ORIGINAL ARTICLE

Gefitinib or Chemotherapy for Non–Small-Cell Lung Cancer with Mutated EGFR

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ABSTRACT

BACKGROUND

Non–small-cell lung cancer with sensitive mutations of the epidermal growth factor receptor (EGFR) is highly responsive to EGFR tyrosine kinase inhibitors such as gefitinib, but little is known about how its efficacy and safety profile compares with that of standard chemotherapy.

METHODS

We randomly assigned 230 patients with metastatic, non–small-cell lung cancer and EGFR mutations who had not previously received chemotherapy to receive gefitinib or carboplatin–paclitaxel. The primary end point was progression-free survival; secondary end points included overall survival, response rate, and toxic effects.

RESULTS

In the planned interim analysis of data for the first 200 patients, progression-free survival was significantly longer in the gefitinib group than in the standard-chemotherapy group (hazard ratio for death or disease progression with gefitinib, 0.36; P<0.001), resulting in early termination of the study. The gefitinib group had a significantly longer median progression-free survival (10.8 months, vs. 5.4 months in the chemotherapy group; hazard ratio, 0.30; 95% confidence interval, 0.22 to 0.41; P<0.001), as well as a higher response rate (73.7% vs. 30.7%, P<0.001). The median overall survival was 30.5 months in the gefitinib group and 23.6 months in the chemotherapy group (P=0.31). The most common adverse events in the gefitinib group were rash (71.1%) and elevated aminotransferase levels (55.3%), and in the chemotherapy group, neutropenia (77.0%), anemia (64.6%), appetite loss (56.6%), and sensory neuropathy (54.9%). One patient receiving gefitinib died from interstitial lung disease.

CONCLUSIONS

First-line gefitinib for patients with advanced non–small-cell lung cancer who were selected on the basis of EGFR mutations improved progression-free survival, with acceptable toxicity, as compared with standard chemotherapy. (UMIN-CTR number, C000000376.)

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Non–small-cell lung cancer is a major cause of death from cancer. The use of cytotoxic chemotherapy is associated with a response rate of 20 to 35% and a median survival time of 10 to 12 months among patients with advanced non–small-cell lung cancer.[1,2] Gefitinib is an orally administered tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR). In two phase 2 studies of patients with previously treated non–small-cell lung cancer, the response rate was 9 to 19%.[3,4] In subsequent phase 3 trials, the noninferiority of gefitinib as compared with docetaxel with respect to overall survival was shown in one study (hazard ratio, 1.02)[5] but not another (hazard ratio, 1.12).[6] Meanwhile, demographic and clinical factors such as Asian race, female sex, nonsmoking status, and adenocarcinoma were shown to be predictive of the efficacy of gefitinib, warranting a large comparative trial (First Line Iressa vs. Carboplatin/Paclitaxel in Asia [IPASS]; ClinicalTrials.gov number, NCT00322452) in which patients were selected in accordance with these factors.[7]

In May 2004, two pivotal studies showed that the presence of somatic mutations in the kinase domain of EGFR strongly correlates with increased responsiveness to EGFR tyrosine kinase inhibitors in patients with non–small-cell lung cancer.[8,9] It was later found that subgroups of patients with non–small-cell lung cancer who had sensitivity to gefitinib had a high incidence of EGFR mutations. In Japan, 30% or more of patients with mutated-EGFR non–small-cell lung cancer are male or have a history of smoking.[10,11] Therefore, we hypothesized that selecting patients on the basis of EGFR mutations rather than clinical factors would result in a population with a greater sensitivity to gefitinib.

Our previous prospective, phase 2 studies of gefitinib therapy in patients with advanced non–small-cell lung cancer and EGFR mutations[12-14] revealed a response rate of more than 70% and progression-free survival of 9 to 10 months. We also developed a rapid, sensitive method for detecting sensitive EGFR mutations: the peptide nucleic acid–locked nucleic acid (PNA-LNA) polymerase-chain-reaction (PCR) clamp method.[15] We then undertook a phase 3 study comparing gefitinib and standard carboplatin–paclitaxel chemotherapy in patients who had advanced non–small-cell lung cancer with sensitive EGFR mutations and who had not previously received chemotherapy.

METHODS

PATIENT POPULATION

This multicenter, randomized, phase 3 trial was approved by the institutional review board of each participating center. Eligibility criteria included the presence of advanced non–small-cell lung cancer harboring sensitive EGFR mutations, the absence of the resistant EGFR mutation T790M (in which threonine at amino acid 790 is substituted by methionine), no history of chemotherapy, and an age of 75 years or younger (because a benefit of a platinum-based regimen in patients >75 years of age is not established). Table 1 in the Supplementary Appendix (available with the full text of this article at NEJM.org) lists the detailed eligibility and exclusion criteria. The authors attest to the fidelity of the article to the full protocol and statistical-analysis plan.

DETECTION OF *EGFR* MUTATIONS

Cytologic or histologic specimens were examined for *EGFR* mutations by means of the PNA-LNA PCR clamp method. Briefly, genomic DNA fragments containing mutation hot spots of the *EGFR* gene were amplified with the use of a PCR assay in the presence of a peptide nucleic acid clamp primer synthesized from a peptide nucleic acid with a wild-type sequence. This method results in preferential amplification of the mutant sequence, which is then detected by a fluorescent primer that incorporates locked nucleic acids to increase the specificity. As a result, a mutant *EGFR* sequence is detected in specimens that contain 100 to 1000 excess copies of wild-type *EGFR* sequence. The sensitivity and specificity of the PNA-LNA PCR clamp method are 97% and 100%, respectively.[15,16]

STUDY DESIGN AND TREATMENT

Before randomization, patients were stratified according to sex, clinical stage of non–small-cell lung cancer (IIIB, IV, or postoperative relapse), and institution. Eligible patients were randomly assigned to receive either gefitinib (at a dose of 250 mg per day orally) or standard chemotherapy. The standard chemotherapy consisted of paclitaxel (at a dose of 200 mg per square meter of body-surface area, given intravenously over a 3-hour period) and carboplatin (at a dose equivalent to an area under the concentration–time curve [AUC] of 6, given intravenously over a 1-hour period), both administered on the first day of every 3-week cycle. The

carboplatin dose in milligrams was calculated by means of the Calvert formula (AUC × [the calculated creatinine clearance in milliliters per minute + 25]; www.freekinetics.com/auccalc1.htm). The glomerular filtration rate was estimated according to the Cockcroft–Gault method ([140 − age in years] × [actual weight in kilograms] ÷ [72 × serum creatinine level in milligrams per deciliter {× 0.85 in women}]). Chemotherapy was continued for at least three cycles. Gefitinib was administered until disease progression, development of intolerable toxic effects, or withdrawal of consent.

CLINICAL ASSESSMENTS

Assessments made before enrollment are summarized in Table 2 in the Supplementary Appendix. Assessment of the tumor for a response to treatment was performed by means of computed tomography (CT) every 2 months. Unidirectional measurements were adopted on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0).[17] Progression-free survival was evaluated for the period from the date of randomization to the date when disease progression was first observed or death occurred. Treatment response and progression-free survival were determined by external review of the CT films by experts who were not aware of the treatment assignments. Overall survival was evaluated for the period from the date of randomization to the date of death. Toxic effects were assessed according to the National Cancer Institute Common Terminology Criteria (NCI-CTC, version 3.0; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

STATISTICAL ANALYSIS

The primary end point was progression-free survival, as a measure of the superiority of gefitinib over carboplatin–paclitaxel. From our previous data, we hypothesized that the progression-free survival with gefitinib was 9.7 months; from the results of the Iressa NSCLC Trial Assessing Combination Treatment (INTACT),[18] we hypothesized that the progression-free survival with standard chemotherapy was 6.7 months. We estimated that a total of 230 events would be needed for the study to have a power of 80% to confirm the superiority of gefitinib over standard chemotherapy, with the use of a log-rank test and a two-sided significance level of 5%. Setting the duration of enrollment to 2 years with a minimum follow-up period of 6 months, we initially planned to enroll 320 patients.

Kaplan–Meier survival curves were drawn for progression-free survival and were compared by means of a log-rank test. Hazard ratios (and 95% confidence intervals) were calculated with the use of a Cox proportional-hazards analysis. Prespecified adjustment factors included sex and clinical stage.

Secondary end points included overall survival, response rate, time to the deterioration of performance status (Eastern Cooperative Oncology Group [ECOG] performance status score of ≥3, capability of only limited self-care, or confinement to a bed or chair for >50% of waking hours[19]), and toxic effects. Overall survival and the time to ECOG performance status score of 3 or more were analyzed in the same way as progression-free survival. The response rate and rate of toxic effects were compared between the two groups with Fisher's exact test and the Wilcoxon test, respectively. Each analysis was performed with the use of a two-sided, 5% significance level and a 95% confidence interval by means of SAS for Windows software (release 9.1, SAS Institute).

One interim analysis was planned to analyze the primary end point (significance level, P=0.003). The Lan–DeMets method was used to adjust for multiple comparisons. The O'Brien–Fleming type alpha-spending function was also used.

RESULTS

PATIENT CHARACTERISTICS

The study was begun in March 2006. The preplanned interim analysis was performed 4 months after the 200th patient was enrolled (May 2009); it showed a significant difference in progression-free survival between the two treatment groups (P<0.001), and the independent data and safety monitoring committee recommended termination of the study. Therefore, the study was stopped at the end of May 2009.[20]

In total, 230 patients were enrolled from 43 institutions in Japan (Fig. 1). Half (115 patients) were randomly assigned to receive gefitinib and half to receive carboplatin–paclitaxel. Two patients were excluded because they were found to be ineligible. In the chemotherapy group, 1 patient was not evaluated for safety, owing to lack of receipt of the study drugs, and 3 others were excluded from the analysis of progression-free survival.

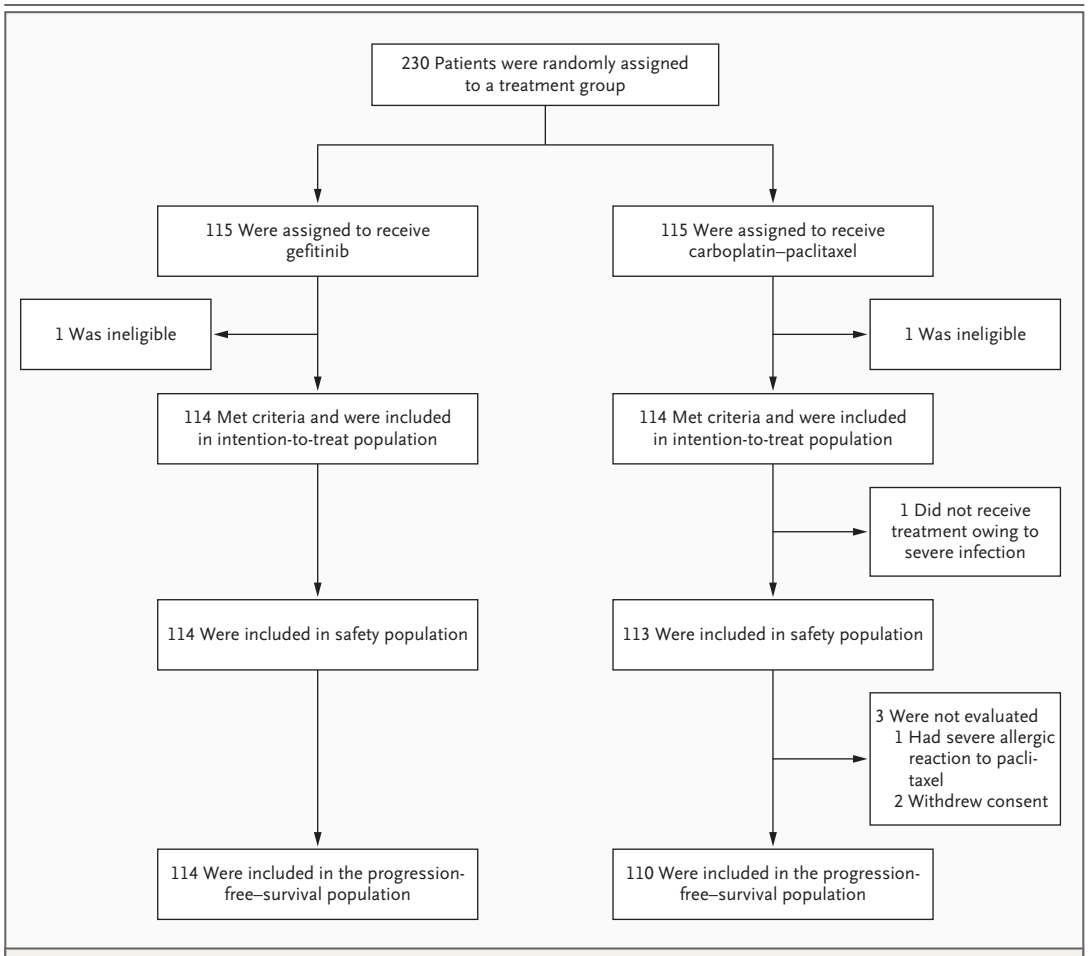

Figure 1. Randomization and Follow-up of the Study Patients, According to Treatment Group.

At the data cutoff point (early December 2009), the median follow-up period was 527 days (>17 months; range, 30 to 1261). The median duration of gefitinib treatment was 308 days (range, 14 to 1219); the median number of 3-week cycles of chemotherapy was 4 (range, 1 to 7). Three patients in the gefitinib group and 11 patients in the chemotherapy group received second-line treatment before they had RECIST-defined disease progression. The data on progression-free survival for these patients were censored at the time of the last CT evaluation at which they did not yet have evidence of disease progression. Demographic and disease characteristics at baseline were well balanced between the two groups (Table 1).

EFFICACY

The interim analysis performed in May 2009 showed that progression-free survival was significantly longer in the gefitinib group than in the chemotherapy group (median, 10.4 months vs. 5.5 months; hazard ratio for death or disease progression with gefitinib, 0.36; 95% confidence interval [CI], 0.25 to 0.51; P<0.001) (Fig. 1 in the Supplementary Appendix). A significant difference was again observed in the final analysis, performed in December 2009 (median progression-free survival, 10.8 months with gefitinib vs. 5.4 months with chemotherapy; hazard ratio, 0.30; 95% CI, 0.22 to 0.41; P<0.001) (Fig. 2A). The 1-year and 2-year rates of progression-free survival were 42.1% and 8.4%, respectively, in the gefitinib group and 3.2% and 0%, respectively, in the chemotherapy group. Subgroup analyses showed that women had significantly longer progression-free survival than men (median, 6.5 vs. 6.0 months; hazard ratio for death or disease progression, 0.68; 95% CI, 0.51 to 0.92; P=0.01). The objective response rate was significantly higher in the gefitinib group than the chemotherapy group (73.7% vs. 30.7%,

Table 1. Baseline Characteristics of the Intention-to-Treat Population, According to Treatment Group.*

Characteristic	Gefitinib (N=114)	Carboplatin–Paclitaxel (N=114)
Sex — no. (%)		
Male	42 (36.8)	41 (36.0)
Female	72 (63.2)	73 (64.0)
Age — yr		
Mean	63.9±7.7	62.6±8.9
Range	43–75	35–75
Smoking status — no. (%)		
Never smoked	75 (65.8)	66 (57.9)
Previous or current smoker	39 (34.2)	48 (42.1)
ECOG performance status score — no. (%)		
0	54 (47.4)	57 (50.0)
1	59 (51.8)	55 (48.2)
2	1 (0.9)	2 (1.8)
Histologic diagnosis — no. (%)		
Adenocarcinoma	103 (90.4)	110 (96.5)
Large-cell carcinoma	1 (0.9)	0
Adenosquamous carcinoma	2 (1.8)	1 (0.9)
Squamous-cell carcinoma	3 (2.6)	2 (1.8)
Other	5 (4.4)	1 (0.9)
Clinical stage — no. (%)		
IIIB	15 (13.2)	21 (18.4)
IV	88 (77.2)	84 (73.7)
Postoperative relapse	11 (9.6)	9 (7.9)
Type of EGFR mutation — no. (%)		
Exon 19 deletion	58 (50.9)	59 (51.8)
L858R	49 (43.0)	48 (42.1)
Other	7 (6.1)	7 (6.1)

* Plus–minus values are means ±SD. ECOG denotes Eastern Cooperative Oncology Group.

P<0.001) (Table 2). The median progression-free survival and response rate did not differ significantly between patients with the EGFR mutation consisting of an exon 19 deletion (11.5 months and 82.8%) and those with the L858R point mutation (in which leucine at amino acid 858 is replaced by arginine) (10.8 months and 67.3%) (Fig. 2B).

The overall survival did not differ significantly between the two treatment groups. The median survival time and the 2-year survival rate were 30.5 months and 61.4% for the gefitinib group, as compared with 23.6 months and 46.7%, respectively, for the carboplatin–paclitaxel group (P=0.31) (Fig. 2C). Neither sex nor clinical stage had a significant effect on overall survival. The time to an ECOG performance status score of 3 or more did not differ significantly between the two groups.

SAFETY

All patients who had received at least one dose of a study drug were included in the safety analysis. The most common adverse events in the gefitinib group were rash and elevated levels of aspartate aminotransferase or alanine aminotransferase, and in the chemotherapy group, appetite loss, neutropenia, anemia, and sensory neuropathy (Table 3, and Table 3 in the Supplementary Appendix). Interstitial lung disease was reported in six patients (5.3%) in the gefitinib group; three cases were severe, and one of the three was fatal. One grade 4 seizure in the gefitinib group and one grade 4 cerebral infarction and one grade 4 bowel obstruction in the chemotherapy group were observed. The incidence of severe toxic effects (NCI-CTC grade ≥3) was significantly higher in the chemotherapy group than in the gefitinib group (71.7% vs. 41.2%, P<0.001).

TREATMENT AFTER PROTOCOL DISCONTINUATION

Data on treatment given after the study protocol was discontinued were collected retrospectively. Though any treatment was permitted, the protocol recommended that the crossover regimen be used as second-line treatment. As of the data cutoff point, 37 patients in the gefitinib group had continued their first-line gefitinib therapy. Among the remaining 77 patients in the gefitinb group who had stopped receiving gefitinib, 52 (67.5%) were receiving carboplatin–paclitaxel as second-line treatment, with a response rate of 28.8%. Sixteen other patients in the gefitinib group were receiving other therapies such as carboplatin–gemcitabine. Among the 112 patients who had completed first-line carboplatin–paclitaxel, 106 patients (94.6%) received second-line gefitinib; 58.5% of these patients had a response.

DISCUSSION

Previous phase 2 studies have suggested that EGFR tyrosine kinase inhibitors are highly effective against mutated-EGFR non–small-cell lung cancer. The current phase 3, prospective, randomized study showed that the use of gefitinib results in progression-free survival that is twice as long

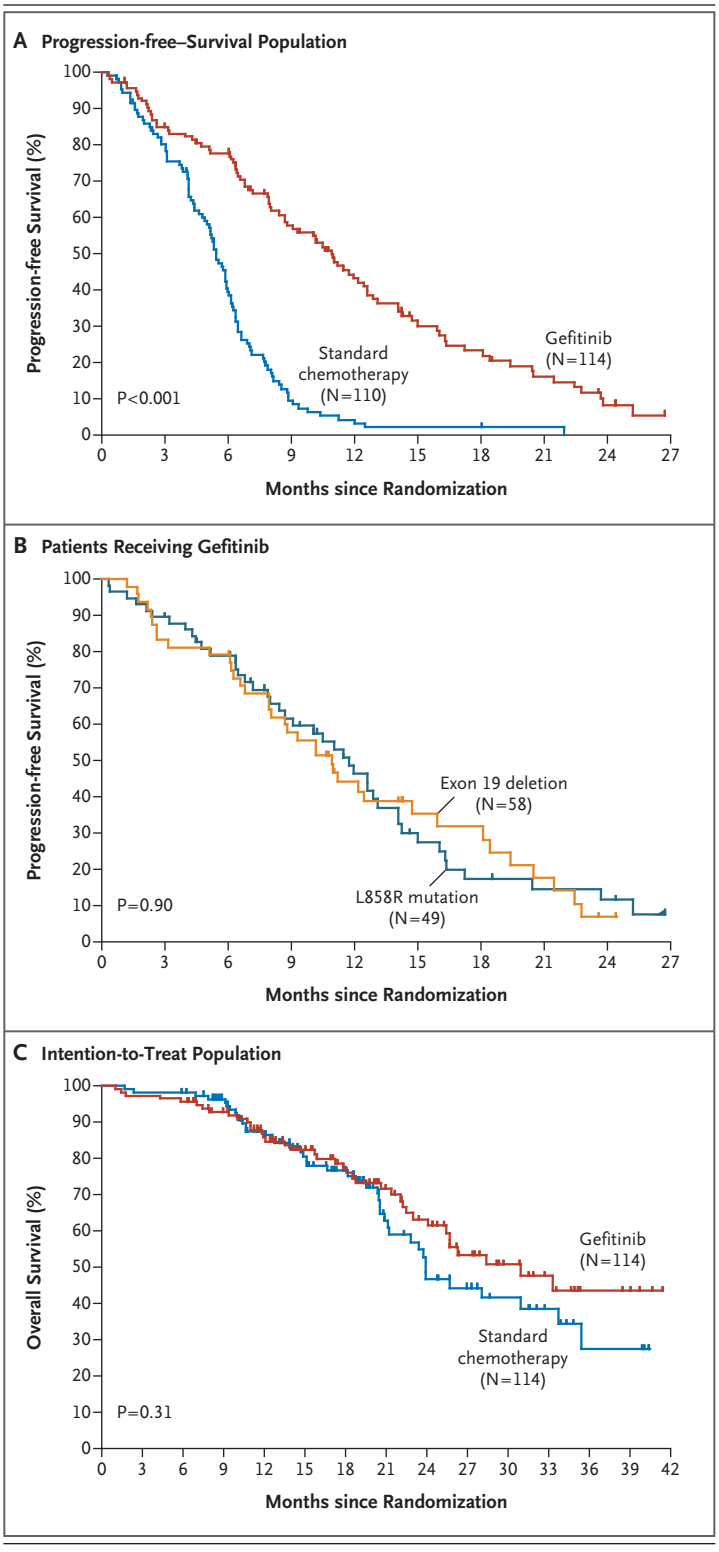

Figure 2. Progression-free Survival and Overall Survival among the Study Patients.

Kaplan–Meier curves for progression-free survival are shown for the progression-free–survival population (Panel A) and for the 107 patients in the gefitinib group with either of the two most common types of epidermal growth factor receptor (EGFR) mutation (Panel B). Kaplan–Meier curves for overall survival in the intention-to-treat population are shown in Panel C. In Panels B and C, tick marks indicate patients for whom data were censored at the data cutoff point (early December 2009).

as that obtained with the use of carboplatin–paclitaxel in patients with mutated-EGFR non–small-cell lung cancer, with a tolerable toxicity profile, including less hematologic toxicity and neurotoxicity than is seen with chemotherapy.

The IPASS, which was conducted in Asia, compared gefitinib with carboplatin–paclitaxel as the first-line treatment for advanced non–small-cell lung cancer in patients selected on the basis of clinical characteristics that included a history of no smoking or light smoking as well as histologic evidence of adenocarcinoma.[7] Although IPASS showed the overall superiority of gefitinib (rate of 1-year progression-free survival, 24.9%, vs. 6.7% with chemotherapy; hazard ratio for death or disease progression, 0.74; P<0.001), the most impressive result emerged from subgroup analysis: as compared with chemotherapy, gefitinib was effective in patients with mutant EGFR (hazard ratio for death or disease progression, 0.48) but was ineffective in those with wild-type EGFR (hazard ratio, 2.85). This finding suggested that the presence of EGFR mutations is the best criterion for selection of patients who benefit from gefitinib, an idea that is validated by the present study.[20] Recently, another Japanese phase 3 study (WJTOG3405; University Hospital Medical Information Network Clinical Trials Registry [UMIN-CTR] number, UMIN000000539) compared gefitinib to cisplatin–docetaxel as the first-line treatment for advanced non–small-cell lung cancer with EGFR mutations.[21] Although this study also showed the superiority of gefitinib over standard chemotherapy with respect to progression-free survival, the magnitude of the benefit was somewhat smaller than in our study, possibly because of differences in the characteristics of the patients (since 41% of patients in WJTOG3405 had had surgery, vs. only 9% in our study) and the duration of follow-up (median, 81 days in WJTOG3405 vs. 527 days in our study).

The standard end point of phase 3 trials of treatments for advanced non–small-cell lung cancer has been overall survival. However, when our trial was begun in 2006, we had data only on

Table 2. Response to Treatment in the Intention-to-Treat Population, According to Treatment Group.*

Response	Gefitinib (N=114)	Carboplatin–Paclitaxel (N=114)
	number of patients (percent)	
Complete response	5 (4.4)	0
Partial response	79 (69.3)	35 (30.7)
Complete or partial response†	84 (73.7)	35 (30.7)
Stable disease	18 (15.8)	56 (49.1)
Progressive disease	11 (9.6)	16 (14.0)
Response that could not be evaluated	1 (0.9)	7 (6.1)

* All responses differed significantly between the two groups (P<0.001 by Fisher's exact test).
† The percentage of patients in whom there was either a complete or a partial response was considered to be the rate of objective response.

progression-free survival from our phase 2 studies in patients with non–small-cell lung cancer and EGFR mutations. The data on overall survival first became available in 2008, when the combined analysis of Japanese phase 2 studies (Iressa — Combined Analysis of Mutation Positives [I-CAMP]) and the subgroup analyses of IPASS were reported.[7,22] We thus planned to have progression-free survival as the primary end point in the current study, because it allowed us to calculate the statistical power of the study.

Several studies have suggested that the EGFR copy number may be a better predictive biomarker for the efficacy of EGFR tyrosine kinase inhibitors than the presence of an EGFR mutation.[23] However, its predictive capacity has been reported only in placebo-controlled trials (Iressa Survival Evaluation in Lung Cancer [ISEL][24] and the BR.21 study[23]). Moreover, the subgroup analysis in IPASS showed that longer progression-free survival was significantly associated with sensitive EGFR mutations but not with a high EGFR copy number. We therefore believe that evaluation of the copy number is not necessary when an EGFR mutation test is available. In the current study, EGFR mutations were detected with the use of the PNA-LNA PCR clamp method, the usefulness of which has been validated.[15,16] With this method, EGFR mutations can be detected from small cytologic specimens, such as those from bronchial washings, pleural effusions, and sputum collection, which are frequently used for the diagnosis of advanced non–small-cell lung cancer. The results of the analyses are obtained within several days, so the treatment is usually not delayed. The PNA-LNA PCR clamp approach is readily available and is covered by health insurance in Japan.

The best timing of treatment with an EGFR tyrosine kinase inhibitor for patients with EGFR mutations remains undetermined. A recent study showed that overall survival did not differ significantly between first-line and second-line treatments with erlotinib.[25] Overall survival is considered to be influenced by the second-line or later treatment. In the current study, 95% of the patients in whom first-line carboplatin–paclitaxel failed crossed over to gefitinib therapy. Such a high crossover rate has not been reported in previous studies of EGFR tyrosine kinase inhibitors. For example, in IPASS, only 39% of patients in the first-line chemotherapy group later received an EGFR-tyrosine kinase inhibitor. Considering that in our study the median overall survival in the gefitinib group was 7 months longer than that in the chemotherapy group (30.5 months vs. 23.6 months), in which virtually all patients were given gefitinib as the second-line treatment, and that the rate of response to gefitinib was slightly worse in the second-line setting than in the first-line setting (58.5% vs. 73.7%), first-line gefitinib may be more effective than gefitinib as second-line or later therapy. This idea needs to be tested in studies with large samples or in a meta-analysis.

We believe that the prolonged progression-free survival provided by the use of first-line gefitinib is valuable for patients with advanced non–small-cell lung cancer, who have a poor prognosis. If gefitinib is administered as second-line or third-line treatment, patients may miss the opportunity to receive treatment with gefitinib because of rapidly progressive disease during or after first-line treatment. We believe that the current study, in combination with our previous study of patients with mutated-EGFR non–small-cell lung cancer and poor performance status,[26] establishes the clinical benefit of an EGFR tyrosine kinase inhibitor as first-line treatment in patients with non–small-cell lung cancer and sensitive EGFR mutations.

Predictable toxicity profiles were observed with gefitinib and with carboplatin–paclitaxel in the current study. Diarrhea and rash were seen more often in the gefitinib group, whereas hematologic and neurologic toxic effects were more common in the chemotherapy group. Gefitinib appears to

Table 3. Common Toxic Effects in the Safety Population, According to Treatment Group.*

Toxic Effect	Gefitinib (N=114)					Carboplatin–Paclitaxel (N=113)					P Value for Grade ≥3
	Grade 1	Grade 2	Grade 3	Grade 4	Grade ≥3	Grade 1	Grade 2	Grade 3	Grade 4	Grade ≥3	
	no. of patients				*no. (%)*	*no. of patients*				*no. (%)*	
Diarrhea	32	6	1	0	1 (0.9)	7	0	0	0	0	<0.001
Appetite loss	7	4	6	0	6 (5.3)	39	18	7	0	7 (6.2)	<0.001
Fatigue	8	1	3	0	3 (2.6)	19	11	1	0	1 (0.9)	0.002
Rash	38	37	6	0	6 (5.3)	8	14	3	0	3 (2.7)	<0.001
Neuropathy (sensory)	0	1	0	0	0	28	27	7	0	7 (6.2)	<0.001
Arthralgia	1	2	1	0	1 (0.9)	25	21	8	0	8 (7.1)	<0.001
Pneumonitis	3	0	2	1†	3 (2.6)	0	0	0	0	0	0.02
Aminotransferase elevation	20	13	29	1	30 (26.3)	31	5	0	1	1 (0.9)	<0.001
Neutropenia	5	1	0	1	1 (0.9)	4	9	37	37	74 (65.5)	<0.001
Anemia	19	2	0	0	0	35	32	6	0	6 (5.3)	<0.001
Thrombocytopenia	8	0	0	0	0	25	3	3	1	4 (3.5)	<0.001
Any	17	44	43	4†	47 (41.2)	4	25	41	40	81 (71.7)	<0.001

* Toxic-effect grades are based on the National Cancer Institute Common Terminology Criteria (version 3.0).
† One patient counted here had a grade 5 toxic effect.

be less toxic than carboplatin–paclitaxel. The only exception was interstitial lung disease; there were three cases of severe interstitial lung disease (≥grade 3) in the gefitinib group and none in the chemotherapy group; one of the cases was fatal. The patient who died was a woman who had no history of smoking and thus had a relatively low risk of interstitial lung disease. Gefitinib sometimes causes diffuse alveolar or interstitial damage, especially during the first 3 months of treatment.[27] The estimated incidence of interstitial lung disease is low in many countries (e.g., 0.3% in United States)[28] but is relatively high (4 to 6%) in Japan.[29,30] Every patient treated with an EGFR tyrosine kinase inhibitor should be carefully monitored for this toxic effect.

In conclusion, the efficacy of first-line gefitinib was superior to that of standard chemotherapy, with acceptable toxicity, in patients with advanced non–small-cell lung cancer harboring sensitive EGFR mutations. Selection of patients on the basis of EGFR-mutation status is strongly recommended.

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APPENDIX

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