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JOURNAL OF CLINICAL ONCOLOGY

Human Epidermal Growth Factor Eyedrops for Cetuximab-Related Filamentary Keratitis

Case Report

A 68-year-old woman with lung metastases from colorectal cancer was treated with weekly cetuximab plus biweekly CPT-11 (CPT-11+cetuximab) beginning in December 2009. On March 16, 2010, after five cycles of CPT-11+cetuximab, stable disease was confirmed on the basis of Response Evaluation Criteria in Solid Tumors (RECIST) on chest/abdominal computed tomography scans and this therapy was therefore continued. However, the patient developed grade 2 xerosis and periungual inflammation as well as grade 1 hair loss and trichomegaly related to the treatment with cetuximab.

At the end of April, the patient began to experience bilateral ocular discomfort with diminished visual acuity. She had no history of ophthalmologic problems. On April 22, an ophthalmologic fluorescein examination revealed small filamentous agents that covered the entire corneal surface of both eyes (Figure 1A), an indication of filamentary keratitis. The Schirmer test was performed without topical anesthesia and results for both eyes were normal, suggesting normal tear production. There was no apparent relationship between trichomegaly of the patient's eyelashes and the corneal lesions (Figure 1B). Despite administration of three types of eyedrops (ie, levofloxacin, fluorometholone, and sodium hyaluronate) as standard therapy for 1 month, the filamentous agents persisted with no amelioration of the patient's symptoms.

After obtaining informed consent from the patient, we chose off-label use of recombinant human epidermal growth factor (EGF) eyedrops as an alternative therapy; these eyedrops are widely used in the treatment of intractable corneal wounds. On May 26, the patient began using the EGF eyedrops (5 μg/mL of recombinant EGF; AF-100-15; PeproTech, Rocky Hill, NJ) diluted with phosphate buffered saline twice a day. Thereafter, her symptoms gradually diminished, and the filamentous agents almost completely disappeared within 3 weeks (Figure 1C). It was not necessary to stop treatment with cetuximab as a result of the keratitis. For 3 months, until tumor progression was detected on July 26, the patient was able to continue receiving treatment with CPT-11+cetuximab, using human EGF eyedrops concomitantly, and experienced no recurrence of filamentary keratitis. Despite discontinuation of CPT-11+cetuximab and human EGF eyedrops on July 29, her filamentary keratitis has not recurred to date.

Discussion

Filamentary keratitis is usually a chronic corneal lesion that is characterized by filamentous agents that are attached, at one or both ends, to the cornea. Patients often experience foreign-body sensations, discomfort, photophobia, increased blinking, and can occasionally experience severe pain. Filament generation is assumed to be triggered by an injury, possibly associated with inflammation, to the surface

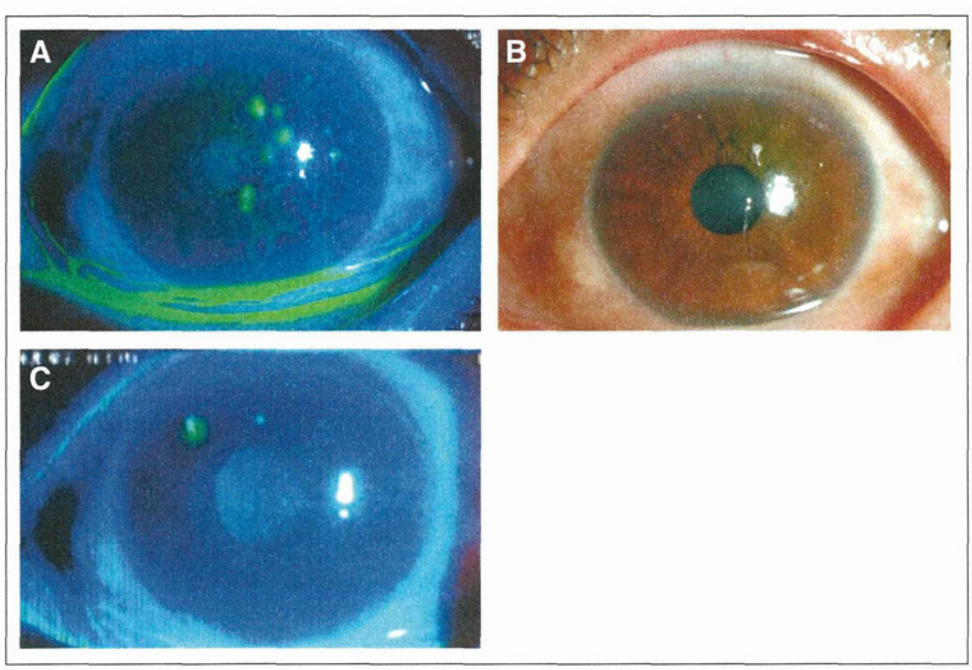

Fig 1.

epithelium of the cornea.[1] The management of filamentary keratitis can be clinically challenging. Current best-practice management of filamentary keratitis involves treatment of the underlying dry eye and specific treatments that are aimed at the corneal filaments.[2] Proposed treatments include lubricants, topical steroidal and nonsteroidal anti-inflammatory agents, and punctal plugs for aqueous-deficient dry eye, as well as mechanical removal of filaments, hypertonic saline, mucolytic agents, and bandage contact lenses for the filaments. However, the fundamental management strategy is treatment of the underlying cause of filament generation.

Cetuximab, a monoclonal antibody directed against the epidermal growth factor receptor (EGFR), has been demonstrated to improve overall and progression-free survival in patients with colorectal cancer that is refractory to traditional chemotherapy. EGFR inhibitors (EGFRIs) such as cetuximab typically induce adverse effects such as papulopustular rash, dry skin, itching, and hair and periungual alterations. It is not surprising that these adverse reactions occur as dermatologic symptoms because cutaneous tissues are critically dependent on EGFR signaling for normal function.[3]

We had two reasons for considering the cause of this patient's filamentary keratitis to be cetuximab, an EGFRI. First, EGFR signaling is known to play an important role in normal ocular homeostasis.[4] EGFRs are strongly expressed on the corneal epithelium, keratinocytes, and the endothelium. Endogenous EGF is found in high concentrations in tears, promoting the migration and proliferation of epithelial cells and thereby facilitating corneal epithelial wound healing.[4,5] Several clinical studies of topically applied EGF yielded promising results in terms of corneal epithelial healing after severe corneal damage, such as with corneal trauma. Recently, EGF eyedrops have been confirmed as an efficacious topical treatment for traumatic corneal ulcers[6] and herpetic corneal ulcers.[7] At present, human EGF eyedrops are an option, although off-label, for treating intractable corneal wounds.

Second, there is evidence that indicates that the inhibition of EGFR-mediated signaling pathways will evoke corneal damage in vivo.[8] For example, in preclinical toxicity studies, the systemic administration of gefitinib, an EGFR tyrosine kinase inhibitor, was reported to significantly delay the corneal epithelial healing and to decrease corneal epithelial cell proliferation in rats and dogs.[9,10] A small number of cases of EGFRI-associated corneal wounds in humans have also been reported.[11,12] Most required discontinuation of EGFRI because of exacerbation of symptoms. It is regrettable when EGFRI must be stopped because of adverse effects. Thus, treatment options for these adverse reactions are needed so that patients can continue their anticancer treatment as scheduled.

To our knowledge, this is the first report of filamentary keratitis associated with cetuximab that was successfully treated with EGF eyedrops. Although there is one report that describes the use of topical human EGF for the treatment of corneal damage during cetuximab treatment,[13] the filamentary keratitis was nonspecific in that case. Our case is noteworthy in that it was not necessary to stop antitumor treatment with cetuximab because of adverse effects. This raises the possibility that human EGF eyedrops are an effective therapy for EGFRI-associated corneal damage. It is important for patients to continue treatment with cetuximab as long as this agent remains effective. Use of EGF eyedrops for EGFRI-associated corneal damage is a reasonable treatment option, given that such eyedrops may augment endogenous EGF in tears and thereby locally reverse the inhibition of EGFR signaling by EGFRI. EGFR eyedrops also seem to be safe, given that there is no evidence of carcinogenesis associated with topical application of EGF. With the increasing use of cetuximab in cancer therapy, cetuximab-associated corneal damage may occur more frequently. Moreover, the topical EGF treatment administered to our patient might be applicable to serious adverse dermatologic reactions to EGFRI. Given that EGFRIs are such a promising anticancer therapy, we anticipate future studies aimed at establishing therapies for some of the adverse effects that typically occur with EGFRI administration.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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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)

Masahiro Fukuoka, Yi-Long Wu, Sumitra Thongprasert, Patrapim Sunpaweravong, Swan-Swan Leong, Virote Sriuranpong, Tsu-Yi Chao, Kazuhiko Nakagawa, Da-Tong Chu, Nagahiro Saijo, Emma L. Duffield, Yuri Rukazenkov, Georgina Speake, Haiyi Jiang, Alison A. Armour, Ka-Fai To, James Chih-Hsin Yang, and Tony S.K. Mok

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

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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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,

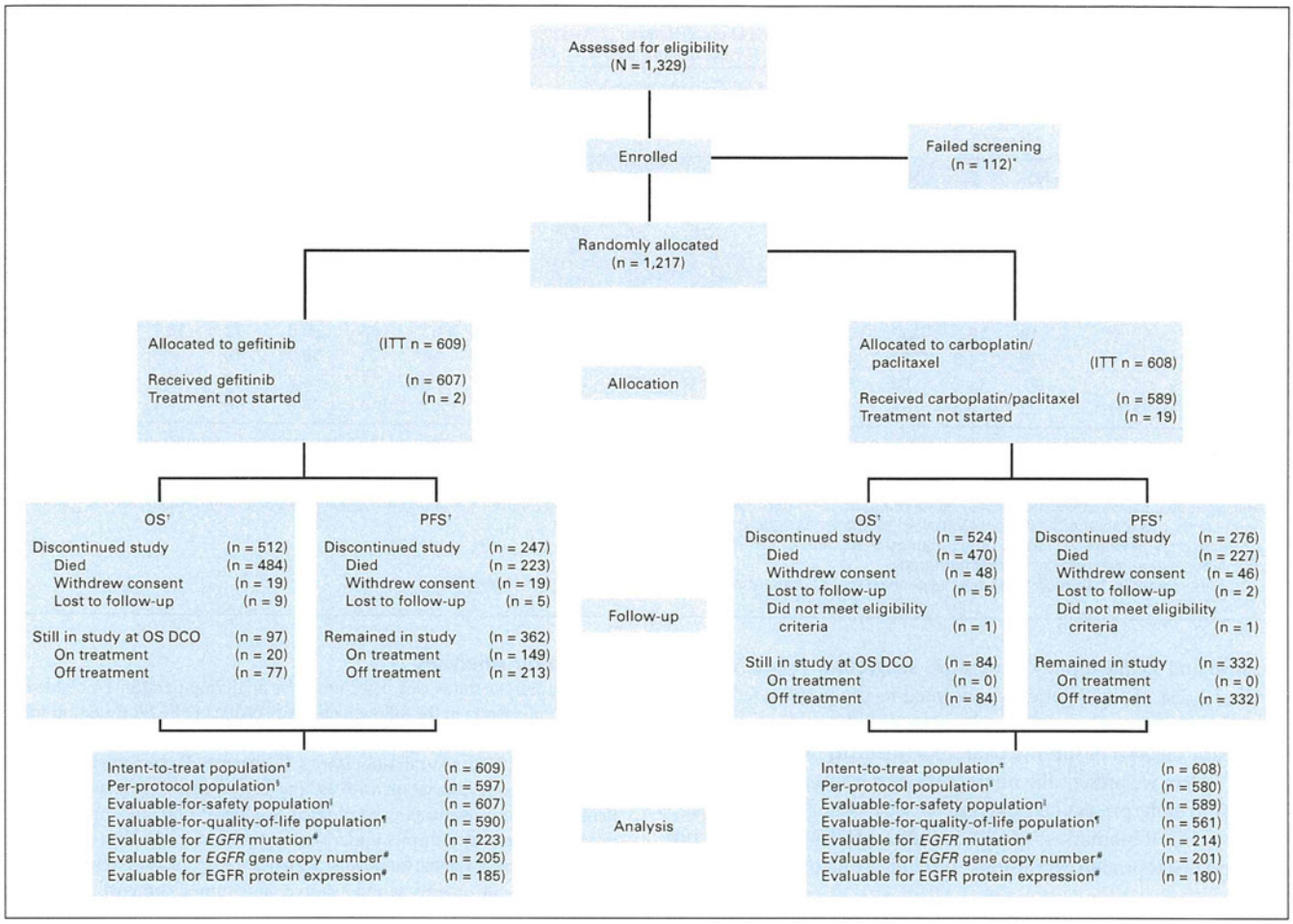

Fig 1. CONSORT diagram. (*) Among the 112 patients who failed screening, the main reasons for exclusion were abnormal serum creatinine (> 1.5 × upper limit of reference range)/creatinine clearance (≤ 60 mL/min) levels; untreated CNS metastases; or low neutrophil (< 2.0 × 10^9/L), platelet (< 100 × 10^9/L), 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.

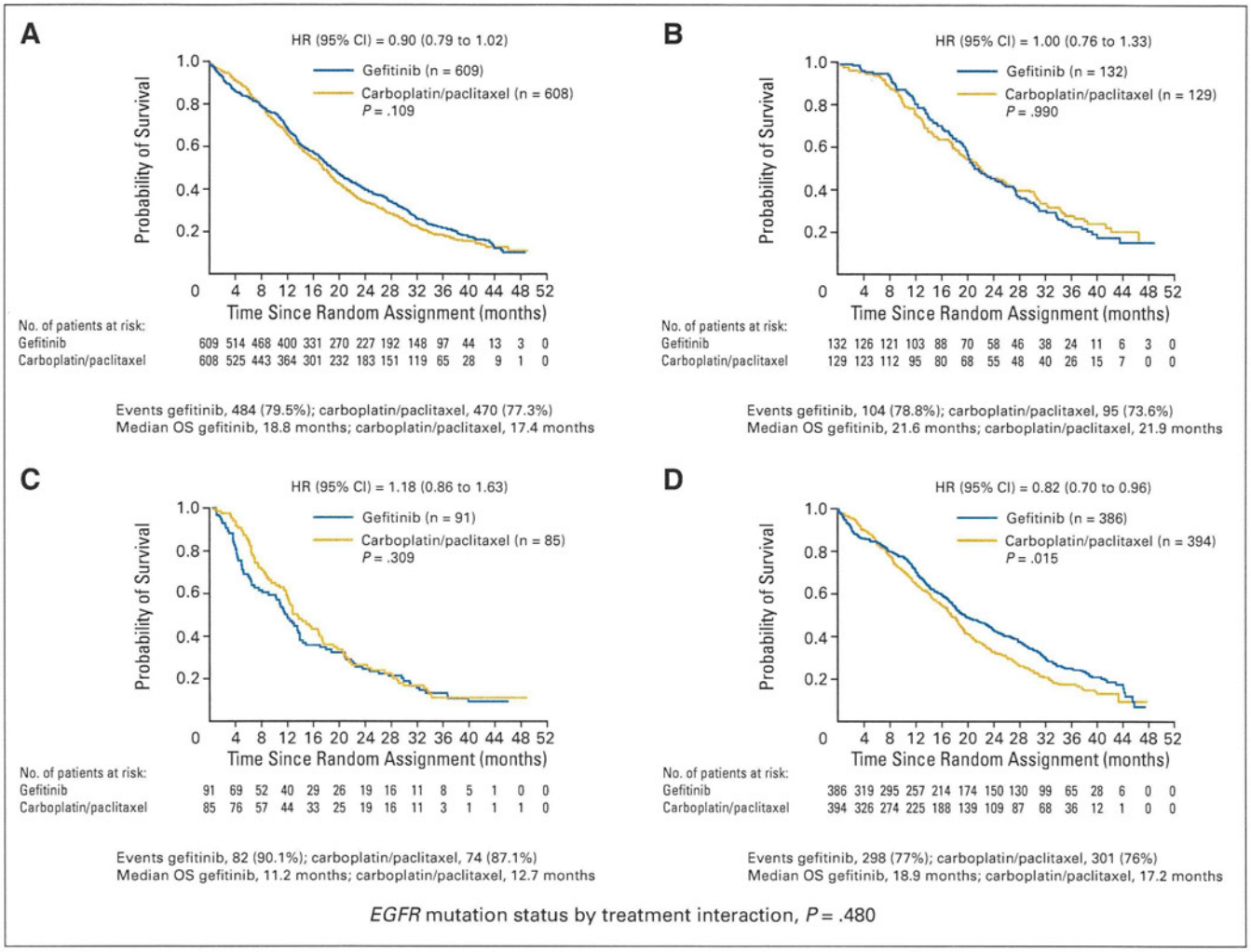

Fig 2. Kaplan-Meier curves for overall survival (OS) in the overall population and by epidermal growth factor receptor (*EGFR*) mutation status (intent-to-treat population). Hazard ratio (HR) < 1 implies a lower risk of death for patients treated with gefitinib. Cox analysis with covariates (performance 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

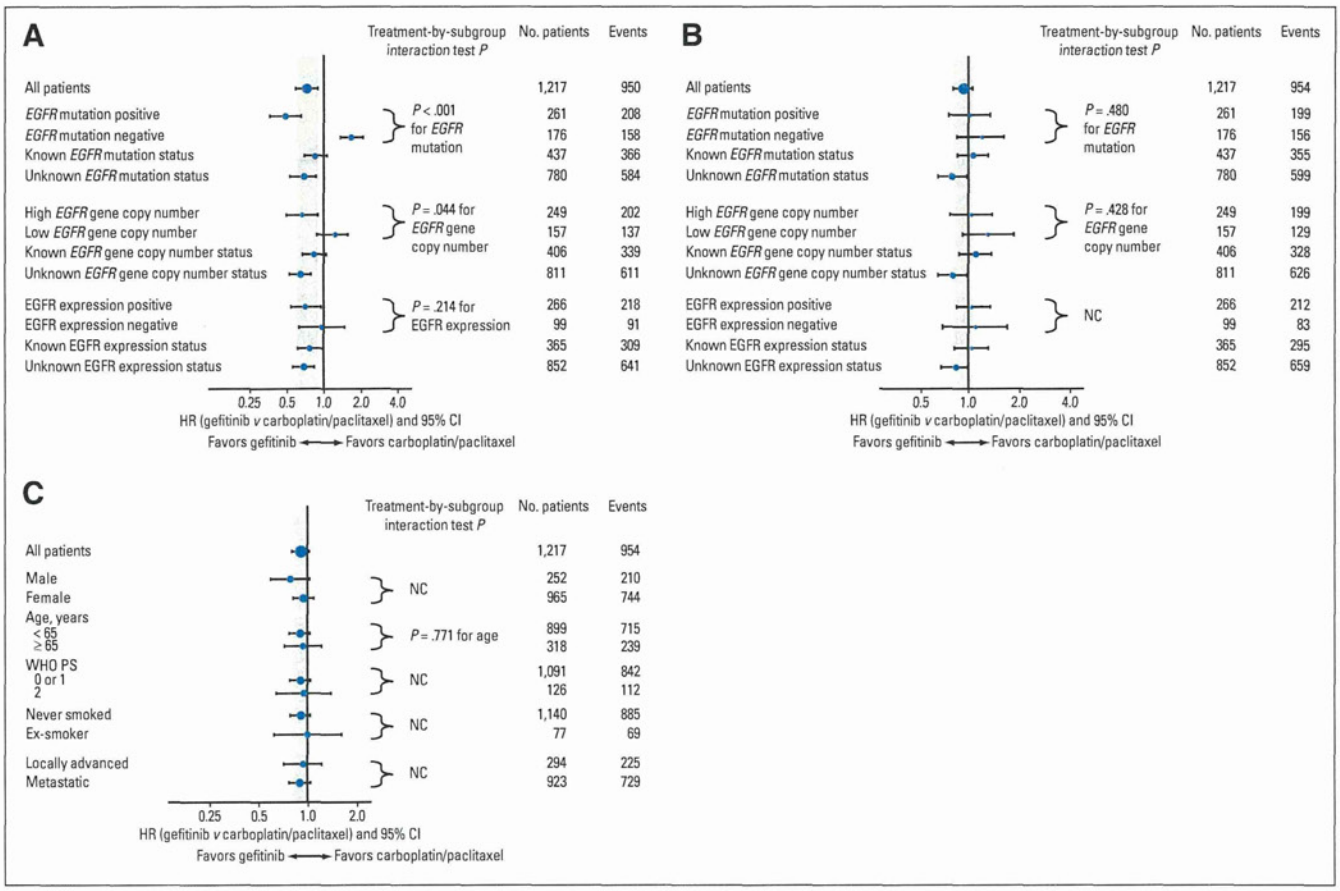

Fig 3. Forest plot of progression-free survival (PFS) and overall survival (OS) by epidermal growth factor receptor (EGFR) mutation status, gene copy number, and protein expression status (intent-to-treat population). (A) PFS by biomarker status. (B) OS by biomarker status. (C) OS by clinical subgroup. Hazard ratio < 1 implies a lower risk of progression or death for patients treated with gefitinib. The size of the point estimate reflects the number of events in the subgroup, with a larger circle indicating more events. Cox analysis with covariates (performance status [PS], 0 to 1 or 2; smoking history, never-smoker, light ex-smoker; and sex). OS by biomarker status; no formal adjustment for multiple testing was made, therefore, statistical significance at the traditional 5% level (95% CI < 1) cannot be claimed. Protocoled interaction tests were calculated only for OS and clinical subgroups if there was a significant interaction test for PFS. NC, not calculated.

EGFR gene copy number, and 365 (30.0%) for EGFR protein expression (Fig 1); the percentage of patients with a positive EGFR biomarker status was 59.7% (261 of 437), 61.3% (249 of 406), and 72.9% (266 of 365), respectively. A summary of EGFR biomarker status is presented in the Data Supplement.

The demographics, baseline characteristics, and efficacy results of patients with evaluable samples for assessment of *EGFR* mutation status, gene copy number, and protein expression were generally comparable with the ITT population (Table 2). There was a high degree of overlap between patients who were positive for all three biomarkers; 190 patients (78.5%) with high *EGFR* gene copy number also harbored an *EGFR* mutation; 132 patients were positive for all three biomarkers.

EGFR *Mutation Status*

Demographic and baseline characteristics by *EGFR* mutation status are shown in the Data Supplement. PFS results by *EGFR* mutation status have been previously published[19] (Fig 3A).

There was no differential treatment effect for OS by *EGFR* mutation (treatment by *EGFR* mutation interaction test $P = .480$). There was no significant difference in OS for gefitinib versus carboplatin/paclitaxel in the subgroups of patients with *EGFR* mutation–positive tumors (104 and 95 events, respectively; HR, 1.00; 95% CI, 0.76 to 1.33; $P = .990$; median OS, 21.6 *v* 21.9 months); *EGFR* mutation–negative tumors (82 and 74 events, respectively; HR, 1.18; 95% CI, 0.86 to 1.63; $P = .309$; median OS, 11.2 *v* 12.7 months), or mutation status unknown tumors (298 and 301 events, respectively; HR, 0.82; 95% CI, 0.70 to 0.96; $P = .015$; Figs 2B, 2C, 2D, and 3B). Postdiscontinuation treatments by *EGFR* mutation status are listed in Table 1.

EGFR *Gene Copy Number*

EGFR gene copy number was a predictive biomarker for the effect of gefitinib compared with carboplatin/paclitaxel on PFS (treatment by *EGFR* gene copy number interaction test $P = .044$; Fig 3A). In patients with high *EGFR* gene copy number (fluorescent in situ hybridization scores 5 and 6; n = 249), PFS was significantly longer with gefitinib versus carboplatin/paclitaxel (HR, 0.66; 95% CI, 0.50 to 0.88; $P = .005$). ORR also significantly favored gefitinib in these patients (58.9% *v* 44.8% for gefitinib *v* carboplatin/paclitaxel, respectively; odds ratio [OR], 1.79; 95% CI, 1.08 to 2.96; $P = .024$). Conversely, in

Table 2. Demographics, Baseline Characteristics, and Analysis Outcomes for Patients with Evaluable Tissue Samples for Each Biomarker Compared With the ITT Population

	Evaluable for *EGFR* Mutation Status* (n = 437)					Evaluable for *EGFR* Gene Copy Number Status* (n = 406)					Evaluable for EGFR Protein Expression Status* (n = 365)					ITT Population (n = 1,217)				
Variable	No.	%	HR	OR	95% CI	No.	%	HR	OR	95% CI	No.	%	HR	OR	95% CI	No.	%	HR	OR	95% CI
Demographic characteristic																				
Female	335	76.7				313	77.1				285	78.1				965	79.3			
Age < 65 years	326	74.6				303	74.6				262	71.8				899	73.9			
WHO PS 0 or 1	402	92.0				375	92.4				334	91.5				1,091	89.6			
Never-smoker	405	92.7				375	92.4				334	91.5				1,140	93.7			
Locally advanced	83	19.0				77	19.0				67	18.4				295	24.2			
Efficacy																				
PFS			0.85		0.69 to 1.06			0.83		0.66 to 1.03			0.79		0.62 to 0.99			0.74		0.65 to 0.85
ORR				1.21	0.83 to 1.78				1.31	0.88 to 1.95				1.43	0.94 to 2.18				1.59	1.25 to 2.01
OS			1.05		0.85 to 1.29			1.10		0.89 to 1.37			1.04		0.82 to 1.30			0.90		0.79 to 1.02

NOTE. Hazard ratio (HR) < 1 implies a lower risk of progression or death on gefitinib; odds ratio (OR) > 1 implies a greater chance of response on gefitinib.
Abbreviations: ITT, intent to treat; EGFR, epidermal growth factor receptor; PS, performance status; PFS, progression-free survival; ORR, objective response rate; OS, overall survival.
*Irrespective of whether positive or negative for each biomarker.

patients with low *EGFR* gene copy number (n = 157), PFS was numerically longer (HR, 1.24; 95% CI, 0.87 to 1.76; $P = .237$) and ORR was numerically higher (26.3% *v* 22.2%; OR, 0.80; 95% CI, 0.38 to 1.68; $P = .558$) with carboplatin/paclitaxel versus gefitinib.

A total of 190 patients (78%) with high *EGFR* gene copy number also harbored *EGFR* mutations. Of the 153 patients with low *EGFR* gene copy number, only 51 (33%) were also *EGFR* mutation positive. Post hoc analyses found that PFS was significantly shorter with gefitinib versus carboplatin/paclitaxel in patients with high *EGFR* gene copy number in the absence of a coexisting *EGFR* mutation (n = 55; HR, 3.85; 95% CI, 2.09 to 7.09), although patients with *EGFR* mutation achieved significantly longer PFS with gefitinib versus carboplatin/paclitaxel irrespective of whether they had high (HR, 0.48; 95% CI, 0.34 to 0.67; n = 190) or low (HR, 0.51; 95% CI, 0.25 to 1.04; n = 51) *EGFR* gene copy number (Figs 4A to 4D).

There was no differential treatment effect for OS by *EGFR* gene copy number (treatment by *EGFR* gene copy number interaction test $P = .428$). There was no significant difference in OS for gefitinib versus carboplatin/paclitaxel in patients with high *EGFR* gene copy number (104 and 95 events, respectively; HR, 1.03; 95% CI, 0.78 to 1.37; $P = .816$) or low *EGFR* gene copy number (67 and 62 events, respectively; HR, 1.30; 95% CI, 0.92 to 1.85; $P = .137$; Fig 3B).

EGFR Protein Expression

There was no differential treatment effect for PFS by EGFR protein expression (treatment by EGFR protein expression status interaction test $P = .214$; Fig 3A). PFS was significantly longer for gefitinib versus carboplatin/paclitaxel in patients with EGFR protein expression–positive tumors (HR, 0.73; 95% CI, 0.55 to 0.96; $P = .024$; n = 266). There was no significant difference in PFS between treatments in patients with EGFR protein expression–negative tumors (HR, 0.97; 95% CI, 0.64 to 1.48; $P = .893$; n = 99).

ORRs were similar between the gefitinib and carboplatin/paclitaxel groups for patients with either EGFR protein expression–positive (51.5% *v* 41.8%; OR, 1.49; 95% CI, 0.92 to 2.42; $P = .109$) or EGFR protein expression–negative (34.0% *v* 26.1%; OR, 1.44; 95% CI, 0.60 to 3.47; $P = .415$) tumors.

There was no significant difference in OS for gefitinib versus carboplatin/paclitaxel in patients with EGFR protein expression–positive (107 and 105 events, respectively; HR, 1.05; 95% CI, 0.80 to 1.37; $P = .731$) or EGFR protein expression–negative (46 and 37 events, respectively; HR, 1.09; 95% CI, 0.70 to 1.70; $P = .692$) tumors.

Activating EGFR *Mutation Type*

Of the 261 patients with *EGFR* mutation–positive tumors, 53.6% (n = 140) had tumors with exon 19 deletions, and 42.5% (n = 111) had exon 21 L858R mutations (Data Supplement); demography was generally similar between these groups (Data Supplement).

In post hoc analyses, PFS was significantly longer for gefitinib versus carboplatin/paclitaxel in both the exon 19 deletions (HR, 0.38; 95% CI, 0.26 to 0.56) and the exon 21 L858R mutation (HR, 0.55; 95% CI, 0.35 to 0.87; Figs 5A and 5B) subgroups. Within-treatment analysis indicated no significant difference in PFS with gefitinib in the exon 19 deletions versus exon 21 L858R mutation subgroup (HR, 0.78; 95% CI, 0.51 to 1.19). ORR was significantly higher with gefitinib (84.8%) versus carboplatin/paclitaxel (43.2%; OR, 7.23; 95% CI, 3.19 to 16.37) in the exon 19 deletions subgroup and higher (but not statistically significant) in the L858R subgroup (60.9% *v* 53.2%; OR, 1.41; 95% CI, 0.65 to 3.05).

DISCUSSION

Gefitinib showed similar OS to doublet chemotherapy with no significant difference in the overall population or in patients with *EGFR* mutation–positive or *EGFR* mutation–negative status. The significant treatment-related differences for PFS and ORR according to *EGFR* mutation status were not observed for OS. Although there may be other contributing factors, the subsequent treatments that patients received are likely to have confounded the true effect of the initial, randomized first-line treatment on OS. Of the *EGFR* mutation–positive subgroup randomly assigned to carboplatin/paclitaxel, 64.3% received EGFR TKIs postdiscontinuation. Fewer patients with unknown mutation status randomly assigned to carboplatin/paclitaxel received EGFR TKIs (47.5%) compared with patients with *EGFR* mutation–positive status (64.3%), which may potentially contribute to the numerical trend in favor of gefitinib in this subgroup; statistical significance at the traditional 5% level ($P < .05$) cannot be claimed because no adjustment was made for multiple testing. The First-SIGNAL study had a study design similar to that of IPASS[23] and

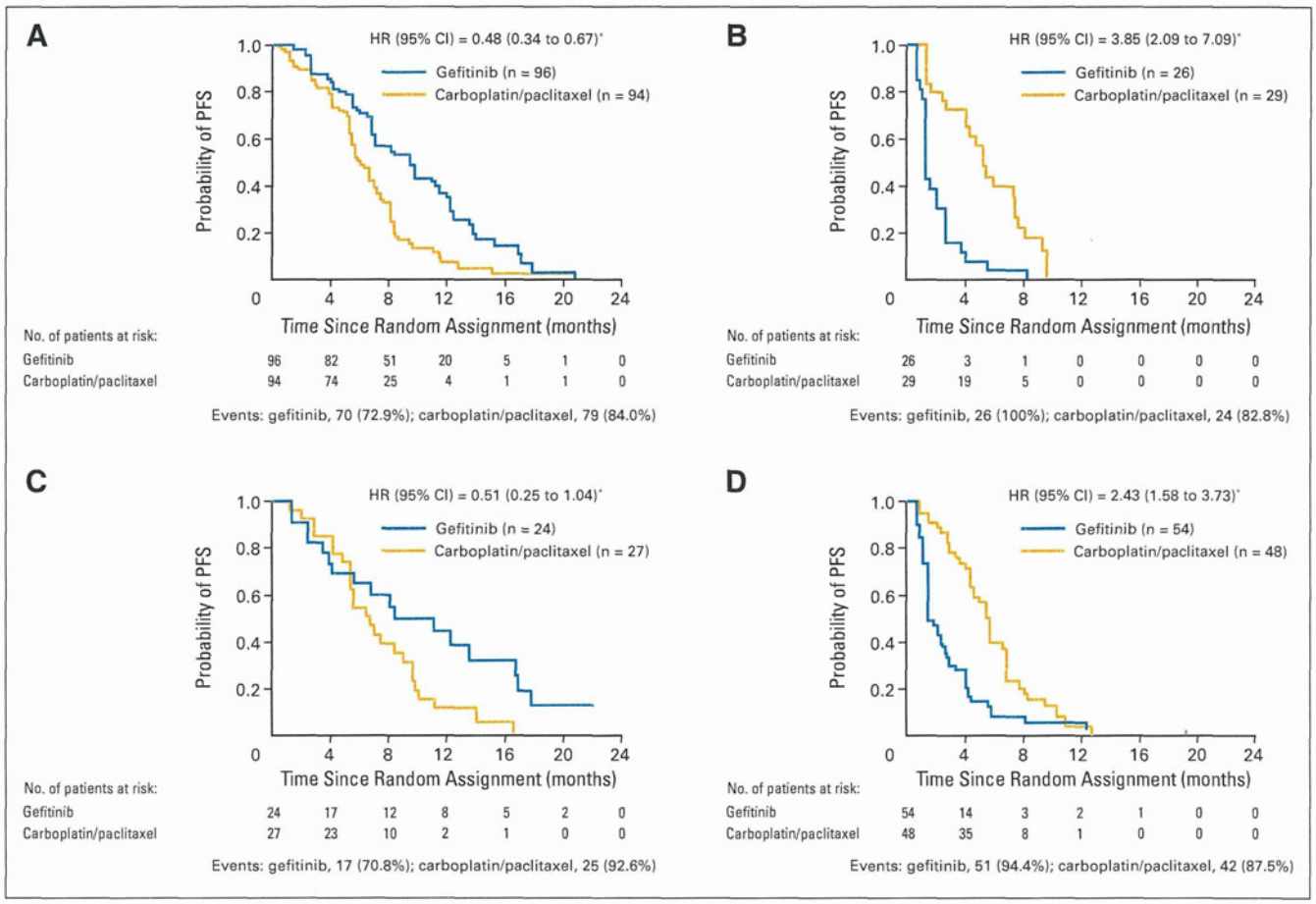

Fig 4. Kaplan-Meier curves for progression-free survival (PFS) by epidermal growth factor receptor (*EGFR*) mutation status and *EGFR* gene copy number. Hazard ratio (HR) < 1 implies a lower risk of progression/death for patients treated with gefitinib. (A) High *EGFR* gene copy number *EGFR* mutation–positive. (B) High *EGFR* gene copy number *EGFR* mutation–negative. (C) Low *EGFR* gene copy number *EGFR* mutation–positive. (D) Low *EGFR* gene copy number *EGFR* mutation–negative. (*) Cox analysis with covariates (performance status [0-1, 2], smoking history [never, light ex-smoker], and sex).

reported no significant difference in OS (primary end point) between gefitinib versus gemcitabine/cisplatin (overall population, 182 events; 59% maturity; mutation-positive HR, 0.82; 95% CI, 0.35 to 1.92; $P = .648$; median survival, 30.6 *v* 26.5 months, respectively). The randomized Japanese NEJ002 study also reported that OS did not differ significantly between gefitinib and carboplatin/paclitaxel in patients selected by *EGFR* mutation status (median survival, 30.5 *v* 23.6 months, respectively; $P = .31$), likely explained by treatment crossover.[24]

Although collection of tumor material was not mandatory or feasible in all patients, IPASS has the largest group of patients with *EGFR* mutation–positive tumors studied in a randomized controlled trial in NSCLC and has confirmed *EGFR* mutation to be the strongest predictive biomarker for the effect of gefitinib with a statistically significant interaction test for PFS. Patients with mutation-negative tumors have a poorer outcome in terms of PFS and ORR with gefitinib compared with carboplatin/paclitaxel, indicating that in the first-line setting, gefitinib should not be used in preference to doublet chemotherapy in patients with a negative mutation status.

Our findings were broadly consistent with those of previous first-line, single-arm studies of gefitinib in patients with *EGFR* mutation–positive tumors.[25-32] Recently, outcomes similar to those of IPASS among patients with *EGFR* mutation–positive tumors have been reported in two randomized phase III studies[24,33] comparing first-line gefitinib with doublet chemotherapy, with PFS as the primary end point. The NEJ002 study prospectively randomly assigned 230 patients with *EGFR* mutation–positive tumors to gefitinib or carboplatin/paclitaxel. PFS favored gefitinib over carboplatin/paclitaxel (PFS HR, 0.30; 95% CI, 0.22 to 0.41; $P < .001$; median PFS, 10.8 *v* 5.4 months; tumor response rate, 73.7% *v* 30.7%, respectively; $P < .001$).[24] The similarly designed West Japan Thoracic Oncology Group 3405 (WJTOG3405) study reported increased PFS with gefitinib over cisplatin/docetaxel in 172 patients with *EGFR* mutation–positive tumors (PFS HR, 0.49; 95% CI, 0.34 to 0.70; $P < .001$; median PFS, 9.2 *v* 6.3 months; 295 events; 95% maturity).[33] Tumor response rates (n = 117) were 62.1% and 32.2%. In the First-SIGNAL study, PFS (secondary end point) increased with gefitinib compared with gemcitabine/cisplatin in 42 patients with *EGFR* mutation–positive tumors (PFS HR, 0.61; 95% CI, 0.31 to 1.22; $P = .084$; median PFS, 8.4 *v* 6.7 months).[23] The OPTIMAL study compared erlotinib with gemcitabine/cisplatin in 154 patients with *EGFR* mutation–positive tumors and also reported a significant difference in PFS (HR, 0.16; 95% CI, 0.10 to 0.26; $P = .001$).[34] The similarly designed European Tarceva

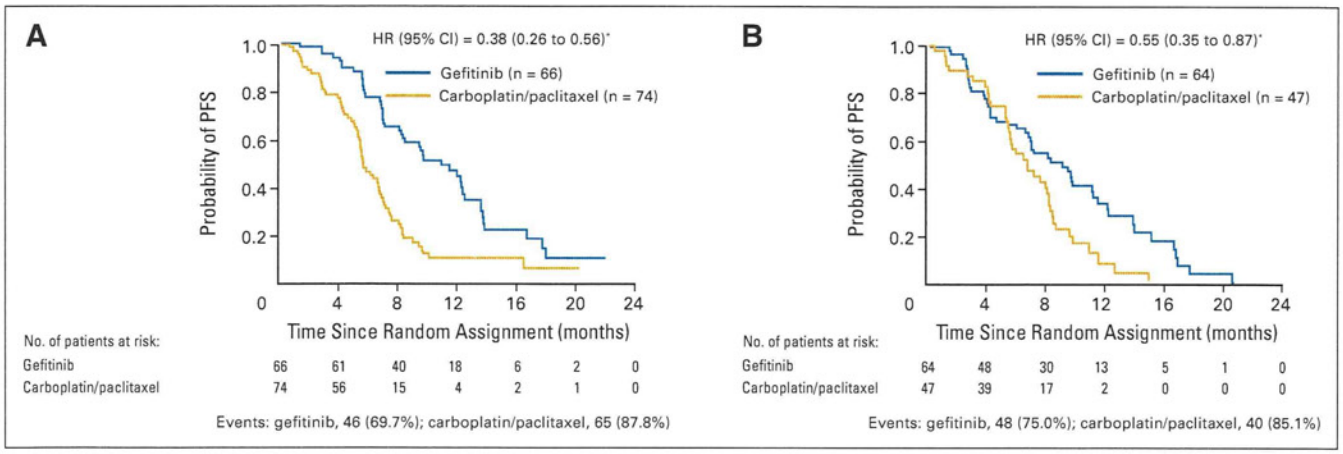

Fig 5. Kaplan-Meier curves for progression-free survival (PFS) by epidermal growth factor receptor (*EGFR*) mutation type (intent-to-treat population). Hazard ratio (HR) < 1 implies a lower risk of progression/death for patients treated with gefitinib. (A) Exon 19 deletion. (B) L858R. (*) Cox analysis with covariates (performance status [0-1, 2], smoking history [never, light ex-smoker], and sex).

versus Chemotherapy (EURTAC) study is ongoing. Therefore to date, including IPASS, five randomized studies have shown that EGFR TKIs offer significant benefits over standard chemotherapy in patients with *EGFR* mutation–positive tumors.

In IPASS, high *EGFR* gene copy number was predictive for the effect of gefitinib versus carboplatin/paclitaxel on PFS. The significantly longer PFS with gefitinib in patients with both high *EGFR* gene copy number and *EGFR* mutation–positive tumors was not observed in patients with high *EGFR* gene copy number without an accompanying mutation, suggesting that the apparent PFS benefit was driven by overlap with a coexisting *EGFR* mutation (77.6% of patients with high *EGFR* gene copy number also had *EGFR* mutation–positive tumors). Patients with *EGFR* mutation–positive tumors without accompanying high *EGFR* gene copy number showed longer PFS with gefitinib than with carboplatin/paclitaxel, suggesting that *EGFR* mutations determine the treatment outcomes independent of the status of *EGFR* gene copy number.

Post hoc analyses of PFS by *EGFR* mutation type showed that PFS was significantly longer for gefitinib than for carboplatin/paclitaxel in both the exon 19 deletions and exon 21 L858R subgroups, with a slightly greater advantage in the exon 19 deletions subgroup. First-line, single-arm studies[35,36] have reported an increased response to EGFR TKIs in patients with exon 19 deletions *v* exon 21 L858R mutation. However, IPASS (HR, 0.78; 95% CI, 0.51 to 1.19), WJTOG3405 (HR, 1.13; 95% CI, 0.63 to 2.03; $P = .681$), and NEJ002 (11.5 *v* 10.8 months; $P = .90$) randomized phase III studies and the prospective phase II iTARGET study ($P = .600$) showed no significant difference in PFS for gefitinib between the exon 19 deletions and exon 21 L858R mutation subgroups.[24,25,33]

In summary, *EGFR* mutation was the strongest predictive biomarker for benefit of gefitinib over carboplatin/paclitaxel on PFS and ORR. Post hoc analyses suggested that the predictive value of *EGFR* gene copy number for PFS benefit with gefitinib was driven by the overlap of high *EGFR* gene copy number with a positive *EGFR* mutation status. Treatment-related differences for PFS seen in patients with a positive *EGFR* mutation status were not apparent for OS. The OS results were likely confounded by the high proportion of patients receiving different types of subsequent therapies and, in particular, crossing over to the alternative treatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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ORIGINAL REPORT

Phase III Trial Comparing Oral S-1 Plus Carboplatin With Paclitaxel Plus Carboplatin in Chemotherapy-Naïve Patients With Advanced Non–Small-Cell Lung Cancer: Results of a West Japan Oncology Group Study

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

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ABSTRACT

Purpose
The primary goal of this open-label, multicenter, randomized phase III trial was to determine whether treatment with carboplatin plus the oral fluoropyrimidine derivative S-1 was noninferior versus that with carboplatin plus paclitaxel with regard to overall survival (OS) in chemotherapy-naive patients with advanced non–small-cell lung cancer (NSCLC).

Patients and Methods
A total of 564 patients were randomly assigned to receive either carboplatin (area under the curve, 5) on day 1 plus oral S-1 (40 mg/m^2 twice per day) on days 1 to 14 or carboplatin (area under the curve, 6) plus paclitaxel (200 mg/m^2) on day 1 every 21 days.

Results
At the planned interim analysis, with a total of 268 death events available, the study passed the O'Brien-Fleming boundary of 0.0080 for a positive result and noninferiority of carboplatin and S-1 compared with carboplatin and paclitaxel was confirmed for OS (hazard ratio, 0.928; 99.2% CI, 0.671 to 1.283). Median OS was 15.2 months in the carboplatin and S-1 arm and 13.3 months in the carboplatin and paclitaxel arm, with 1-year survival rates of 57.3% and 55.5%, respectively. Rates of leukopenia or neutropenia of grade 3/4, febrile neutropenia, alopecia, and neuropathy were more frequent in the carboplatin and paclitaxel arm, whereas thrombocytopenia, nausea, vomiting, and diarrhea were more common in the carboplatin and S-1 arm. The carboplatin and S-1 arm had significantly more dose delays than the carboplatin and paclitaxel arm.

Conclusion
Oral S-1 with carboplatin was noninferior in terms of OS compared with carboplatin and paclitaxel in patients with advanced NSCLC, and is thus a valid treatment option.

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INTRODUCTION

Lung cancer is the leading cause of death related to cancer worldwide,[1] with non–small-cell lung cancer (NSCLC) accounting for 85% of lung cancer cases. For individuals with advanced or metastatic NSCLC, platinum-based chemotherapy is the mainstay of first-line treatment on the basis of the moderate improvement in survival and quality of life it affords compared with best supportive care alone.[2-5] Thus, there is still a need for new treatment regimens to ameliorate symptoms and prolong survival in patients with advanced NSCLC in a manner that is both convenient and safe.

S-1 (TS-1; Taiho Pharmaceutical Co Ltd, Tokyo, Japan) is an oral fluoropyrimidine agent that consists of tegafur, 5-chloro-2,4-dihydroxypyridine, and potassium oxonate in a molar ratio of 1:0.4:1.[6,7] A phase II trial of oral S-1 as a single agent for the treatment of advanced NSCLC yielded a response rate of 22% and a median survival time of 10.2 months in 59 patients without prior chemotherapy.[8] We previously performed a phase I/II study of carboplatin/S-1 combination therapy and found that administration of S-1 (40 mg/m^2 twice per day) on days 1 to 14 in combination with carboplatin (area under the curve [AUC], 5) on day 1 of every 3-week cycle yielded efficacy results similar to those of other platinum doublets.[9] The carboplatin and S-1 combination had a more favorable toxicity profile than that typically seen with platinum-based regimens,

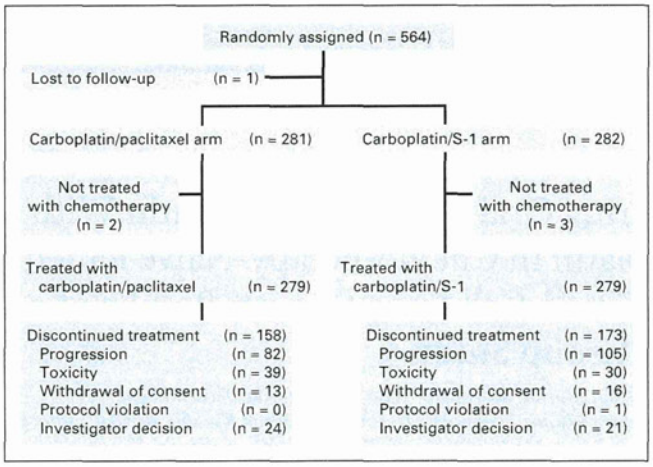

Fig 1. CONSORT diagram for the study.

especially with regard to neutropenia, febrile neutropenia, neuropathy, and alopecia.[9] In addition, replacement of paclitaxel with oral S-1 in combination therapy with carboplatin avoids the need for premedication to ameliorate paclitaxel-induced hypersensitivity and the 3-hour infusions required for paclitaxel administration. We therefore undertook and now report the results of the LETS (Lung Cancer Evaluation of TS-1) study, a multicenter, randomized, phase III, noninferiority trial of carboplatin and S-1 in comparison with carboplatin and paclitaxel combination therapy in chemotherapy-naive patients with advanced NSCLC.

PATIENTS AND METHODS

Patients

The criteria for patient eligibility included a diagnosis of NSCLC confirmed either histologically or cytologically; a clinical stage of IIIB not amenable to curative treatment or of stage IV; a measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST)[10]; no prior chemotherapy; an age of 20 to 74 years; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and a projected life expectancy of at least 3 months. Patients had adequate bone marrow reserve and organ function including a calculated creatinine clearance of ≥ 60 mL/min based on the standard Cockcroft and Gault formula. Radiation therapy for metastatic disease was permitted if it was completed at least 2 weeks before random assignment. Main exclusion criteria included active concomitant malignancy, symptomatic brain metastasis, interstitial pneumonia, watery diarrhea, heart failure, uncontrolled diabetes mellitus, active infection, and a past history of drug allergy. These inclusion and exclusion criteria are consistent with those of previous studies involving carboplatin and paclitaxel treatment.[11] Written informed consent was obtained from all patients, and the study protocol was approved by the institutional ethics committee of each of the participating institutions.

Treatment Plan

Eligible patients were randomly assigned to receive either carboplatin (AUC, 6) plus paclitaxel (200 mg/m^2) on day 1[11] or carboplatin (AUC, 5) on day 1 plus oral S-1 (40 mg/m^2 twice per day) on days 1 to 14. Chemotherapy was repeated every 3 weeks for a maximum of six cycles unless there was earlier evidence of disease progression or intolerance of the study treatment.

End Points

The primary objective of this open-label, multicenter, randomized phase III trial was to establish the noninferiority of S-1 plus carboplatin compared with paclitaxel plus carboplatin as first-line therapy in terms of overall survival (OS) in patients with advanced NSCLC. Secondary end points included tumor response, treatment safety, quality of life (QOL), and progression-free survival (PFS).

Baseline and Follow-Up Assessments

Baseline evaluations included medical history, physical examination, ECG, tumor status, ECOG performance status, and laboratory analyses. During treatment, blood counts and biochemical tests were performed at least biweekly. A computed tomography scan was performed for tumor assessment within 14 days of initiation of study treatment and was repeated after every 1 to 2 months of planned therapy. All responses were defined according to RECIST. If a patient was documented as having a complete response (CR) or a

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	Carboplatin/Paclitaxel (n = 281) No.	Carboplatin/Paclitaxel (n = 281) %	Carboplatin/S-1 (n = 282) No.	Carboplatin/S-1 (n = 282) %	*P*
Age, years					
Median	63		64		.510
Range	36-74		38-74		
Sex					
Male	215	76.5	217	77.0	.902
Female	66	23.5	65	23.0	
ECOG PS					
0	90	32.0	86	30.5	.695
1	191	68.0	196	69.5	
Histology					
Adenocarcinoma	195	69.4	195	69.1	.560
Nonadenocarcinoma	86	30.6	87	30.9	
Clinical stage					
IIIB	68	24.2	68	24.1	.981
IV	213	75.8	214	75.9	
Smoking status					
Smoker	229	81.5	230	81.6	.984
Nonsmoker	52	18.5	52	18.4	

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

partial response (PR), a confirmatory evaluation was performed after an interval of 4 weeks. Disease control was defined as the best tumor response among CR, PR, or stable disease that was confirmed and sustained for 6 weeks or longer. Patients were evaluated for adverse events during therapy and until 42 days after administration of the last dose of the study treatment. Toxicity was evaluated according to the National Cancer Institute Cancer Common Toxicity Criteria, version 3. QOL was assessed with the lung cancer subscale of the Functional Assessment of Cancer Therapy–Lung (FACT-L)[12] and the neurotoxicity subscale of the FACT/Gynecology Oncology Group-Neurotoxicity (GOG-Ntx) version 4.[13] In addition, alopecia was evaluated on the basis of the single item "I have been bothered by hair loss," which was included in the former version of FACT-L. The maximum attainable scores on the lung cancer subscale, neurotoxicity subscale, and alopecia item were 28, 44, and 4, respectively, with which the patient was considered to be asymptomatic. Patients were asked to complete each instrument at the time of enrollment and at 6 and 9 weeks after initiation of treatment.

Statistical Analysis

Eligible patients were randomly assigned according to a 1:1 ratio to receive either carboplatin and paclitaxel or carboplatin and S-1. After a check of patient eligibility, random assignment was performed centrally at the West Japan Oncology Group data center by minimization with stratification factors including disease stage (IIIB *v* IV), type of histology (adenocarcinoma *v* nonadenocarcinoma), sex (male *v* female), and investigator center. The intent-to-treat (ITT) patient population included all patients who underwent random assignment. The per-protocol (PP) population was defined as the ITT population minus patients considered to have major violations of inclusion or exclusion criteria and those who did not receive any protocol treatment. The safety population was defined as all patients receiving at least one dose of study drugs. The primary end point of the study was OS, which was analyzed in the ITT population by estimation of the hazard ratio (HR) and two-sided 95% CI derived from a Cox regression model with adjustment for the stratification factors with the exception of investigator center. Median OS in both treatment arms was assumed to be 14 months on the basis of data from previous clinical trials.[11] Noninferiority of carboplatin and S-1 was to be concluded if the upper limit of the 95% CI of the HR was lower than 1.33; that is, the null hypothesis that the median OS of the carboplatin and S-1 group would be up to 3.48 months shorter than that of the carboplatin and paclitaxel group was analyzed. Demonstration of noninferiority with a statistical power of 85% at a two-sided significance level of .05 and 2 years of follow-up after 2.5 years of accrual would require 263 patients in each treatment group. Given the possibility of variance inflation due to censoring, the sample size was set at 560 (280 per arm). One interim analysis was planned when all the patients had been enrolled. For analysis of the primary end point, adjustment for multiple comparisons was handled by the method of Lan and DeMets, with the use of the O'Brien-Fleming type α spending function. The significance level was set at .008 for the interim analysis, taking the numbers of observed events (n = 268) and expected events (n = 442) into account. Survival curves (PFS and OS) were analyzed by the Kaplan-Meier method and were compared between groups by the Cox regression model. The 95% CI for median PFS and OS was calculated by the method of Brookmeyer and Crowley. Planned subgroup analyses for OS were performed to examine the interaction effect of treatment arm with each of performance status, sex, disease stage, type of histology, and smoking status. Patient characteristics (ie, sex, ECOG PS, histology, clinical stage, and smoking status) as well as response and toxicity incidence were compared between the two treatment arms by the χ^2 test, and age was compared by the Wilcoxon test. Longitudinal QOL data were analyzed with a linear mixed-effects model. All *P* values were two sided. Statistical analyses were performed with SAS for Windows, release 9.1 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

From August 2006 to May 2008, 564 patients from 30 institutions were enrolled in the study. One patient was excluded from the carboplatin and paclitaxel arm because of loss to follow-up. The ITT population thus consisted of 563 patients: 281 individuals randomly assigned to the carboplatin and paclitaxel group and 282 individuals randomly assigned to the carboplatin and S-1 group (Fig 1). The baseline demographic and disease-related characteristics of the study subjects were well-balanced between the two treatment arms (Table 1). Two patients in the carboplatin and paclitaxel arm and three patients in the carboplatin and S-1 arm did not receive any chemotherapy, with the result that 558 patients were eligible for safety analysis (Fig 1).

Delivered Chemotherapy

The number of treatment courses administered was 1,037 in the carboplatin and paclitaxel arm (median, 4; range, 1 to 6) and 987 in the carboplatin and S-1 arm (median, 4; range, 1 to 6). Dose reductions occurred in 90 (8.7%) of the carboplatin and paclitaxel courses and in 49 (5.0%) of the carboplatin and S-1 courses. Carboplatin and paclitaxel dose reductions were mainly due to neuropathy, whereas those for carboplatin and S-1 were most commonly attributable to thrombocytopenia. Dose delays occurred in 47.9% of carboplatin and paclitaxel courses and 68.5% of carboplatin and S-1 courses. Delays due to

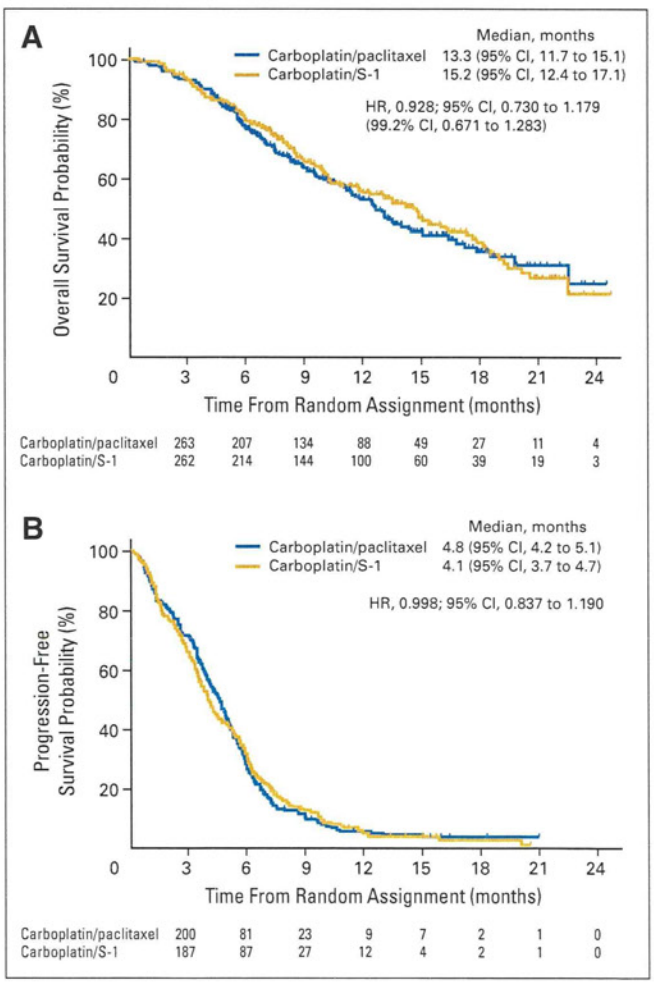

Fig 2. (A) Overall survival and (B) progression-free survival for the intent-to-treat population (n = 563). HR, hazard ratio.

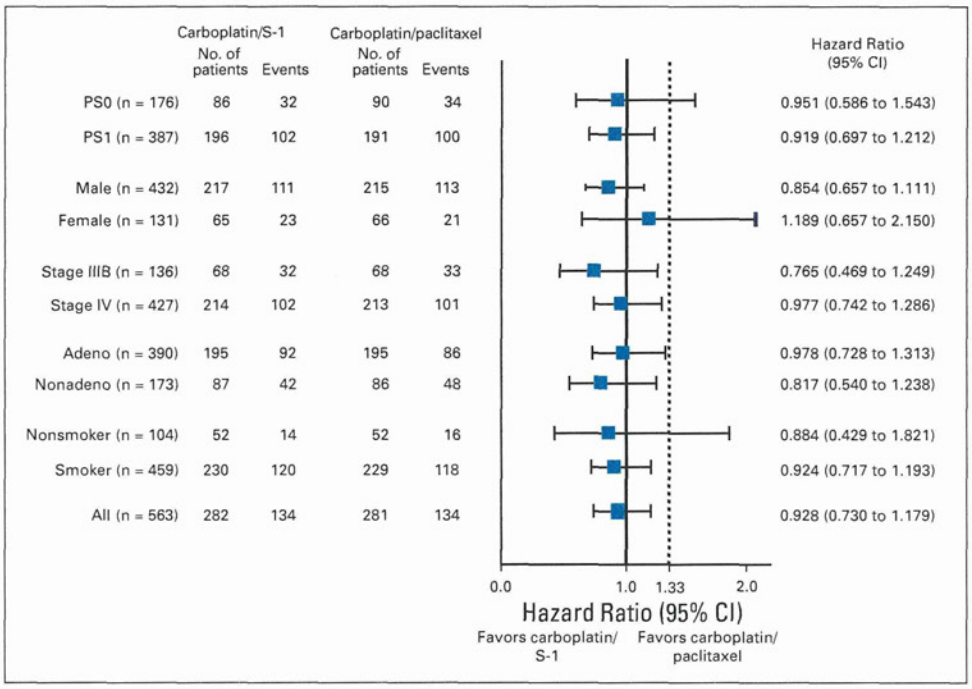

Fig 3. Subgroup analysis of overall survival in the intent-to-treat population (n = 563). PS, performance status; Adeno, adenocarcinoma; Nonadeno, nonadenocarcinoma.

hematologic toxicity occurred in a higher proportion of carboplatin and S-1 courses (51.6%) than carboplatin and paclitaxel courses (9.6%). S-1 was administered for the planned 14 days without interruption in 89.1% of carboplatin and S-1 courses. The median relative dose intensities were high for both carboplatin and paclitaxel (89.6% and 87.6%, respectively) and carboplatin and S-1 arms (83.3% and 94.3%, respectively). The most frequent reason for discontinuation of therapy was disease progression in both arms. Treatment was withdrawn before completion from a similar proportion of patients in each group (13.6% for carboplatin and paclitaxel and 10.7% for carboplatin and S-1) because of adverse events.

Efficacy

At the interim analysis planned for when patient enrollment was completed, 268 death events were available in total. The study passed the O'Brien-Fleming boundary of 0.0080 for a positive result with a *P* value of .002. The HR for OS (carboplatin and S-1 *v* carboplatin and paclitaxel) in the ITT population was 0.928, with a two-sided 99.2% CI after adjustment for multiplicity due to interim analysis of 0.671 to 1.283 (Fig 2A). Noninferiority of carboplatin and S-1 therapy was thus confirmed at the interim analysis by the upper limit of the CI being less than the protocol-specified margin of 1.33. The crude (unadjusted) 95% CI of the HR for OS of 0.928 was 0.730 to 1.179 in the ITT population, and an HR for OS of 0.931 (95% CI, 0.732 to 1.186) was obtained with the PP population. Median OS was 15.2 months (95% CI, 12.4 to 17.1) in the carboplatin and S-1 arm and 13.3 months (95% CI, 11.7 to 15.1) in the carboplatin and paclitaxel arm, with the 1-year survival rates being 57.3% and 55.5%, respectively. Subgroup analysis of OS in the ITT population according to stratification variables and other baseline characteristics were consistent with the primary analysis. A significant interaction effect between treatment arm and subgroups was not observed. The 95% CI for the HR in each subgroup included 1.00 (Fig 3).

The median PFS was 4.1 months in the carboplatin and S-1 arm and 4.8 months in the carboplatin and paclitaxel arm in the ITT population, with a corresponding HR of 0.998 and 95% CI of 0.837 to 1.190 (Fig 2B). In the PP population, the median values of PFS were 4.2 and 4.8 months for the carboplatin and S-1 and carboplatin and paclitaxel arms, respectively, with a corresponding HR of 0.992 and 95% CI of 0.832 to 1.184. Response to treatment was assessed in 279 patients (99.3%) of the carboplatin and paclitaxel group and in 279 patients (98.9%) of the carboplatin and S-1 group. For overall response (CR + PR) rate, carboplatin and paclitaxel was superior to carboplatin and S-1 (29.0% *v* 20.4%; $P = .019$, χ^2 test), whereas the overall disease control (CR + PR + stable disease) rate was similar in both treatment groups (73.5% *v* 71.7%, respectively; $P = .635$).

Safety

The incidence of leukopenia or neutropenia of grade 3 or 4 was significantly lower for patients in the carboplatin and S-1 arm than for those in the carboplatin and paclitaxel arm (leukopenia, 5% *v* 33%; neutropenia, 21% *v* 77%, respectively), as was the incidence of febrile neutropenia (1% *v* 7%; Table 2). Conversely, treatment with carboplatin and S-1 was associated with a higher rate of thrombocytopenia of grade 3 or 4 than was that with carboplatin and paclitaxel (33% *v* 9%, respectively). Platelet transfusion was also necessary for more patients in the carboplatin and S-1 arm than in the carboplatin and paclitaxel arm (8% *v* 2%, respectively; $P = .002$). The overall rates of neuropathy and alopecia were much lower in the carboplatin and S-1 arm (neuropathy, 16% *v* 81%; alopecia, 9% *v* 77%), whereas nausea, vomiting, and diarrhea occurred more frequently in the carboplatin/S-1 arm (Table 2). Death as a result of toxicity occurred in two patients; one death in the carboplatin and S-1 arm was associated with gastrointestinal hemorrhage, and another patient in the carboplatin and paclitaxel arm died of febrile neutropenia and pneumonia.

Table 2. Incidence of Drug-Related Toxicities in Randomly Assigned and Treated Patients

Toxicity	Regimen by Grade (%)						*P*	
	Carboplatin/Paclitaxel (n = 279)			Carboplatin/S-1 (n = 279)				
	All	3	4	All	3	4	All	3 or 4
Hematologic								
Leukopenia	86.0	29.7	2.9	55.4	5.0	0.4	< .001	< .001
Neutropenia	89.6	31.9	44.8	58.3	18.3	2.9	< .001	< .001
Anemia	82.4	14.3	2.5	86.7	15.5	3.6	.165	.680
Thrombocytopenia	63.1	7.2	2.2	87.4	19.4	13.3	< .001	< .001
Nonhematologic								
Febrile neutropenia	7.2	6.8	0.4	1.1	1.1	0	< .001	< .001
Nausea	49.1	2.2	0	62.4	1.8	0	.002	.475
Vomiting	23.7	1.1	0	34.1	1.8	0	.007	.837
Diarrhea	20.8	1.1	0	32.6	3.2	0	.002	.302
Neuropathy: sensory	81.0	2.9	0	15.8	0.4	0	< .001	.668
Arthralgia	67.4	2.5	0	7.9	0	0	< .001	.357
Alopecia	76.7			9.3			< .001	

NOTE. Differences between the two arms were evaluated by the χ^2 test.

QOL

At random assignment, 99.6% of patients (562 of 564) completed baseline questionnaires, with the questionnaire completion rates being 93.4% at 6 weeks and 90.1% at 9 weeks. Compliance rates were not significantly different between the treatment arms. QOL data were missing in 38 surveys due to death or severe impairment of the patient's general condition, which accounted for 2.3% of the total number of the surveys scheduled. There was no significant difference in the lung cancer subscale of FACT-L between the treatment arms (Fig 4). Scores on the neurotoxicity subscale of FACT/GOG-Ntx had decreased significantly in the carboplatin and paclitaxel arm after two cycles of chemotherapy (Fig 4); the adjusted mean scores at 6 and 9 weeks were 41.2 and 41.0 for the carboplatin and S-1 arm and 38.2 and 37.1 for the carboplatin and paclitaxel arm. The alopecia score was also significantly worse in the carboplatin and paclitaxel arm than in the carboplatin and S-1 arm ($P < .001$, analysis of variance), with the adjusted means at 6 and 9 weeks being 3.8 and 3.7 for carboplatin and S-1 and 1.7 and 1.9 for carboplatin and paclitaxel ($P < .001$ at both 6 and 9 weeks, Tukey-Kramer multiple-comparison test).

Poststudy Treatment

There were no major differences in poststudy treatment between the two arms. Overall, 69.4% of carboplatin and paclitaxel patients and 75.5% of carboplatin and S-1 patients received an additional line of therapy ($P = .103$, χ^2 test). Docetaxel was administered in 43.4% and 52.0% of patients and epidermal growth factor receptor tyrosine kinase inhibitors were administrated in 24.0% and 27.2% of patients in the carboplatin and paclitaxel and carboplatin and S-1 arms, respectively.

DISCUSSION

Our phase III study is the first to evaluate the efficacy of an S-1–containing regimen in comparison with standard platinum-doublet chemotherapy for first-line treatment of patients with advanced NSCLC. The primary objective of the study—determination of the noninferiority of carboplatin and S-1 compared with carboplatin and paclitaxel in terms of OS—was met at the planned interim analysis.

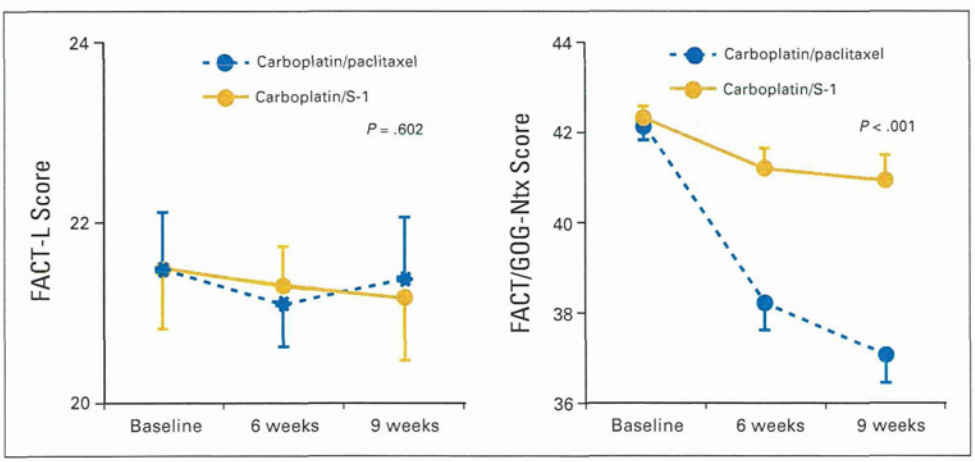

Fig 4. Quality of life assessments with the (left) seven-item Functional Assessment of Cancer Therapy–Lung (FACT-L) and (right) 11-item FACT/Gynecology Oncology Group-Neurotoxicity (GOG-Ntx) scales. Data are least square means ± 95% CI. Higher scores indicate better quality of life. *P* values shown were determined by analysis of variance, with *P* being less than .001 for comparison of FACT/GOG-Ntx scores between the two arms at both 6 and 9 weeks by the Tukey-Kramer multiple-comparison test.

Analysis of OS in the ITT and PP populations as well as in subgroups of the study subjects demonstrated the noninferiority of carboplatin and S-1. Although there was a significant difference in response rate favoring carboplatin and paclitaxel, disease control rate and PFS were similar for carboplatin and S-1 and carboplatin and paclitaxel. Given that subsequent therapies after discontinuation of the study treatment were well-balanced between the treatment groups, it is unlikely that poststudy therapy confounded survival results. Collectively, our secondary data indicate that the findings of the main analysis are robust. Although the protocol-specified noninferiority margin of 1.33 may be large, the survival curves themselves mostly coincided for the two treatment arms and median OS in the carboplatin and S-1 group was noteworthy at approximately 15 months.

The profile of adverse events associated with carboplatin and S-1 and carboplatin and paclitaxel was as expected, but there were marked differences in the incidence of some of these events. Carboplatin and paclitaxel treatment resulted in a typically high incidence of neutropenia of grade 3 or 4 (76.7%) as well as of febrile neutropenia (7.2%), compared with incidences of only 21.1% and 1.1%, respectively, for carboplatin and S-1. These rates of neutropenia associated with carboplatin and paclitaxel treatment are consistent with those observed in previous studies of Japanese patients.[11,14] Carboplatin and S-1 treatment showed a significantly higher rate of thrombocytopenia, which was the most frequent reason for dose delays in the carboplatin and S-1 group. However, this condition was considered manageable because it was associated with bleeding of grade 3 in only one patient. With regard to nonhematologic toxicities, neuropathy, arthralgia, and alopecia were much less frequent in patients treated with carboplatin and S-1 than in those receiving carboplatin and paclitaxel. Consistent with these results, carboplatin and S-1 treatment showed a clinically relevant improvement in QOL as assessed by the FACT/GOG-Ntx scale and alopecia score. Despite these QOL benefits with carboplatin and S-1, however, there was no significant difference in FACT-L score between carboplatin and S-1 and carboplatin and paclitaxel, possibly because of other more toxic effects of carboplatin and S-1. The incidence of nausea, vomiting, and diarrhea of any grade was higher in patients assigned to the carboplatin and S-1 arm than in those assigned to carboplatin and paclitaxel, although grades 3 or 4 of these toxicities were uncommon ($< 4\%$) in both groups. The relative dose intensity of S-1 was 94.3% in the carboplatin and S-1 arm (median of four cycles administered), and treatment was discontinued in only approximately 10% of patients in this arm because of adverse events. Overall, these data indicate that carboplatin and S-1 was well-tolerated, with continuation of treatment as specified in the protocol not being a problem. According to our previous phase I/II study of carboplatin and S-1,[9] this study excluded elderly (≥ 75 years old) patients. Given its efficacy and favorable toxicity profile, the combination of S-1 and carboplatin warrants further evaluation in elderly patients.

In conclusion, our present study demonstrates the noninferiority of carboplatin and S-1 relative to carboplatin and paclitaxel in terms of OS for patients with advanced NSCLC. Carboplatin and S-1 is therefore a valid therapeutic option for the first-line treatment of patients with advanced NSCLC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Ethnic Difference in Hematological Toxicity in Patients with Non-small Cell Lung Cancer Treated with Chemotherapy

A Pooled Analysis on Asian versus Non-Asian in Phase II and III Clinical Trials

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Introduction: There are a large number of global clinical trials ongoing for patients with non-small cell lung cancer (NSCLC). Ethnic difference in toxicity has not been adequately studied.

Methods: We performed a systematic search in PubMed for randomized phase II and III trials of NSCLC from January 2000 to December 2009, examining ethnic difference in hematological toxicity due to cytotoxic chemotherapy. Ethnicity was classified into Asian and non-Asian. We chose three treatment regimens used for NSCLC globally: cisplatin plus gemcitabine (CG), cisplatin plus vinorelbine (CV), and carboplatin plus paclitaxel (CP). We applied sensitivity analysis to examine unreported ethnic differences in hematological toxicities by changing the percentage of Asian patients from 0 to 18% in trials reported from the United States and Europe.

Results: We identified 12 phase II trials and 38 phase III trials of NSCLC with a total of 11,271 patients. Among these, 14 trials had reported ethnic origins. Grade 3/4 toxicities were more frequently observed in the Asian studies. On the basis of sensitivity analysis, odds ratio of grade 3/4 neutropenia was significantly higher in Asian patients than non-Asian, when treated with CG (OR = 1.55–3.45, $p < 0.001$), CV (OR = 2.99–4.43, $p < 0.001$), and CP (OR = 4.79–6.22, $p < 0.001$). Grade 3/4 anemia was also significantly higher in Asians with CG (OR = 3.10–3.27, $p < 0.001$), CV (OR = 1.99–2.43, $p < 0.001$), and CP (OR = 1.34–1.52, $p < 0.001$–0.004). However, no significant difference was observed in thrombocytopenia with CG (OR = 0.66–2.04, $p < 0.001$–1.000), CV (OR = 0.42–0.57, $p = 0.097$–0.323), or CP (OR = 1.21–1.39, $p = 0.114$–0.152).

Conclusions: Severe hematological toxicity was frequently observed in Asian patients compared with non-Asian (mostly whites) in the treatment of chemotherapy for NSCLC.

Key Words: Non-small cell lung cancer, Chemotherapy, Ethnic difference, Sensitivity analysis.

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A growing number of global clinical trials are ongoing for patients with non-small cell lung cancer (NSCLC), which will likely be further enhanced by the recent emergence of molecular targeting agents. Differences in toxicity because of several chemotherapeutic agents for lung cancer among different ethnicity have been reported.[1,2] Epidermal growth factor receptor (EGFR)-targeting agents are the first molecular targeting agents on which ethnic differences have been intensively discussed between white and Asian patients.[3,4]

Ethnic difference in clinical benefit from EGFR tyrosine kinase inhibitors (TKIs) treatment has been emphasized, whereas the side effects caused by cytotoxic chemotherapy have not been fully studied. There is some evidence for ethnic differences in the pharmacokinetics and in toxicity from anticancer drugs, in particular between Asian and white patients. It has been reported that allelic variants of genes encoding drug-metabolizing enzymes are expressed with different incidences in different ethnic groups.[5]

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