl J Med* 2009; **361:** 958–67.

14 Mitsudomi T, Kosaka T, Endoh H, et al. Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non-small-cell lung cancer with postoperative recurrence. *J Clin Oncol* 2005; **23:** 2513–20.

15 Takano T, Ohe Y, Sakamoto H, et al. Epidermal growth factor receptor gene mutations and increased copy numbers predict gefitinib sensitivity in patients with recurrent non-small-cell lung cancer. *J Clin Oncol* 2005; **23:** 6829–37.

16 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* 2008; **26:** 4244–52.

17 Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 2005; **366:** 1527–37.

18 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* 2008; **372:** 1809–18.

19 Yatabe Y, Hida T, Horio Y, Kosaka T, Takahashi T, Mitsudomi T. A rapid, sensitive assay to detect EGFR mutation in small biopsy specimens from lung cancer. *J Mol Diagn* 2006; **8:** 335–41.

20 Nagai Y, Miyazawa H, Huqun, et al. Genetic heterogeneity of the epidermal growth factor receptor in non-small cell lung cancer cell lines revealed by a rapid and sensitive detection system, the peptide nucleic acid-locked nucleic acid PCR clamp. *Cancer Res* 2005; **65:** 7276–82.

21 Mast A, de Arruda M. Invader assay for single-nucleotide polymorphism genotyping and gene copy number evaluation. *Methods Mol Biol* 2006; **335:** 173–86.

22 Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975; **31:** 103–15.

23 Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. *J Clin Oncol* 2005; **23:** 5900–09.

24 Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009; **361:** 947–57.

25 Kobayashi K, Inoue A, Maemondo M, et al. First-line gefitinib versus first-line chemotherapy by carboplatin (CBDCA) plus paclitaxel (TXL) in non-small cell lung cancer (NSCLC) patients (pts) with EGFR mutations: a phase III study (002) by North East Japan Gefitinib Study Group. *J Clin Oncol* 2009; **27** (suppl): abstr 8016.

26 ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. International Conference on Harmonisation E9 Expert Working Group. *Stat Med* 1999; **18:** 1905–42.

27 Kris M, Mok T, Kim E, Douillard JY, Fukuoka M, Thatcher N. Response and progression-free survival in 1006 patients with known EGFR mutation status in phase III randomized trials of gefitinib in individuals with non-small cell lung cancer. *Eur J Cancer* 2009; **7** (suppl): abstr O-9003.

28 Cappuzzo F, Coudert BP, Wierzbicki R, et al. Efficacy and safety of erlotinib as first-line maintenance in NSCLC following non-progression with chemotherapy: results from the phase III SATURN study. *J Thorac Oncol* 2009; **4** (suppl): abstr A21.

29 Mok TS, Wu YL, Yu CJ, et al. Randomized, placebo-controlled, phase II study of sequential erlotinib and chemotherapy as first-line treatment for advanced non-small-cell lung cancer. *J Clin Oncol* 2009; **27:** 5080–87.

30 Mok TS, To KF, Srimunimimit V, et al. Clinical outcomes of patients with epidermal growth factor receptor (EGFR) mutations (Mut) in IPASS IRESSATM Pan Asia Study. *J Thorac Oncol* 2009; **4** (suppl): abstr B9.5.

31 Kudoh S, Kato H, Nishiwaki Y, et al. Interstitial lung disease in Japanese patients with lung cancer: a cohort and nested case-control study. *Am J Respir Crit Care Med* 2008; **177:** 1348–57.

32 Ando M, Okamoto I, Yamamoto N, et al. Predicitive factors for interstitial lung disease, anti-tumor response and survival in non-small cell lung cancer patients treated with gefiitinib. *J Clin Oncol* 2006; **24:** 2549–56.

33 Lee JS, Park K, Kim S-W, et al. A randomized phase III study of gefitinib versus standard chemotherapy (gemcitabine plus cisplatin) as a first-line treatment for never-smokers with advanced or metastatic adenocarcinoma of the lung. *J Thorac Oncol* 2009; **4** (suppl): abstr PRS.4.

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase III Study Comparing Second- and Third-Generation Regimens With Concurrent Thoracic Radiotherapy in Patients With Unresectable Stage III Non–Small-Cell Lung Cancer: West Japan Thoracic Oncology Group WJTOG0105

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ABSTRACT

Purpose
This phase III trial of concurrent thoracic radiotherapy (TRT) was conducted to compare third-generation chemotherapy with second-generation chemotherapy in patients with unresectable stage III non–small-cell lung cancer (NSCLC).

Patients and Methods
Eligible patients received the following treatments: A (control), four cycles of mitomycin (8 mg/m^2 on day 1)/vindesine (3 mg/m^2 on days 1, 8)/cisplatin (80 mg/m^2 on day 1) plus TRT 60 Gy (treatment break for 1 week); B, weekly irinotecan (20 mg/m^2)/carboplatin (area under the plasma concentration-time curve [AUC] 2) for 6 weeks plus TRT 60 Gy, followed by two courses of irinotecan (50 mg/m^2 on days1, 8)/carboplatin (AUC 5 on day1); C, weekly paclitaxel (40 mg/m^2)/carboplatin (AUC 2) for 6 weeks plus TRT 60 Gy, followed by two courses of paclitaxel (200 mg/m^2 on day1)/carboplatin (AUC 5 on day 1).

Results
The median survival time and 5-year survival rates were 20.5, 19.8, and 22.0 months and 17.5%, 17.8%, and 19.8% in arms A, B, and C, respectively. Although no significant differences in overall survival were apparent among the treatment arms, noninferiority of the experimental arms was not achieved. The incidences of grade 3 to 4 neutropenia, febrile neutropenia, and gastrointestinal disorder were significantly higher in arm A than in arm B or C ($P < .001$). Chemotherapy interruptions were more common in arm B than in arm A or C.

Conclusion
Arm C was equally efficacious and exhibited a more favorable toxicity profile among three arms. Arm C should be considered a standard regimen in the management of locally advanced unresectable NSCLC.

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INTRODUCTION

Lung cancer remains the leading cause of cancer-related deaths worldwide.[1] Non–small-cell lung cancer (NSCLC) accounts for 80% of all lung cancer cases, and approximately 30% of patients with NSCLC present with locally advanced lung cancer.[2]

The standard treatment for stage III locally advanced NSCLC was a combined modality of thoracic radiotherapy (TRT) and chemotherapy.[3,4] Phase III studies have also been conducted to assess the efficacy and toxicity of concurrent chemoradiotherapy in comparison with that of sequential chemoradiotherapy. In two studies (ie, a Japanese report[5] and the RTOG9410[6]) that employed older, second-generation regimens, the survival period was reported to be significantly prolonged by concurrent chemoradiotherapy, although the toxicity was worse. Thus the standard of treatment for stage III locally advanced lung cancer is currently recognized as concurrent chemoradiotherapy.

During the last decade, the usefulness of several new agents, such as paclitaxel, gemcitabine, vinorelbine, and docetaxel, have been studied, usually administered in combination with the platinum compounds. These newer-agent/platinum combinations, the so-called third-generation regimens, have been proven to be more effective than

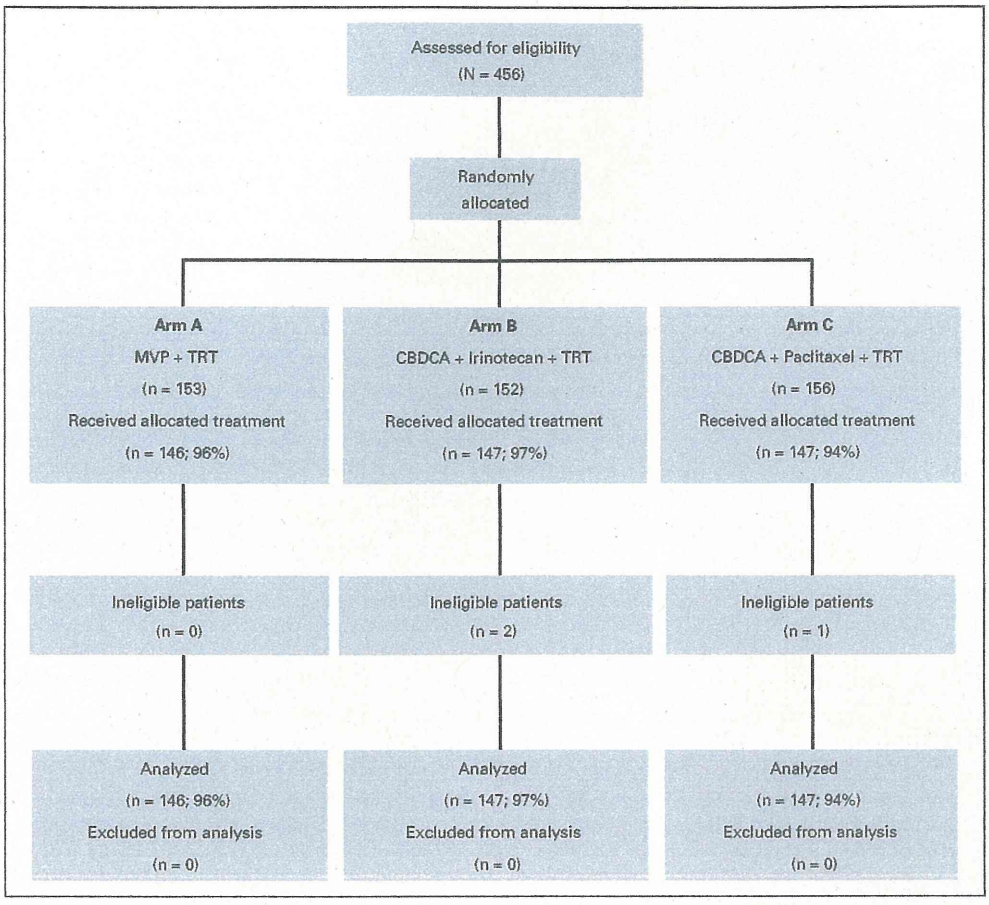

Fig 1. CONSORT diagram. MVP, mitomycin, vindesine, and cisplatin; TRT, thoracic radiotherapy; CBDCA, carboplatin.

second-generation regimens, as demonstrated by the increased survival of patients with metastatic NSCLC treated with these regimens.[7-9]

Because the chemotherapy regimens used in the above-described two reports were second-generation regimens, the benefit of the introduction of third-generation regimens for chemoradiotherapy has begun to be assessed. Although concurrent administration of full-dose chemotherapy and thoracic radiotherapy has been reported to be possible by some investigators, it is considered difficult for many regimens[10,11]; third-generation agents can hardly be used at their full doses for concurrent chemoradiotherapy because of the high incidence of toxicity associated with these agents. Therefore, for concurrent chemotherapy with TRT, these chemotherapeutic agents have been used at reduced doses in several reported clinical studies.[12-14] However, some reports have suggested that the marked efficacy of concurrent chemoradiotherapy using third-generation chemotherapeutic agents can hardly be achieved using these agents at reduced doses.[15]

However, it remains to be clearly established regarding which would be superior in terms of both the efficacy and toxicity: concurrent chemoradiotherapy using the second-generation regimens at full doses or the third-generation regimens at reduced doses. We, the West Japan Thoracic Oncology Group, therefore performed a phase III study to compare these therapeutic strategies. The doses of the chemotherapeutic agents were determined based on the results of Japanese phase I studies.[16,17]

PATIENTS AND METHODS

Patient Selection

Patients with histologically or cytologically confirmed NSCLC with unresectable stage III disease were assessed for eligibility (see CONSORT diagram, Fig 1). Unresectable stage IIIA disease was defined by the presence of multiple and/or bulky N2 mediastinal lymph nodes on computed tomography (CT), which rendered, in the opinion of the treating investigator, the patients unsuitable as candidates for surgical resection. Eligible patients also needed to meet the following criteria: measurable disease of 20 mm or more; no prior history of chemotherapy or TRT; Eastern Cooperative Oncology Group performance status $\leq$ 1; age $\leq$ 75 years; leukocytes $\geq$ 4,000/μL, platelets $>$ 100,000/μL, and hemoglobin $>$ 9.5 g/dL, serum creatinine $<$ institutional upper limit of normal, 24-hour creatinine clearance $\geq$ 60 mL/min, bilirubin $\leq$ 1.5 mg/dL, AST and ALT $\leq$ 2.0$\times$ upper limit of normal, and partial pressure of arterial oxygen $\geq$ 70 mmHg.

Patients were excluded if they had pulmonary fibrosis; other active, invasive malignancies in the 3 years leading up to protocol entry; malignant effusion; pyrexia of 38°C or more at baseline; infections; significant cardiac disease; uncontrolled diabetes mellitus; paresis of the intestine ileus; or regular use of corticosteroids. The institutional ethics committee of each of the participating institutions approved the protocol, and all patients provided written informed consent before the start of the study.

For staging, all patients underwent CT of the thorax, including the upper abdomen, and either a brain CT or brain magnetic resonance imaging. A radioisotopic bone scan was also performed for all patients. Positron emission tomography was not obtained in any of the enrollees at baseline.

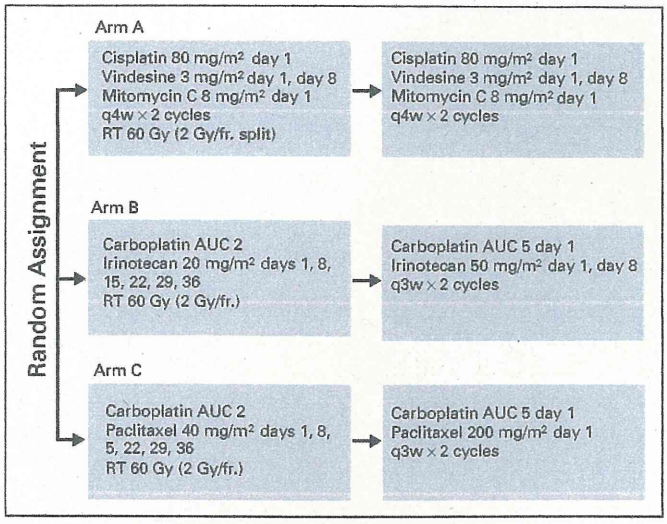

Fig 2. Treatment schema. q4w, every 4 weeks; RT, radiotherapy; fr, fraction; AUC, area under the plasma concentration-time curve.

Treatment Schedules

Patients were randomly assigned to one of the three following treatment arms (Fig 2). Treatment was composed of concurrent chemoradiotherapy and subsequent consolidation chemotherapy.

In arm A, chemotherapy consisted of vindesine 3 mg/m^2 on days 1 and 8, cisplatin 80 mg/m^2 on day 1, and mitomycin 8 mg/m^2 on day 1. This chemotherapy was repeated every 4 weeks, and four courses were administered. On day 2 of chemotherapy, TRT was begun at the dose of 2 Gy/fraction given in 15 fractions over 3 weeks, followed by a rest period of 1 week. Subsequently, radiation was again resumed at the dose of 2 Gy/fraction given in 15 fractions over 3 weeks. The total dose of radiation administered was 60 Gy.

In arms B and C, concurrent chemoradiotherapy was undertaken with the agents administered at reduced doses weekly for 6 weeks, followed by full-dose chemotherapy during the consolidation phase. The consolidation phase chemotherapy, initiated 3 to 4 weeks after the concurrent chemoradiotherapy, was administered in two cycles. TRT was initiated on day 1 at the dose of 2.0 Gy daily, five times per week. The total dose of 60 Gy was given in 30 fractions over a 6-week period.

The concurrent-phase chemotherapy consisted of irinotecan 20 mg/m^2 followed by carboplatin area under the plasma concentration time curve (AUC) 2 mg/mL/min in arm B and paclitaxel 40 mg/m^2 followed by carboplatin AUC 2 mg/mL/min in arm C. The consolidation chemotherapy consisted of 3-week cycles of irinotecan (50 mg/m^2 on days 1 and 8)/carboplatin (AUC 5 mg/mL/min on day 1) in arm B and paclitaxel (200 mg/m^2 administered over 3 hours) followed by carboplatin (AUC 5 mg/mL/min on day 1) in arm C.

Radiation Therapy

All patients were treated with a linear accelerator photon beam of 4 MV or more. The primary tumor and involved nodal disease received 60 Gy in 2-Gy fractions over 6 weeks in arms B and C and 7 weeks in arm A.

At the start of this multi-institutional study, three-dimensional (3D) treatment planning system using CT was not available at all institutions. Therefore, two-dimensional (2D) treatment planning techniques were allowed, and 3D dose constraints for both planning target volume and normal-risk organs were not determined in the protocol. Radiation doses were specified at the center of the target volume. In 2D treatment planning, doses were calculated assuming tissue homogeneity without correction for lung tissues, whereas lung inhomogeneity correction was performed in 3D treatment planning. Among 412 patients who received > 54 Gy (arm A, n = 139; arm B, n = 137; and arm C, n = 136), 2D and 3D treatment planning was performed for 200 and 212 patients, respectively.

The initial 40 Gy was delivered to clinical target volume 1 (CTV1), and the final 20 Gy was delivered to a reduced volume defined as clinical target volume 2 (CTV2). CTV1 included the primary tumor, ipsilateral hilum, and mediastinal nodal areas from the paratracheal (no. 2) to subcarinal lymph nodes (no. 7). The contralateral hilum was not included in CTV1. The supraclavicular areas were not to be treated routinely, but could be treated when supraclavicular nodes were involved. For the primary tumors and the involved lymph nodes of 1 cm in the shortest diameter, a margin of 1.5 to 2 cm was added. CTV2 included only the primary tumor and the involved lymph nodes with a margin of 0.5 to 1 cm. The spinal cord was excluded from the fields for CTV2 by appropriate methods, such as the oblique opposing method. Appropriate planning target volume margin and leaf margin were added for CTV1 and CTV2. When grade 4 hematologic toxicity, grade 3 to 4 esophagitis or dermatitis, pyrexia of ≥ 38°C, or a partial pressure of arterial oxygen of less than 60 mmHg occurred, the TRT was interrupted.

Evaluation of Response and Toxicity

All eligible patients who received any treatment at all were considered as assessable for response and toxicity. Chest x-rays, CBCs, and blood chemistry studies were repeated once a week during the treatment period. Thoracic CT was performed once a month during the treatment period. After the treatment, thoracic CT was obtained every 3 months, and other imaging examinations were obtained when recurrence was suspected. The response was evaluated in accordance with Response Evaluation Criteria in Solid Tumors (RECIST). In the evaluation of the antitumor effects, extramural review was conducted. Overall survival (OS) was defined as the time from registration until death from any cause. Progression-free survival (PFS) was defined as the time between random assignment and disease progression, death, or last known follow-up. OS and PFS were estimated by the Kaplan-Meier method.

Statistical Analysis

The primary end point of this study was comparison of the OS between the control group (arm A) and each of the treatment groups (arm B or C). It was projected that the control group would achieve a median OS time of 16.5 months,[5] whereas the treatment group would show an increase in the median OS to 20.5 months, on the basis of previously published data.[14] When the upper limit of the adjusted CI of the hazard ratio of the control group to each treatment group was low 1.176 (1/0.85), the results were recognized as demonstrating noninferiority of the experimental treatment to the control treatment. The sample size was calculated assuming a 2.5% one-sided type I error and 80% power. The patient accumulation period was 4.5 years, and the follow-up period was 3 years. In view of the possibility of variance inflation owing to censoring, the sample size was set at 450 patients.

Baseline characteristics were compared among the treatment groups using the Kruskal-Wallis test for continuous variables and Fisher's exact test for discrete variables. Rates of occurrence of specific toxicities and treatment delivery were compared among the groups using Fisher's exact test.

RESULTS

Patient Characteristics

From September 2001 to September 2005, a total of 456 patients were registered for the study, and 153, 152, and 151 patients were allocated to arms A, B, and C, respectively. Of the total, 16 patients (arm A, n = 7; arm B, n = 5; arm C, n = 4) did not receive the protocol treatment because they were deemed ineligible for the study before the start of treatment after registration in five patients (large irradiation area, n = 2; stage IIB, n = 1; stage IV, n = 2), worsening of the underlying disease in four patients, worsening of complications in five patients, patient refusal in one patient, and unknown reason in one patient. The safety and antitumor effects of the treatments were eventually assessed on the basis of the data of 440 patients after exclusion of these 16 patients from the total of 456 patients enrolled. After the start of the treatment, three patients were found to be ineligible because of stage IV disease, but the data of these patients were included in all the analyses.

Table 1. Patient Characteristics

Characteristic	Arm A No.	Arm A %	Arm B No.	Arm B %	Arm C No.	Arm C %	P
Sex							.879
Female	18	12.3	21	14.3	19	12.9	
Male	128	87.7	126	85.7	128	87.1	
Age, years							.378
Median	63.0		62.0		63.0		
Range	31-74		30-74		38-74		
≥ 70	27	18.5	36	24.5	31	21.1	
Smoking history							.240
Absence	17	11.6	15	10.2	9	6.1	
Presence	129	88.4	132	89.8	138	93.9	
Performance status							.447
0	56	38.4	66	44.9	65	44.2	
1	90	61.6	81	55.1	81	55.1	
Unknown	0	0.0	0	0.0	1	0.7	
Weight loss during the previous 6-month period							.680
< 5%	92	63.0	100	68.0	95	64.6	
≥ 5%	28	19.2	24	16.3	29	19.7	
Unknown	26	17.8	23	15.6	23	15.6	
Staging							.901
IIIA	49	33.6	46	31.3	49	33.3	
IIIB	97	66.4	101	68.7	98	66.7	
N status							—
N2	94	64.4	86	58.5	99	67.3	
N3	33	22.6	43	29.3	32	21.8	
Histology							—
Adenocarcinoma	58	39.7	69	46.9	62	42.2	
Squamous cell carcinoma	70	47.9	62	42.2	71	48.3	

There were no statistically significant differences among the three arms in terms of patient characteristics (Table 1).

Treatment Administered

Table 2 shows the status of implementation of chemotherapy. During the concurrent phase, 40.8% of patients in arm B and 58.5% of patients in arm C received six weekly cycles of chemotherapy ($P = .003$); 67.3% of patients in arm B and 87.8% patients in arm C completed at least five cycles ($P < .001$). In regard to the consolidation phase, 41.1%, 29.3%, and 49.7% in arms A, B, and C, respectively, received the two scheduled courses of therapy ($P = .002$). Chemotherapy interruptions were more common in arm B than in arms A and C in both the concurrent and consolidation phases.

In most of the patients, TRT at 60 Gy was completed, and 6.8%, 8.2%, and 8.8% of patients in arms A, B, and C, respectively, received a radiation dose of less than 60 Gy. The reason for the reduced radiation dose was toxicity in two thirds of the patients (three patients from arm A; six patients from arm B, including two cases of esophagitis and two cases of pneumonitis; and seven patients from arm C, including one case of esophagitis and two cases of pneumonitis).

Table 2. Chemotherapy Administered

Chemotherapy Cycles	No. of Patients Arm A	Arm B	Arm C	P
Concurrent chemotherapy cycles				
1	18.5	0.7	2.0	
2	81.5	2.0	2.0	
3		5.4	1.4	
4		24.5	6.8	
5		26.5	29.3	B *v* C: .003
6		40.8	58.5	B *v* C: < .001
Consolidation chemotherapy				
0	46.6	34.0	30.6	
1	12.3	36.7	19.7	
2	41.1	29.3	49.7	A *v* B *v* C: .002

Toxicity

Table 3 lists the grade 3 or worse severe toxicities. There were a total of 11 treatment-related deaths. The cause of death was radiation pneumonitis in one patient and sepsis in one of the two patients in arm A; meningitis in one patient, pneumonia in one patient, radiation pneumonitis in two patients, and mycosis in one of the five patients in arm B; and radiation pneumonitis in three patients and death from other cause in one of the four patients in arm C. The clinical course of the patients who died of radiation pneumonitis are presented next. One patient from arm A developed pneumonitis on day 2 of the fourth course of treatment. In this patient, the pneumonitis subsided temporarily in response to corticosteroid therapy, but it aggravated again subsequently, resulting in death. In arm B, one patient developed pneumonitis after 54 Gy of TRT and died despite mechanical ventilation, and another patient developed pneumonitis at the end of the concurrent phase. In the latter patient, the pneumonitis subsided temporarily in response to pulsed corticosteroid therapy, but it aggravated again, resulting in death. In arm C, two patients developed pneumonitis at the end of the concurrent phase. Another patient from arm C developed pneumonitis on day 16 of the concurrent phase.

The incidences of grade 3 or worse severe hematologic toxicity, infection, febrile neutropenia, and gastrointestinal toxicity were significantly higher in arm A than in arm B or C. The incidence of grade

Table 3. Grade 3 or Worse Toxicity

Toxicity	All Treatment Arm A	Arm B	Arm C	P	Concurrent Phase Arm A	Arm B	Arm C	P
Neutropenia	95.9	60.5	61.9	< .001	93.8	53.7	23.1	< .001
Leukopenia	96.6	75.5	66.0	< .001	95.9	72.1	46.9	< .001
Anemia	25.3	17.7	8.8	< .001	15.8	8.8	6.1	0.019
Thrombocytopenia	28.8	28.6	7.5	< .001	21.9	11.6	5.4	< .001
Febrile neutropenia	37.0	8.8	10.2	< .001	30.8	6.1	3.4	< .001
Nausea	21.9	4.8	4.8	< .001	21.9	3.4	3.4	< .001
Vomiting	6.8	2.7	0.7	.012	6.2	1.4	0.0	.001
Fatigue	13.0	6.1	4.8	.019	9.6	2.0	1.4	< .001
Constipation	11.6	6.1	2.7	.009	8.9	6.1	1.4	.015
Diarrhea	0.7	2.0	1.4	.606	0.7	0.7	0.7	.999
Neurogenic (sensory)	0.7	0.7	4.8	.017	0.0	0.0	0.0	—
Esophagitis	5.5	2.7	8.2	.121	4.1	2.0	7.5	.077
Infection	26.0	16.3	17.0	.066	22.6	12.2	10.2	.006
Dyspnea	6.2	5.4	6.1	.957	2.7	0.7	2.0	.406
Pneumonitis	1.4	4.1	4.1	.312	0.0	0.0	0.7	.368

Table 4. Objective Response

Response	Arm A (n = 146)		Arm B (n = 147)		Arm C (n = 147)	
	No.	%	No.	%	No.	%
CR	3	2.1	4	2.7	5	3.4
PR	94	64.4	79	53.7	88	59.9
SD	16	11.0	32	21.8	32	21.8
PD	19	13.0	19	12.9	16	10.9
NE	14	9.6	13	8.8	6	4.1
Response rate, CR + PR*	97	66.4	83	56.5	92	63.0

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated.
*P = .198.

3 or worse severe neurogenic toxicity was significantly higher in arm C as compared with that in the other two arms. There were no statistically significant differences in the incidences of esophagitis, dyspnea, or pneumonitis, which are manifestations of radiation-related toxicity, among the three groups. The incidence of grade 2 or worse severe esophagitis was significantly higher in arm C (20.5%, 23.1%, and 33.3% from arms A, B and C, respectively; P = .003).

Efficacy

The objective response rates were 66.4%, 56.5%, and 63.3% in arms A, B, and C, respectively (Table 4). The response rates in arms B and C were not statistically significantly different from the rate in arm A.

The OS and PFS are shown in Figure 3. Most of the patients had been observed for more than 3 years, and 343 patients had died. The median survival time and 3- and 5-year survival rates in arm A were 20.5 months, 35.3%, and 17.5%, respectively. The corresponding values were 19.8 months, 24.2%, and 17.8% in arm B, and 22.0 months, 26.4%, and 19.5% in arm C. There was no statistically significant difference in the OS between arm B or C and arm A (arm A *v* B, P = .392; arm A *v* C, P = .876). The upper limits of the adjusted CI of the hazard ratio between arm A and B (1.402) or C (1.204) exceeded 1.176. Thus the results did not show noninferiority of the three experimental regimens (arm B and C) as compared with the reference treatment (arm A).

The OS was not significantly different according to sex (male, female), stage (IIIA, IIIB), and weight loss (< 5%, ≥ 5%) among the three arms. The causes of death after the third year are disease progression (n = 15, 6, and 9 in arms A, B, and C, respectively) and other disease (n = 3, 1, and 0 in arms A, B, and C, respectively).

The median PFS was 8.2, 8.0, and 9.5 months in arms A, B, and C, respectively. There was also no statistically significant difference of the PFS between arm B or C and A (arm A *v* B, P = .466; arm A *v* C, P = .621).

DISCUSSION

To our knowledge, this is the first phase III trial designed for direct comparison between second-generation and third-generation regimens applied in combination with concurrent TRT in patients with locally advanced lung carcinoma. This study was additionally aimed at comparing a cisplatin-based regimen with a carboplatin-based regimen and also more frequent radiosensitizing doses during TRT with systemic doses of chemotherapy during radiotherapy. In regard to chemotherapy for advanced lung cancer, a previous meta-analysis demonstrated that a cisplatin-based regimen is superior to a carboplatin-based regimen in terms of OS. In the present study, however, the OS in arm A (cisplatin-based regimen) was not significantly longer than that in arm B or C (carboplatin-based regimen). The observed intergroup differences possibly reflect the differences between the second- and third-generation regimens or between more frequent radiosensitizing doses and systemic doses of chemotherapy. In any event, the results of this study suggest that the third-generation

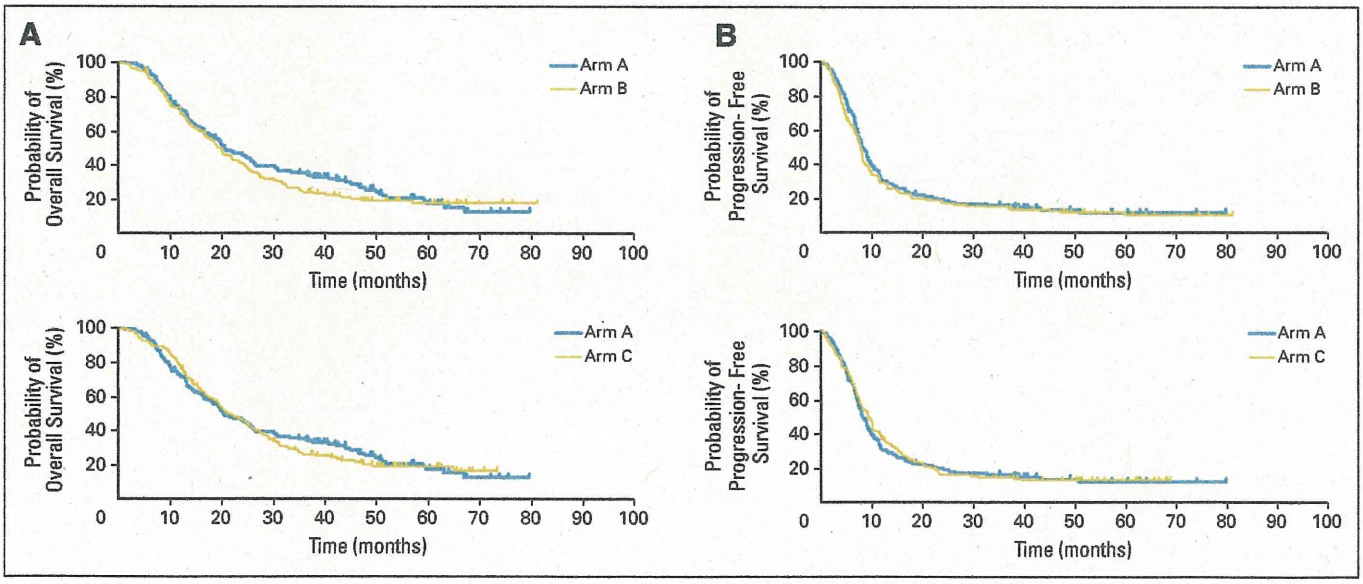

Fig 3. (A) Comparison of overall survival among the three randomly assigned arms. (B) Comparison of progression-free survival among the three randomly assigned arms.

carboplatin regimen (particularly carboplatin plus paclitaxel) was at least comparable to the second-generation cisplatin regimen, which is the conventionally used therapeutic regimen, in terms of the survival-prolonging effect when applied in combination with concurrent thoracic radiotherapy.

Unfortunately, noninferiority of OS was not demonstrated in the present study, probably because the number of the patients in this study resulted in a deficiency of power, because the therapeutic outcome in the reference arm was more favorable than that in conventional reports. The therapeutic outcome in the reference arm in recent phase III studies of chemoradiotherapy was more favorable than the estimated numerical data.[18] The favorable data may be attributable to bias as a result of the patient inclusion criteria or the development of radiotherapy, but no distinct cause could be identified.

Although noninferiority in terms of OS was not demonstrated in this study, the survival curves themselves mostly coincided among the three groups, as shown in Figure 2. The hematologic and gastrointestinal toxicities noted in arm A were significantly serious as compared with those in the experimental arms. Although the incidence of grade 3 or worse severe neurotoxicity was significantly higher, most of the other toxicities were the mildest in arm C among the three groups. Between the experimental arms, the rate of implementation of chemotherapy tended to be lower for arm C than for arm B. It was considered, from the viewpoint of feasibility, that arm C may be superior to arm B.

From these data on the efficacy and toxicity, we judged that concurrent chemoradiotherapy involving the combined use of carboplatin plus paclitaxel and TRT yielded the best results among the three groups, and we, the West Japan Thoracic Oncology Group, will select this treatment method as the reference arm for phase III studies in the future.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Jemal A, Siegel R, Ward E, et al: Cancer statistics. Ca Cancer J Clin 57:43-66, 2007
2. van Meerbeeck JP: Staging of non-small cell lung cancer: Consensus, controversies and challenges. Lung Cancer 34:S95-S107, 2001 (suppl 2)
3. Dillman RO, Seagren SL, Propert KJ, et al: A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. N Engl J Med 323:940-945, 1990
4. Sause W, Kolesar P, Taylor SIV, et al: Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. Chest 117: 358-364, 2000
5. Furuse K, Fukuoka M, Kawahara M, et al: Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol 17: 2692-2699, 1999
6. Curran WJ, Scott CB, Langer CJ, et al: Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemo-radiation for patients with unresected stage III NSCLC: RTOG 9410. Proc Am Soc Clin Oncol 22:621, 2003 (suppl; abstr 2499)
7. Schiller JH, Harrington D, Belani CP, et al: Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346:92-98, 2002
8. Bunn PA Jr, Kelly K: New chemotherapeutic agents prolong survival and improve quality of life in non-small cell lung cancer: A review of the literature and future directions. Clin Cancer Res 4:1087-1100, 1998
9. Hoffman PC, Mauer AM, Vokes EE: Lung cancer. Lancet 355:479-485, 2000
10. Movsas B, Hudes RS, Schol J: Induction and concurrent paclitaxel/carboplatin every 3 weeks with thoracic radiotherapy in locally advanced non-small-cell lung cancer: An interim report. Clin Lung Cancer 3:125-132, 2001
11. Govindan G, Bogart J, Wang X, et al: Phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small cell lung cancer: CALGB 30407. J Clin Oncol 27:383s, 2009 (abstr 7505)
12. Vokes EE, Herndon JE 2nd, Crawford J, et al: Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small-cell lung cancer: Cancer and Leukemia Group B study 9431. J Clin Oncol 20:4191-4198, 2002
13. Belani CP, Choy H, Bonomi P, et al: Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: A randomized phase II locally advanced multi-modality protocol. J Clin Oncol 23: 5883-5891, 2005
14. Choy H, Akerley W, Safran H, et al: Multi-institutional phase II trial of paclitaxel, carboplatin, and concurrent radiation therapy for locally advanced non-small-cell lung cancer. J Clin Oncol 16:3316-3322, 1998

15. Vokes EE, Herndon JE 2nd, Kelley MJ, et al: Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III non–small-cell lung cancer: Cancer and Leukemia Group B. J Clin Oncol 25:1698-1704, 2007

16. Uejima H: Dose-finding study of weekly irinotecan (CPT-11) and carboplatin (CBDCA) with concurrent thoracic radiotherapy (TRT) in locally advanced non-small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 21:220b, 2002 (abstr 2699)

17. Endo M, Takada Y, Obayashi K, et al: Weekly paclitaxel and carboplatin with concurrent radiation therapy in locally advanced non-small cell lung cancer: Phase I study. Radiat Med 23:331-335, 2005

18. Hanna N, Neubauer M, Yiannoutsos C, et al: Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non–small-cell lung cancer: The Hoosier Oncology Group and U.S. Oncology. J Clin Oncol 26:5755-5760, 2008

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ORIGINAL REPORT

Biomarker Analyses and Final Overall Survival Results From a Phase III, Randomized, Open-Label, First-Line Study of Gefitinib Versus Carboplatin/Paclitaxel in Clinically Selected Patients With Advanced Non–Small-Cell Lung Cancer in Asia (IPASS)

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See accompanying editorial on page 2843; listen to the podcast by Dr Sequist on www.jco.org/podcast

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ABSTRACT

Purpose

The results of the Iressa Pan-Asia Study (IPASS), which compared gefitinib and carboplatin/paclitaxel in previously untreated never-smokers and light ex-smokers with advanced pulmonary adenocarcinoma were published previously. This report presents overall survival (OS) and efficacy according to epidermal growth factor receptor (EGFR) biomarker status.

Patients and Methods

In all, 1,217 patients were randomly assigned. Biomarkers analyzed were *EGFR* mutation (amplification mutation refractory system; 437 patients evaluable), *EGFR* gene copy number (fluorescent in situ hybridization; 406 patients evaluable), and EGFR protein expression (immunohistochemistry; 365 patients evaluable). OS analysis was performed at 78% maturity. A Cox proportional hazards model was used to assess biomarker status by randomly assigned treatment interactions for progression-free survival (PFS) and OS.

Results

OS (954 deaths) was similar for gefitinib and carboplatin/paclitaxel with no significant difference between treatments overall (hazard ratio [HR], 0.90; 95% CI, 0.79 to 1.02; $P = .109$) or in *EGFR* mutation–positive (HR, 1.00; 95% CI, 0.76 to 1.33; $P = .990$) or *EGFR* mutation–negative (HR, 1.18; 95% CI, 0.86 to 1.63; $P = .309$; treatment by *EGFR* mutation interaction $P = .480$) subgroups. A high proportion (64.3%) of *EGFR* mutation–positive patients randomly assigned to carboplatin/paclitaxel received subsequent EGFR tyrosine kinase inhibitors. PFS was significantly longer with gefitinib for patients whose tumors had both high *EGFR* gene copy number and *EGFR* mutation (HR, 0.48; 95% CI, 0.34 to 0.67) but significantly shorter when high *EGFR* gene copy number was not accompanied by *EGFR* mutation (HR, 3.85; 95% CI, 2.09 to 7.09).

Conclusion

EGFR mutations are the strongest predictive biomarker for PFS and tumor response to first-line gefitinib versus carboplatin/paclitaxel. The predictive value of *EGFR* gene copy number was driven by coexisting *EGFR* mutation (post hoc analysis). Treatment-related differences observed for PFS in the *EGFR* mutation–positive subgroup were not apparent for OS. OS results were likely confounded by the high proportion of patients crossing over to the alternative treatment.

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INTRODUCTION

The epidermal growth factor receptor (EGFR) represents an important signaling pathway that regulates tumorigenesis and cell survival and is frequently overexpressed in the development and progression of non–small-cell lung cancer (NSCLC).[1-4] EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib (Iressa, AstraZeneca, Macclesfield, United Kingdom) are effective in the treatment of relapsed NSCLC,[5,6] with certain clinical subgroups deriving greater clinical benefit (adenocarcinoma histology,

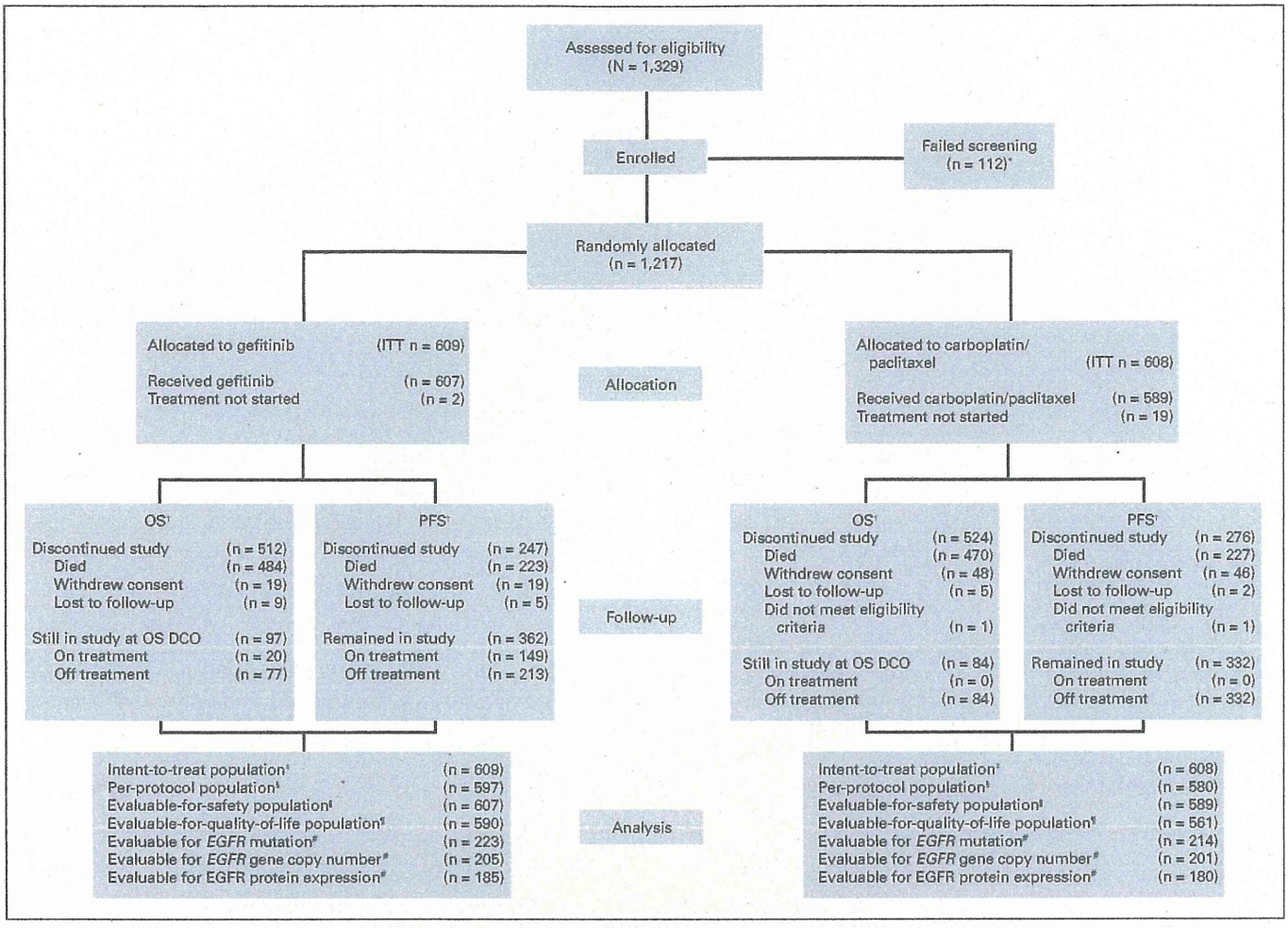

Fig 1. CONSORT diagram. (*) Among the 112 patients who failed screening, the main reasons for exclusion were abnormal serum creatinine (> 1.5 × upper limit of reference range)/creatinine clearance (≤ 60 mL/min) levels; untreated CNS metastases; or low neutrophil (< 2.0 × 10^9/L), platelet (< 100 × 10^9/L), or hemoglobin (< 10 g/dL) counts. (†) Cutoff dates: June 14, 2010, for overall survival (OS) and April 14, 2008, for progression-free survival (PFS). (‡) All patients who were randomly assigned to a study group were included in the intent-to-treat (ITT) analysis. (§) Patients who did not deviate substantially from the inclusion and exclusion criteria at entry or from the protocol were included in the per-protocol analysis. (‖) All patients who received at least one dose of study treatment were included in the safety analysis. (¶) All patients with a baseline and at least one postbaseline quality-of-life assessment that could be evaluated were included in the quality-of-life analysis. (#) All patients in the ITT population with an evaluable tumor sample. Of 683 patients (56%) who provided samples, 118 were cytology samples, and 128 were histologic samples of insufficient quality and were therefore not included in the main analysis. DCO, data cutoff; EGFR, epidermal growth factor receptor.

Asian ethnicity, female sex, and never-smoker status).[5-7] These subgroups are associated with a higher incidence of activating somatic mutations of the *EGFR* gene.[8-10] Optimization of anti-EGFR therapy depends on patient selection, and the exploration and identification of predictive biomarkers is important.

EGFR mutations, *EGFR* gene copy number, and EGFR protein expression are three EGFR-related biomarkers that have been studied in major clinical trials.[11-14] The significant overlap between EGFR biomarkers and limited availability of tumor samples in some studies made the interpretation of their individual predictive and prognostic values difficult.

Prolonged progression-free survival (PFS) and higher objective response rate (ORR) have been reported in patients with high *EGFR* gene copy number in single-arm and placebo-controlled randomized studies.[12,15-17] However, in the large phase III, randomized Iressa NSCLC Trial Evaluating Response and Survival Versus Taxotere (INTEREST) study with an active comparator, high *EGFR* gene copy number was not predictive for differential survival between gefitinib and docetaxel in patients with advanced NSCLC.[18]

The Iressa Pan-Asia Study (IPASS) is a phase III, randomized study of gefitinib versus carboplatin/paclitaxel in previously untreated never-smokers and light ex-smokers with advanced pulmonary adenocarcinoma in East Asia. As previously reported, IPASS exceeded its primary objective of noninferiority, demonstrating superiority of gefitinib relative to carboplatin/paclitaxel for PFS in this clinically selected population.[19] The treatment effect was not constant over time, driven by different outcomes according to mutation status. In the subgroup of patients with *EGFR* mutation–positive tumors, PFS was significantly longer for gefitinib versus carboplatin/paclitaxel (hazard ratio [HR], 0.48; 95% CI, 0.36 to 0.64; $P < .001$; median PFS, 9.5 *v* 6.3 months). Conversely, carboplatin/paclitaxel was superior in the *EGFR* mutation–negative subgroup (HR, 2.85; 95% CI, 2.05 to 3.98; $P < .001$; median PFS, 5.5 *v* 1.5 months); similarly, ORR significantly favored gefitinib and carboplatin/paclitaxel in the *EGFR* mutation–

Table 1. Summary of All Systemic Treatment After Discontinuation of Randomly Assigned Treatment in the Overall Population and in *EGFR* Mutation Subgroups (ITT population; data from OS data cutoff)

	Overall Population				*EGFR* Mutation Positive				*EGFR* Mutation Negative				*EGFR* Mutation Unknown			
	G (n = 609)		C/P (n = 608)		G (n = 132)		C/P (n = 129)		G (n = 91)		C/P (n = 85)		G (n = 386)		C/P (n = 394)	
Treatment	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Still on study treatment	20	3.3	0	0	3	2.3	0	0	1	1.1	0	0	16	4.1	0	0
None	190	31.2	230	37.8	29	22.0	37	28.7	21	23.1	25	29.4	140	36.3	168	42.6
Chemotherapy	393	64.5	251	41.3	99	75.0	61	47.3	69	75.8	44	51.8	225	58.3	146	37.1
Platinum-based†‡	363	59.6	55	9.0	90	68.2	13	10.1	65	71.4	10	11.8	208	53.9	32	8.1
C/P†‡	301	49.4	3	0.5	72	54.5	0	0	52	57.1	0	0	177	45.9	3	0.8
EGFR TKI	119	19.5	313	51.5	34	25.8	83	64.3	13	14.3	43	50.6	72	18.7	187	47.5
Gefitinib*†§	29	4.8	250	41.1	6	4.5	61	47.3	4	4.4	33	38.8	19	4.9	156	39.6
Erlotinib†§	71	11.7	83	13.7	16	12.1	31	24.0	9	9.9	7	8.2	46	11.9	45	11.4
Other EGFR TKI†§	33	5.4	35	5.8	15	11.4	12	9.3	2	2.2	5	5.9	16	4.1	18	4.6

NOTE. A patient may appear in more than one post-discontinuation treatment group. Patients may have received the same first- and second-line therapy. "None" is defined as patients who did not receive any form of cancer treatment after discontinuation of randomly assigned treatment. Radiotherapy, surgery, medical procedures, and other treatments were excluded.

Abbreviations: EGFR, epidermal growth factor receptor; ITT, intent-to-treat; OS, overall survival; G, gefitinib; C/P, carboplatin/paclitaxel; TKI, tyrosine kinase inhibitor.

*Non–study medication after discontinuation of randomly assigned study treatment.

†Patients may have also received other chemotherapy and/or EGFR TKIs during the study.

‡Excludes single platinum-based chemotherapy.

§Patients may have had more than one type of EGFR TKI and are counted once for each type received.

positive and *EGFR* mutation–negative subgroups, respectively.[19] A total of 1,038 of 1,217 patients consented to the preplanned exploratory biomarker analyses; 683 patients provided samples.

Early analysis of survival data (37% maturity) was presented in 2008.[19] Here we present the final results of the survival analyses and the results of the preplanned and post hoc analyses of the relationships between EGFR biomarkers (*EGFR* mutation, *EGFR* gene copy number, and EGFR protein expression) and clinical outcomes from IPASS.

PATIENTS AND METHODS

Study Design and Treatment

Full details of IPASS have been published previously.[19] Eligible patients had stage IIIB to IV pulmonary adenocarcinoma (including bronchoalveolar carcinoma), were either never-smokers (< 100 cigarettes in their lifetime) or light ex-smokers (stopped smoking ≥ 15 years previously and smoked ≤ 10 pack-years), and had received no prior chemotherapy or biologic or immunologic therapy.

Patients were randomly assigned 1:1 to gefitinib (250 mg/d) or carboplatin/paclitaxel (Paraplatin/Taxol, Bristol-Myers Squibb, Princeton, NJ; paclitaxel 200 mg/m^2 was given intravenously over 3 hours on day 1, immediately followed by carboplatin area under the serum concentration-time curve [AUC] 5.0 or 6.0 intravenously over 15 to 60 minutes in once every 3 weeks cycles for ≤ six cycles).

The primary objective of IPASS was noninferiority of gefitinib relative to carboplatin/paclitaxel in terms of PFS. ORR and overall survival (OS) were secondary end points. Evaluation of biomarker status (*EGFR* mutation, gene copy number, and protein expression) and efficacy of gefitinib versus carboplatin/paclitaxel were preplanned exploratory objectives. Post hoc analyses included clinical outcomes according to *EGFR* mutation subtype, *EGFR* gene copy number by *EGFR* mutation status, and clinical outcomes for patients with tumor *EGFR* gene high polysomy, and *EGFR* gene amplification. Correlation between *EGFR* mutation status and *EGFR* gene copy number was also investigated.

Patients provided written, informed consent with separate consent obtained for optional provision of tumor material for biomarker analyses. Study approval was obtained from independent ethics committees at each institution. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization/Good Clinical Practice, applicable regulatory requirements, and AstraZeneca's policy on bioethics.

Biomarker Analyses

Biomarker status was determined by analyzing paraffin-embedded archival tumor tissue in the following priority order: (1) *EGFR* mutation status, (2) *EGFR* gene copy number, (3) EGFR protein expression. Analyses were conducted at two central laboratories (Genzyme, Framingham, MA, and Quintiles-Lab in association with Peking Union Medical College Hospital, Beijing, China); scientists were blinded to clinical outcome and randomly assigned treatment. Samples underwent central histopathologic review; only those considered suitable for downstream biomarker analysis were progressed (on the basis of quality, sample source, and tumor content). If a patient provided more than one sample, the appropriate section was selected before database lock and analyzed on the basis of sample quality and largest area of tumor tissue.[20]

EGFR mutations were detected by using an amplification mutation refractory system with an *EGFR* mutation detection kit (DxS, Manchester, United Kingdom).[21,22] Patients were considered *EGFR* mutation positive if at least one of 29 *EGFR* mutations (Data Supplement) was detected. Additional validation for samples with T790M mutations was performed by using three methods: DNA sequencing, multithreaded electronic polymerase chain reaction sequencing, and an alternative amplification mutation refractory system assay (Data Supplement). *EGFR* gene copy number was measured by using fluorescent in situ hybridization and a previously published methodology.[15] High *EGFR* gene copy number was defined according to the University of Colorado Scoring System, which included both high polysomy (≥ four copies in ≥ 40% of cells; score 5) or gene amplification (presence of tight *EGFR* gene clusters and a ratio of gene/chromosome per cell > two, or > 15 copies of *EGFR* per cell in ≥ 10% of analyzed cells; score 6).[15] EGFR protein expression was assessed by immunohistochemistry by using the DAKO EGFR pharmDx kit (Dako, Glostrup, Denmark). Positive EGFR protein expression status was defined as having ≥ 10% of cells stained.

Statistical Analyses

The study statistician performed the statistical analyses at AstraZeneca. In the overall population and clinical subgroups, OS was analyzed by using a Cox proportional hazards model adjusted for the same covariates as for the primary PFS analysis (WHO performance status, 0 to 1 *v* 2; smoking history, never-smoker *v* light ex-smoker; and sex, female *v* male). The HR (gefitinib: carboplatin/paclitaxel) was estimated with 95% CIs and *P* values. Final analysis of OS was planned for when 944 deaths (78%) had occurred in the intent-to-treat (ITT) population, the same level of maturity as for PFS.

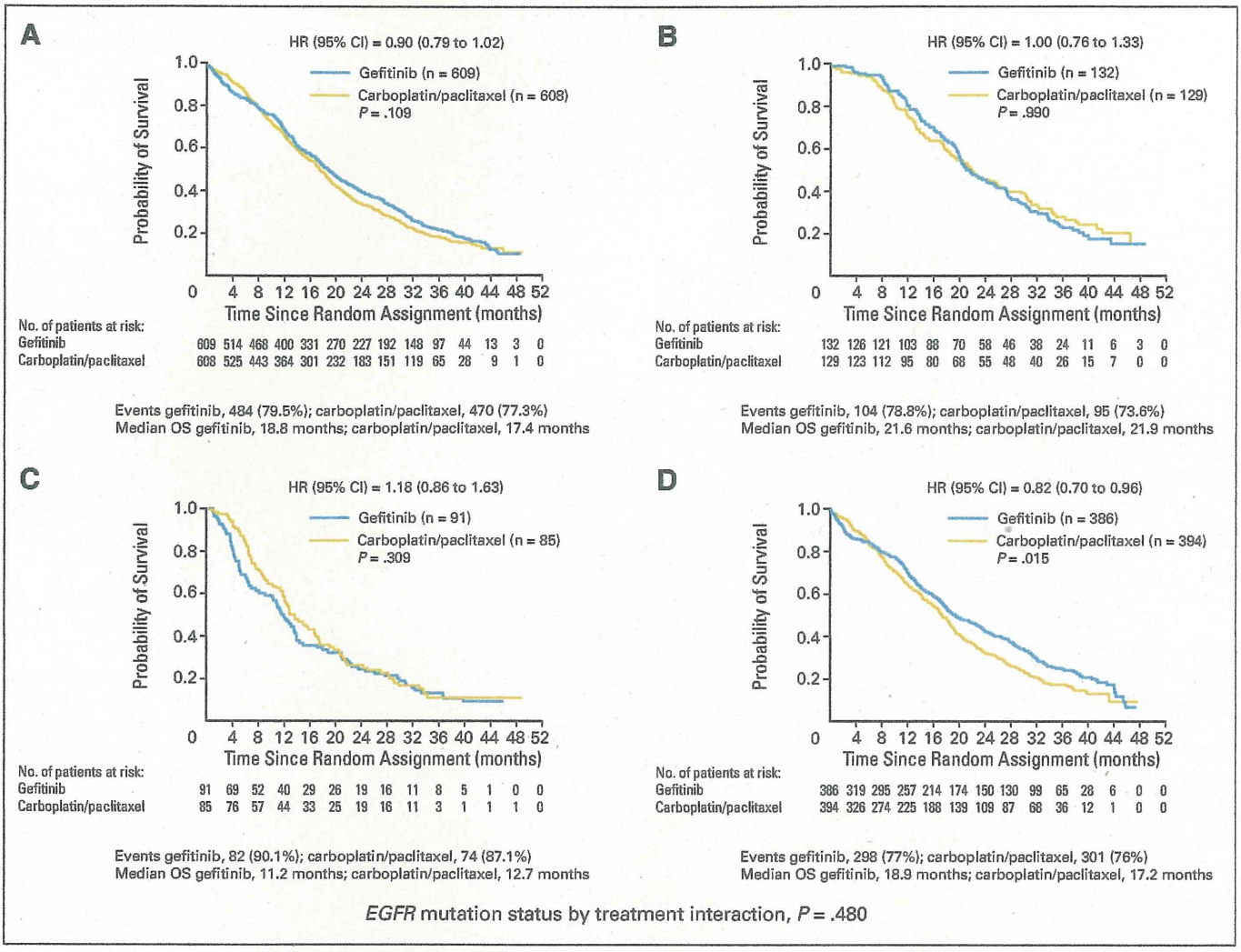

Fig 2. Kaplan-Meier curves for overall survival (OS) in the overall population and by epidermal growth factor receptor (*EGFR*) mutation status (intent-to-treat population). Hazard ratio (HR) < 1 implies a lower risk of death for patients treated with gefitinib. Cox analysis with covariates (performance status [0-1, 2], smoking history [never, light ex-smoker], and sex). (A) Overall population. (B) Patients with *EGFR* mutation–positive tumors. (C) Patients with *EGFR* mutation–negative tumors. (D) Patients with *EGFR* mutation status unknown tumors.

For each biomarker, patients were classified as positive, negative, or unknown. For each of these groups, HRs, 95% CIs, and *P* values were estimated for PFS and OS (by using a Cox proportional hazards model adjusted for the same covariates as for the primary PFS analysis in the ITT population). The biomarker status by randomly assigned treatment interaction was assessed individually for each biomarker for PFS and OS by using a Cox proportional hazards model adjusted for randomly assigned treatment, biomarker status (positive or negative), and the biomarker status by treatment interaction by using a 10% significance level to indicate potential predictive factors for gefitinib versus carboplatin/paclitaxel. When there were fewer than 20 events in a subgroup for PFS or OS, only descriptive summaries were produced. Odds ratios, 95% CIs, and *P* values were estimated for ORRs by using a logistic regression model adjusted for the same covariates as those used in the analysis of PFS in the ITT population.

RESULTS

Patients

Patient disposition is presented in Figure 1. Therapies received postdiscontinuation of randomly assigned treatment are listed in Table 1. Specifically, 83 (64.3%) of 129 patients with *EGFR* mutation–positive tumors randomly assigned to carboplatin/paclitaxel received subsequent EGFR TKIs.

OS (ITT Population)

The median duration of follow-up for OS was 17.0 months. At the time of data cutoff for OS (June 14, 2010), 954 patients (78%) had died (Fig 2A). In the overall population, OS was similar for gefitinib and carboplatin/paclitaxel with no significant difference between treatments (484 and 470 events, respectively; HR, 0.90; 95% CI, 0.79 to 1.02; $P = .109$; median OS for gefitinib, 18.8 months *v* 17.4 months for carboplatin/paclitaxel; Fig 2A). A consistent treatment effect was seen across all clinical subgroups (Fig 3C).

Biomarker Evaluations

Of 683 randomly assigned patients (56.1%) who provided samples for biomarker analysis, 118 were cytology samples, which were not included in the main analysis. The number of patients with an evaluable status was 437 (35.9%) for *EGFR* mutation, 406 (33.4%) for