CT or magnetic resonance imaging of the brain, and bone scintigraphy. Complete blood cell counts, blood chemistry studies and chest radiography were repeated every week. Creatinine clearance was estimated by the Cockcroft–Gault equation every course. Tumor response was assessed with the Response Evaluation Criteria in Solid Tumor (RECIST) criteria (18). Toxicity was evaluated according to the National Cancer Institute-Common Toxicity Criteria (version 2.0).

RESULTS

Patient Characteristics

Between February 2004 and August 2006, 13 patients were enrolled in this study. However, one patient was excluded from the analysis because of the error in dose calculation. Table 2 shows the characteristics of 12 evaluable patients. Eleven patients were male and one was female. The median age of the patients was 68 years (range, 51–72 years). There were five adenocarcinomas, four squamous cell carcinomas, two large cell carcinomas and one pleomorphic carcinoma. Stage IIIB and IV patients were five and six, respectively, and one patient was a relapse after surgical resection.

Dose Escalation

At the dose level 1, DLT was observed in two of the first three patients: one experienced grade 3 hyponatremia and the other experienced grade 3 febrile neutropenia. Thereafter, we amended the protocol, and grade 3 hyponatremia was excluded from DLT criteria after that. Another three patients were treated at the same dose. Since these patients did not show any additional DLT, the dosage was then escalated to the next step. At the dose level 2, DLT was observed in two of the first three patients: one experienced grade 3 nausea/vomiting and omission on day 8 and the other experienced grade 3 febrile neutropenia and anorexia. Therefore, another three patients were assigned to receive the treatment at the same dose. Out of those three patients, one patient developed grade 4 febrile neutropenia and grade 3 anorexia. Thus, DLT was observed in three of six patients at the dose level 2. As a result, the dose level 2 (GEM, 1000 mg/m^2 and CBDCA, AUC of 4) was determined to be the MTD.

Table 2. Characteristics of evaluable patients ($n = 12$)

Characteristics	No. of patients
Gender	
Male	11
Female	1
Age (years)	
Median	68
Range	51–72
Histology	
Adenocarcinoma	5
Squamous cell carcinoma	4
Large cell carcinoma	2
Pleomorphic carcinoma	1
Stage	
IIIB	5
IV	6
Relapse after surgery	1

Toxicity

The worst grades for each patient in the first cycle are listed in Table 3. Grade 3/4 leukopenia or neutropenia was observed in one patient at level 1 and two patients at level 2. Febrile neutropenia was observed in one patient at level 1 and two patients at level 2. Two patients had grade 3/4 anemia at level 1 and one patient required red blood cell

Table 3. Toxicities during the first cycle

NCI-CTC grade	Level 1 ($n = 6$)		Level 2 ($n = 6$)	
	G1/2	G3/4	G1/2	G3/4
Hematologic				
Leukopenia	1/2	0/1	2/1	2/0
Neutropenia	1/1	1/0	1/1	2/0
Febrile neutropenia	0/0	1/0	0/0	1/1
Anemia	1/3	1/1	2/3	0/0
Thrombocytopenia	1/2	2/1	1/1	4/0
Transaminase	2/0	0/0	4/2	0/0
Bilirubin	0/0	0/0	0/0	1/0
Creatinine	0/0	0/0	0/0	0/0
Hyponatremia	4/0	2/0	5/0	0/0
Non-hematologic				
Nausea/vomiting	2/0	0/0	3/1	1/0
Anorexia	4/1	0/0	2/1	3/0
Fatigue	1/0	0/0	1/2	1/0
Diarrhea	0/0	0/0	2/0	0/0
Constipation	0/0	0/0	0/1	0/0
Mucositis	0/0	0/0	0/0	0/0
Pneumonitis	0/0	0/0	0/0	0/0
Infection	0/0	0/0	0/0	0/0
Skin rash	1/0	0/0	1/0	0/0
Omission on day 8	0		1	
No. of patients with DLT	2		3	

NCI-CTC, National Cancer Institute-Common Toxicity Criteria; DLT, dose-limiting toxicity.

transfusion. No grade 3/4 anemia occurred at level 2. Thrombocytopenia was the principal toxicity of this combination chemotherapy. At level 1, grade 3/4 thrombocytopenias were observed in three patients, and two patients received platelet transfusion. At level 2, two patients experienced grade 3/4 thrombocytopenia requiring no platelet transfusions. Non-hematologic toxicities were generally mild at level 1, however, one patient experienced grade 3 nausea/vomiting and omission of day 8 at level 2. This patient also presented grade 3 hyperbilirubinemia suspected to be drug-induced hepatitis, and died 16 days after the start of the treatment. The worst value of his laboratory data was 6.6 mg/dl in total bilirubin on day 12, 40 IU/l in AST on day 7 and 103 IU/l in ALT on day 7. He had a past history of drug-induced hepatitis related to aspirin. The excluded patient was administered GEM at 800 mg/body. Despite the dose was approximately two-thirds of the planned dose, he experienced grade 3 nausea/vomiting and the treatment was discontinued. The median number of administered cycle was 1. The actual administered cycles were one in seven patients, two in one patient, three in two patients and four in two patients. The reasons for the discontinuation in seven patients who terminated the treatment at one cycle were toxicity for three patients, patient refusal for two patients, treatment delay for one patient and both toxicity and disease progression was for one patient.

Anti-tumor Activity

There were seven stable diseases and five progressive diseases (PD). No partial or complete response was observed (Table 4). Four patients received second-line chemotherapy after GC: docetaxel for two patients and gefitinib for two patients. One patient received gefitinib experienced partial response; however, remaining three patients had PD also in the second-line treatment. The MST was 3.8 months (Fig. 1).

DISCUSSION

This is the first PS 2-specific Phase I study of GC in Japanese patients, and the MTD and recommended dose were determined to be GEM 1000 mg/m^2 and CBDCA AUC of 4.

Table 4. Drug delivery and anti-tumor efficacy

Dose level	Number of patients	Median course (range)	Overall response			
			CR	PR	SD	PD
1	6	1 (1–4)	0	0	4	2
2	6	2 (1–4)	0	0	3	3

CR, complete response; PR, partial response; SD, stable diseases; PD, progressive diseases.

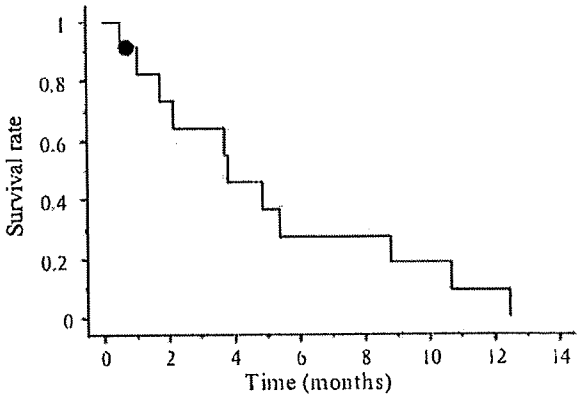

Figure 1. Kaplan–Meier curve of overall survival. Median overall survival time was 3.8 months.

The recommended dose of CBDCA was lower than other studies conducted in the USA (19,20). With respect to the dose of CBDCA, the method of measuring serum creatinine values is critical. In Japan, most institutions use the enzymatic method, whereas the Jaffe method remains the mainstream in the USA (21). According to the study comparing these two methods, serum creatinine values are higher in the Jaffe method than in the enzymatic method by ~0.2 mg/dl (21). Therefore, at the same AUC, higher CBDCA dose is administered in Japan than in the USA. Incidentally, based on the Calvert formula, a difference of 0.2 mg/dl of creatinine leads to the difference of AUC = 1. In short, the AUC = 4 in Japan roughly corresponds to the AUC = 5 in the USA. For global clinical trials, the difference of methods for measurement of laboratory data also should be paid attention to.

PS is one of the most powerful and reliable prognostic factors in advanced NSCLC (6–8), and a worse PS is characterized by lower response rate to chemotherapy and shorter survival (9,10). Median survival of patients with PS 2 is substantially shorter than that of patients with PS 0 or 1. Moreover, patients with PS 2 are at higher risk for severe toxicity than those with better PS. According to the population-based surveys, up to 30–40% of all advanced NSCLC is characterized PS 2 (22,23). Namely, patients with PS 2 constitute a distinctive, non-trivial subgroup in NSCLC. However, little attention has been paid to this special patient population until recently.

The guidelines from the American Society of Clinical Oncology support the single use of third-generation non-platinum agents for patients with PS 2 (24). This recommendation is mainly based on the results of Phase III trials comparing single-agent chemotherapy with best supportive care alone, in which good tolerability and significant survival benefit or improvement of QOL with single-agent chemotherapy have been demonstrated (25–28). However, PS 2 patients accounted for a small proportion of patients in those trials and any conclusive evidence cannot be drawn for the treatment of patients with PS 2. At present, available

data from PS 2-specific clinical trials are quite limited. In this context, no consensus has been developed on the standard chemotherapy in patients with PS 2.

The role of adding platinum to third-generation single agents is still unclear. Recently, the Norwegian Lung Cancer Study Group reported the results of a retrospective study that compared the outcome of patients with PS 2 to that of patients with PS 0 or 1 who had participated in randomized trials comparing two third-generation, CBDCA-based regimens (29). According to the retrospective study, although MST of patients with PS 2 was significantly shorter than that of patients with PS 0 or 1 (4.5 vs. 8.9 months; $P < 0.01$), toxicity was acceptable for patients with PS 2 and they achieved better symptom improvement compared with patients with PS 0 or 1. ECOG conducted the first PS 2-specific randomized trial (19). In the randomized Phase II trial, two platinum-based chemotherapy regimens, PTX + CBDCA (PC) and GP, have been compared, and both regimens were proved feasible with acceptable toxicity. However, survival time was quite limited in both treatment arms: MST was 6.2 months for PC and 6.9 months for GP, respectively. A Greece Group performed a randomized Phase II trial comparing non-platinum single-agent chemotherapy with CBDCA-based chemotherapy (30). In the study, patients were randomly assigned to either GC or GEM alone and MST was 6.7 months for GC and 4.8 months for GEM alone, respectively ($P = 0.49$), whereas neutropenia ($P = 0.007$) and thrombocytopenia ($P < 0.001$) were more common in GC arm. In contrast, according to a subgroup analysis of the Cancer and Leukemia Group B study 9730 comparing PC with PTX alone, patients with PS 2 (107 patients, 18% of the population) achieved significantly better survival when they were treated with PC than those treated with PTX alone (20). Thus, the role of platinum-based chemotherapy for patients with PS 2 is still controversial.

The results could vary even between PS 2-specific trials due to two major reasons. First, determining PS score is inevitably subjective, there is considerable inter-observer variation even between healthcare professionals (31). Second, there can be significant heterogeneity in the PS 2 patient population: the reasons for impaired PS may be due to tumor-related (such as pain, fatigue and weight loss), to pre-existing co-morbidities (such as chronic obstructive pulmonary disease, cardiovascular disease and age-related decline in functional status) or both, furthermore (32). There is a clear need for a more objective classification system that takes into account the individual effects of disease-related symptoms and co-morbidities. The common co-morbidity scales are the Cumulative Illness Rating Scale-Geriatric (CIRS-G) and the Charlson scale. Their prognostic impacts have been validated prospectively (33,34). Moreover, they are more objective than PS. Although our study did not, all future studies for PS 2 patients should use such co-morbidity scales to stratify patients more accurately.

Recently, molecular-targeted agents, especially epidermal growth factor receptor tyrosine kinase inhibitors such as gefitinib or erlotinib, have been tested in clinical trials for patients with poor PS. Inoue et al. (35) conducted a Phase II trial of gefitinib in patients with NSCLC whose tumor harboring EGFR gene mutation. In the study, all patients were not feasible for cytotoxic chemotherapy due to poor PS: 26 of 29 patients were PS 2–4. Overall response rate and MST were 66% and 6.5 months, respectively. In addition, PS improvement rate was 79%, and no treatment-related deaths were observed. These excellent results strongly suggest that stratification with molecular status should be required in the future trial of PS 2 or more.

In this study, we determined the MTD and the recommended dose of GC in Japanese patients with PS 2. Response rate and overall survival of the regimen were disappointing. However, some previous studies clearly support the use of platinum agent in PS 2 patients (19,20). Future clinical trials for PS 2 patients should use more objective criterion such as co-morbidity scales in addition to PS in order to measure patients' risk more accurately. Such studies may reveal that which patients should be treated and not be treated with platinum-based chemotherapy among PS 2 patients.

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Conflict of interest statement

None declared.

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Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma

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ABSTRACT

BACKGROUND

Previous, uncontrolled studies have suggested that first-line treatment with gefitinib would be efficacious in selected patients with non–small-cell lung cancer.

METHODS

In this phase 3, open-label study, we randomly assigned previously untreated patients in East Asia who had advanced pulmonary adenocarcinoma and who were nonsmokers or former light smokers to receive gefitinib (250 mg per day) (609 patients) or carboplatin (at a dose calculated to produce an area under the curve of 5 or 6 mg per milliliter per minute) plus paclitaxel (200 mg per square meter of body-surface area) (608 patients). The primary end point was progression-free survival.

RESULTS

The 12-month rates of progression-free survival were 24.9% with gefitinib and 6.7% with carboplatin–paclitaxel. The study met its primary objective of showing the noninferiority of gefitinib and also showed its superiority, as compared with carboplatin–paclitaxel, with respect to progression-free survival in the intention-to-treat population (hazard ratio for progression or death, 0.74; 95% confidence interval [CI], 0.65 to 0.85; P<0.001). In the subgroup of 261 patients who were positive for the epidermal growth factor receptor gene (*EGFR*) mutation, progression-free survival was significantly longer among those who received gefitinib than among those who received carboplatin–paclitaxel (hazard ratio for progression or death, 0.48; 95% CI, 0.36 to 0.64; P<0.001), whereas in the subgroup of 176 patients who were negative for the mutation, progression-free survival was significantly longer among those who received carboplatin–paclitaxel (hazard ratio for progression or death with gefitinib, 2.85; 95% CI, 2.05 to 3.98; P<0.001). The most common adverse events were rash or acne (in 66.2% of patients) and diarrhea (46.6%) in the gefitinib group and neurotoxic effects (69.9%), neutropenia (67.1%), and alopecia (58.4%) in the carboplatin–paclitaxel group.

CONCLUSIONS

Gefitinib is superior to carboplatin–paclitaxel as an initial treatment for pulmonary adenocarcinoma among nonsmokers or former light smokers in East Asia. The presence in the tumor of a mutation of the *EGFR* gene is a strong predictor of a better outcome with gefitinib. (ClinicalTrials.gov number, NCT00322452.)

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Inhibitors of the epidermal growth factor receptor (EGFR) tyrosine kinase have clinical efficacy, as compared with the best supportive care[1] or standard chemotherapy,[2] when given as second-line or third-line therapy for advanced non–small-cell lung cancer. Treatment with EGFR tyrosine kinase inhibitors is most effective in women, patients who have never smoked, patients with pulmonary adenocarcinomas, and patients of Asian origin. In these populations, such treatment is associated with favorable rates of objective responses, progression-free survival, and overall survival.[1,3,4] These populations also have a relatively high incidence of somatic mutations in the region of the *EGFR* gene that encodes the tyrosine kinase domain.[5,6] Studies have shown that in patients with pulmonary adenocarcinoma who had a base-pair deletion at exon 19 (del746_A750) or a point mutation at exon 21 (L858R), the tumors were highly responsive to EGFR tyrosine kinase inhibitors,[7-9] and subsequent studies of first-line therapy with these agents showed objective response rates of 54.8 to 81.6% and progression-free survival of 9.7 to 13.3 months among patients with these mutations.[10-12]

On the basis of these and other studies,[1,4,13-16] we hypothesized that in a selected population, first-line therapy with an oral EGFR tyrosine kinase inhibitor would be at least as effective as chemotherapy with carboplatin–paclitaxel. In this study, we compared the efficacy, safety, and adverse-event profile of gefitinib with those of carboplatin–paclitaxel when these drugs were used as first-line treatment in nonsmokers or former light smokers in East Asia who had adenocarcinoma of the lung. We also examined the role of an *EGFR* mutation as a predicator of the efficacy of gefitinib or carboplatin–paclitaxel.

METHODS

STUDY DESIGN AND PATIENTS

The First Line Iressa versus Carboplatin/Paclitaxel in Asia (Iressa Pan-Asia Study [IPASS]) study was a phase 3, multicenter, randomized, open-label, parallel-group study comparing gefitinib (Iressa, AstraZeneca) with carboplatin (Paraplatin, Bristol-Myers Squibb) plus paclitaxel (Taxol, Bristol-Myers Squibb) as first-line treatment in clinically selected patients in East Asia who had advanced non–small-cell lung cancer. The primary end point was progression-free survival. Secondary end points included overall survival (an early analysis, since follow-up is ongoing), the objective response rate, quality of life, reduction in symptoms, safety, and the adverse-event profile. Evaluations of efficacy according to the baseline biomarker status of EGFR were planned exploratory objectives.

Patients were eligible for inclusion in the study if they were 18 years of age or older, had histologically or cytologically confirmed stage IIIB or IV non–small-cell lung cancer with histologic features of adenocarcinoma (including bronchoalveolar carcinoma), were nonsmokers (defined as patients who had smoked <100 cigarettes in their lifetime) or former light smokers (those who had stopped smoking at least 15 years previously and had a total of ≤10 pack-years of smoking), and had had no previous chemotherapy or biologic or immunologic therapy. Other eligibility criteria are described in the Supplementary Appendix, available with the full text of this article at NEJM.org.

The principal investigators and the members of the steering committee (see the Appendix at the end of this article) designed the study in collaboration with the sponsor (AstraZeneca) and supervised the conduct of the trial. The sponsor collected and analyzed the data. The lead academic author had unrestricted access to the data and vouches for the validity and completeness of the results of the trial (see the Supplementary Appendix for further details). All patients provided written informed consent; separate consent was provided for the assessment of EGFR biomarkers. An independent ethics committee at each participating institution approved the study protocol. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, applicable regulatory requirements, and AstraZeneca's policy on bioethics. One planned interim analysis was performed by an independent statistician and reviewed by an independent data and safety monitoring committee (see the Supplementary Appendix).

STUDY TREATMENT

Patients were randomly assigned, in a 1:1 ratio, to receive gefitinib (250 mg per day, administered orally) or paclitaxel (200 mg per square meter of body-surface area, administered intravenously over a 3-hour period on the first day of the cycle) fol-

lowed immediately by carboplatin (at a dose calculated to produce an area under the concentration–time curve of 5.0 or 6.0 mg per milliliter per minute, administered intravenously over a period of 15 to 60 minutes) in cycles of once every 3 weeks for up to 6 cycles. Randomization was performed with the use of dynamic balancing[17] with respect to performance status, as assessed by the World Health Organization (WHO) performance scale measuring activity (0 or 1, or 2 on a scale of 0 to 4, with lower numbers indicating a higher degree of activity); smoking status (nonsmoker or former light smoker); sex; and center. Treatment continued until progression of the disease, development of unacceptable toxic effects, a request by the patient or physician to discontinue treatment, serious noncompliance with the protocol, or completion of six chemotherapy cycles. Among patients assigned to gefitinib therapy, those whose tumor progressed were offered the opportunity to switch to treatment with carboplatin–paclitaxel; however, if the patient declined or was not a good candidate for that treatment, he or she could receive another approved therapy of the physician's choice. Among patients who were receiving carboplatin–paclitaxel, further therapy after progression of the disease was at the physician's discretion.

ASSESSMENTS

Progression-free survival was assessed from the date of randomization to the earliest sign of disease progression, as determined by means of the Response Evaluation Criteria in Solid Tumors (RECIST),[18] or death from any cause. Overall survival was assessed from the date of randomization until death from any cause. Tumor response was assessed every 6 weeks until disease progression. Quality of life was assessed with the use of the Functional Assessment of Cancer Therapy–Lung (FACT–L) questionnaire (in which scores range from 0 to 136, with higher scores indicating better quality of life) and the Trial Outcome Index (TOI, which is the sum of the physical well-being, functional well-being, and lung-cancer subscale [LCS] scores of FACT-L; scores range from 0 to 84, with higher scores indicating better quality of life), and symptoms were assessed with the use of the LCS score (scores range from 0 to 28, with higher scores indicating fewer symptoms). The FACT-L questionnaire[19] was administered at randomization and at week 1, once every 3 weeks until day 127, once every 6 weeks from day 128 until disease progression, and when the study drug was discontinued. Clinically relevant improvement was predefined as an improvement of six points or more in FACT-L and TOI scores or an improvement of two points or more in LCS scores, with the higher scores maintained for at least 21 days.[20] Safety and tolerability were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Tumor samples from patients who consented to have biomarkers assessed were analyzed at two central laboratories to determine biomarker status, with *EGFR* mutation status the first priority. Patients were considered to be positive for the *EGFR* mutation if 1 of 29 *EGFR* mutations was detected with the use of the amplification refractory mutation system (ARMS) and the DxS EGFR29 mutation-detection kit.[21,22]

STATISTICAL ANALYSIS

The primary end point (progression-free survival) was analyzed with the use of a Cox proportional-hazards model in the intention-to-treat population (all randomly assigned patients) to assess the noninferiority of gefitinib as compared with carboplatin–paclitaxel, with the WHO performance status (0 or 1, or 2), smoking status (nonsmoker or former light smoker), and sex as covariates. For noninferiority to be demonstrated, the 95% confidence interval for the hazard ratio had to lie entirely below the predefined noninferiority limit of 1.2. We estimated that with a total of 944 progression events, the study would have 80% power to demonstrate noninferiority if the treatments were truly equal, with a two-sided 5% probability of an erroneous demonstration of noninferiority. If the 95% confidence interval for the hazard ratio was also below 1, the P value would be less than 0.05 and superiority could be concluded from the same analysis without statistical penalty (closed test procedure).[23] Supportive secondary analyses are described in the Supplementary Appendix. Planned subgroup analyses were performed to compare progression-free survival between treatments in groups defined according to WHO performance status (0 or 1, or 2), smoking status (nonsmoker or former light smoker), sex, age at randomization (<65 years or ≥65 years), disease stage at screening (stage IIIB or IV), and presence or absence of biomarkers. Tests to determine in-

teractions of treatment with covariates were used to identify predictive factors by assessing whether there was a significant difference in the treatment effect for progression-free survival (hazard ratio for progression or death) between subgroups.

Overall survival was analyzed with the use of methods that were similar to those used for the analysis of progression-free survival. The results of an early analysis are presented; follow-up with respect to overall survival is ongoing. The objective response rate (in the intention-to-treat population) and quality of life and rates of symptom reduction (among all patients with a baseline and at least one post-baseline quality-of-life assessment that could be evaluated) were assessed with the use of a logistic-regression model with the same covariates as those considered for progression-free survival to calculate odds ratios and 95% confidence intervals. Planned subgroup analyses of the objective response rate were performed with the use of methods that were similar to those used for the analysis of progression-free survival.

Adverse events were summarized for all patients who received at least one dose of the assigned study treatment. The incidence rates of 10 specified safety events (5 that were possibly associated with each study treatment) were compared with the use of Fisher's exact test; adjustment for multiple comparisons was performed with the use of the method of Westfall and Young.[24]

RESULTS

PATIENTS AND TREATMENT

From March 2006 through October 2007, a total of 1217 patients from 87 centers in Hong Kong, elsewhere in China, Indonesia, Japan, Malaysia, the Philippines, Singapore, Taiwan, and Thailand were randomly assigned to a study group (Fig. 1). The two groups were well balanced with respect to demographic and baseline characteristics (Table 1). The mean duration of treatment was 6.4 months (median, 5.6; range, 0.1 to 22.8) for gefitinib and 3.4 months (median, 4.1; range, 0.7 to 5.8) for carboplatin–paclitaxel. The median number of treatment cycles in the carboplatin–paclitaxel group was six. At the cutoff date for collection of data (April 14, 2008), a total of 24.5% of the patients in the gefitinib group were continuing to receive the study treatment; all patients in the carboplatin–paclitaxel group had discontinued the drugs. After discontinuation of the assigned treatment at any time during the study, 38.9% of the patients in the gefitinib group received carboplatin–paclitaxel, and 39.5% of the patients in the carboplatin–paclitaxel group received an EGFR tyrosine kinase inhibitor; 10.5% of the patients in the gefitinib group and 14.0% of those in the carboplatin–paclitaxel group received other anticancer treatments.

EFFICACY

The median follow-up period for the analysis of progression-free survival was 5.6 months. The median progression-free survival was 5.7 months in the gefitinib group and 5.8 months in the carboplatin–paclitaxel group, approximately coinciding with crossing of the Kaplan–Meier curves. The 12-month rates of progression-free survival were 24.9% with gefitinib and 6.7% with carboplatin–paclitaxel; a total of 950 patients had progression of disease. The study met its primary objective of demonstrating noninferiority and showed the superiority of gefitinib as compared with carboplatin–paclitaxel for progression-free survival (hazard ratio for progression or death, 0.74; 95% confidence interval [CI], 0.65 to 0.85; P<0.001). The probability that a patient would be free of disease progression was greater with carboplatin–paclitaxel in the first 6 months and greater with gefitinib in the following 16 months (Fig. 2A). Progression-free survival was longer in the gefitinib group than in the carboplatin–paclitaxel group in all clinical subgroups; the only clinical factor that affected progression-free survival was age (<65 years: hazard ratio, 0.81; 95% CI, 0.70 to 0.95; P=0.007; ≥65 years: hazard ratio, 0.58; 95% CI, 0.45 to 0.76; P<0.001; P=0.03 for the interaction of treatment with age) (Fig. 1 in the Supplementary Appendix).

A total of 1038 patients (85.3%) gave their consent for biomarker analyses, and 683 patients (56.1%) provided samples. *EGFR* mutation data for 437 patients (35.9%) could be evaluated. Patients with a tissue sample that could be evaluated had demographic characteristics that were similar to those of the overall population (Table 1 in the Supplementary Appendix). Of the 437 samples, 261 (59.7%) were positive for a mutation. Of these 261 samples, 140 (53.6%) had exon 19 deletions, 111 (42.5%) had a mutation at exon 21 (L858R), 11 (4.2%) had a mutation at exon 20 (T790M), and 10 (3.8%) had other mutations; 11 patients had multiple mutations. The proportions of mutations

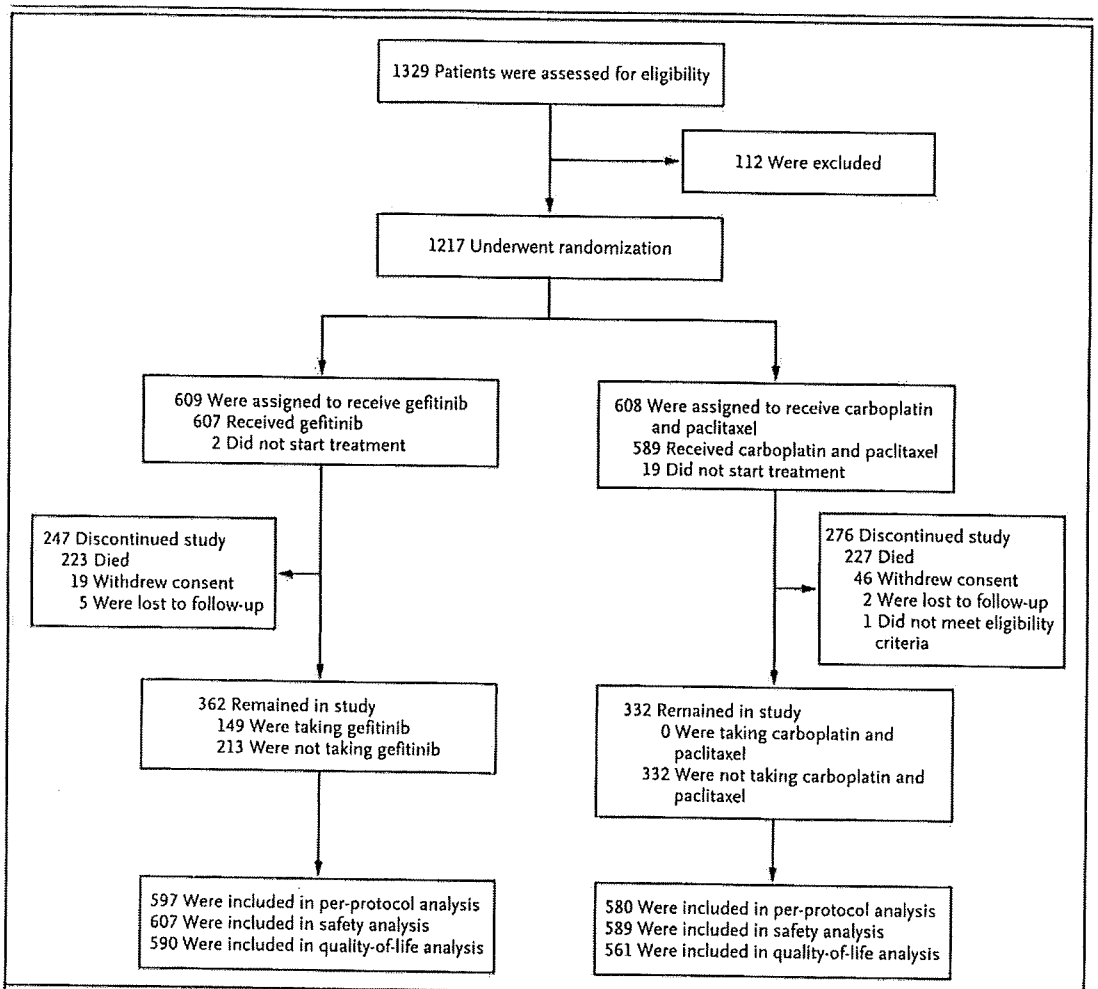

Figure 1. Screening, Group Assignment, and Inclusion in Analyses.

All patients who were randomly assigned to a study group were included in the intention-to-treat analysis; all patients with a baseline and at least one post-baseline quality-of-life assessment that could be evaluated were included in the quality-of-life 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; and all patients who received at least one dose of study treatment were included in the safety analysis. Among the 112 patients who were assessed for eligibility but were not assigned to a study group, the main reasons for exclusion were a serum creatinine level that was higher than 1.5 times the upper limit of the reference range or a creatinine clearance of 60 ml per minute or less; newly diagnosed central nervous system metastases that had not yet been definitively treated with surgery or radiation; or an absolute neutrophil count of less than 2.0×10^9 per liter, a platelet count of less than 100×10^9 per liter, or a hemoglobin level of less than 10 g per deciliter. A total of 63 patients who were treated with gefitinib continued to receive gefitinib after disease progression, and 1 patient who was treated with carboplatin–paclitaxel continued to receive carboplatin–paclitaxel after disease progression because the investigator believed that the treatment was providing a benefit.

were well balanced between the two groups (Table 2 in the Supplementary Appendix).

There was a significant interaction between treatment and *EGFR* mutation with respect to progression-free survival (P<0.001). Progression-free survival was significantly longer among patients receiving gefitinib than among those receiving carboplatin–paclitaxel in the mutation-positive subgroup (hazard ratio for progression, 0.48; 95% CI, 0.36 to 0.64; P<0.001) (Fig. 2B) and significantly shorter among patients receiving gefitinib than among those receiving carboplatin–paclitaxel in the mutation-negative subgroup (hazard ratio, 2.85; 95% CI, 2.05 to 3.98; P<0.001) (Fig. 2C). Results in the subgroup with unknown *EGFR*-mutation status (hazard ratio with gefitinib, 0.68; 95%

Table 1. Demographic and Baseline Characteristics in the Intention-to-Treat Population.*

Characteristic	Gefitinib (N=609)	Carboplatin–Paclitaxel (N=608)
Age — yr		
Median	57	57
Range	24–84	25–84
Sex — no. (%)		
Male	125 (20.5)	127 (20.9)
Female	484 (79.5)	481 (79.1)
Ethnic group — no. (%)†		
Chinese	314 (51.6)	304 (50.0)
Japanese	114 (18.7)	119 (19.6)
Other East Asian‡	179 (29.4)	184 (30.3)
Other	2 (0.3)	1 (0.2)
Smoking history — no. (%)		
Never smoked	571 (93.8)	569 (93.6)
Former light smoker	37 (6.1)	38 (6.2)
Former non–light smoker	1 (0.2)	1 (0.2)
WHO performance status — no. (%)§		
0	157 (25.8)	161 (26.5)
1	391 (64.2)	382 (62.8)
2	61 (10.0)	65 (10.7)
Histologic feature of tumor — no. (%)		
Adenocarcinoma	581 (95.4)	591 (97.2)
Bronchoalveolar carcinoma	27 (4.4)	15 (2.5)
Unknown	1 (0.2)	2 (0.3)
Disease stage at entry — no. (%)		
IIIB	150 (24.6)	144 (23.7)
IV	459 (75.4)	463 (76.2)
Unknown	0	1 (0.2)
Time from diagnosis to randomization — no. (%)		
<6 mo	582 (95.6)	573 (94.2)
≥6 mo	27 (4.4)	34 (5.6)
Unknown	0	1 (0.2)
Disease stage at diagnosis — no. (%)¶		
IA	7 (1.1)	12 (2.0)
IB	2 (0.3)	9 (1.5)
IIA	2 (0.3)	1 (0.2)
IIB	1 (0.2)	6 (1.0)
IIIA	6 (1.0)	3 (0.5)
IIIB	166 (27.3)	163 (26.8)
IV	424 (69.6)	413 (67.9)
Unknown	1 (0.2)	1 (0.2)

* Percentages may not sum to 100 because of rounding.
† Ethnic group was self-reported.
‡ Other East Asian refers to patients who belong to East Asian ethnic groups other than Chinese and Japanese.
§ The World Health Organization (WHO) performance status measures level of activity and is assessed on a scale of 0 to 4, with lower numbers indicating a higher degree of activity.
¶ All patients had Stage IIIB or IV disease at entry.

CI, 0.58 to 0.81; P<0.001) (Fig. 2D) were similar to those for the overall population.

The objective response rate in the overall population was significantly higher with gefitinib than with carboplatin–paclitaxel (43.0% vs. 32.2%; odds ratio, 1.59; 95% CI, 1.25 to 2.01; P<0.001) (Table 3 in the Supplementary Appendix) and numerically or statistically greater with gefitinib in all clinical subgroups. The objective response rate was 71.2% with gefitinib versus 47.3% with carboplatin–paclitaxel in the mutation-positive subgroup (P<0.001) and 1.1% (one patient) versus 23.5%, respectively, in the mutation-negative subgroup (P=0.001) (Table 3 in the Supplementary Appendix).

Overall survival in this early analysis (450 patients [37.0%] died, with follow-up ongoing) was similar between the two groups in the overall population (hazard ratio for death in the gefitinib group, 0.91; 95% CI, 0.76 to 1.10) (Fig. 2A in the Supplementary Appendix). Median survival was 18.6 months among patients receiving gefitinib and 17.3 months among patients receiving carboplatin–paclitaxel. After observing the results with respect to progression-free survival, we performed an analysis of overall survival according to mutation status, although this analysis included only 81 deaths in the mutation-positive subgroup and 94 in the mutation-negative subgroup. The hazard ratios with gefitinib were 0.78 (95% CI, 0.50 to 1.20) in the mutation-positive subgroup and 1.38 (95% CI, 0.92 to 2.09) in the mutation-negative subgroup (Fig. 2B and 2C in the Supplementary Appendix).

Significantly more patients in the gefitinib group than in the carboplatin–paclitaxel group had a clinically relevant improvement in quality of life, as assessed by scores on the FACT-L questionnaire (odds ratio, 1.34; 95% CI, 1.06 to 1.69; P=0.01) and by scores on the TOI (odds ratio, 1.78; 95% CI, 1.40 to 2.26; P<0.001) (Fig. 3). Rates of reduction in symptoms, as assessed on the basis of the LCS scores, were similar between patients who received gefitinib and those who received carboplatin–paclitaxel (odds ratio with gefitinib, 1.13; 95% CI, 0.90 to 1.42; P=0.30) (Fig. 3). Results according to mutation status are provided in Figure 3 in the Supplementary Appendix.

SAFETY AND ADVERSE-EVENT PROFILE

Table 2 lists the most common adverse events. Gefitinib, as compared with carboplatin–paclitaxel, was associated with a lower rate of grade 3 or 4

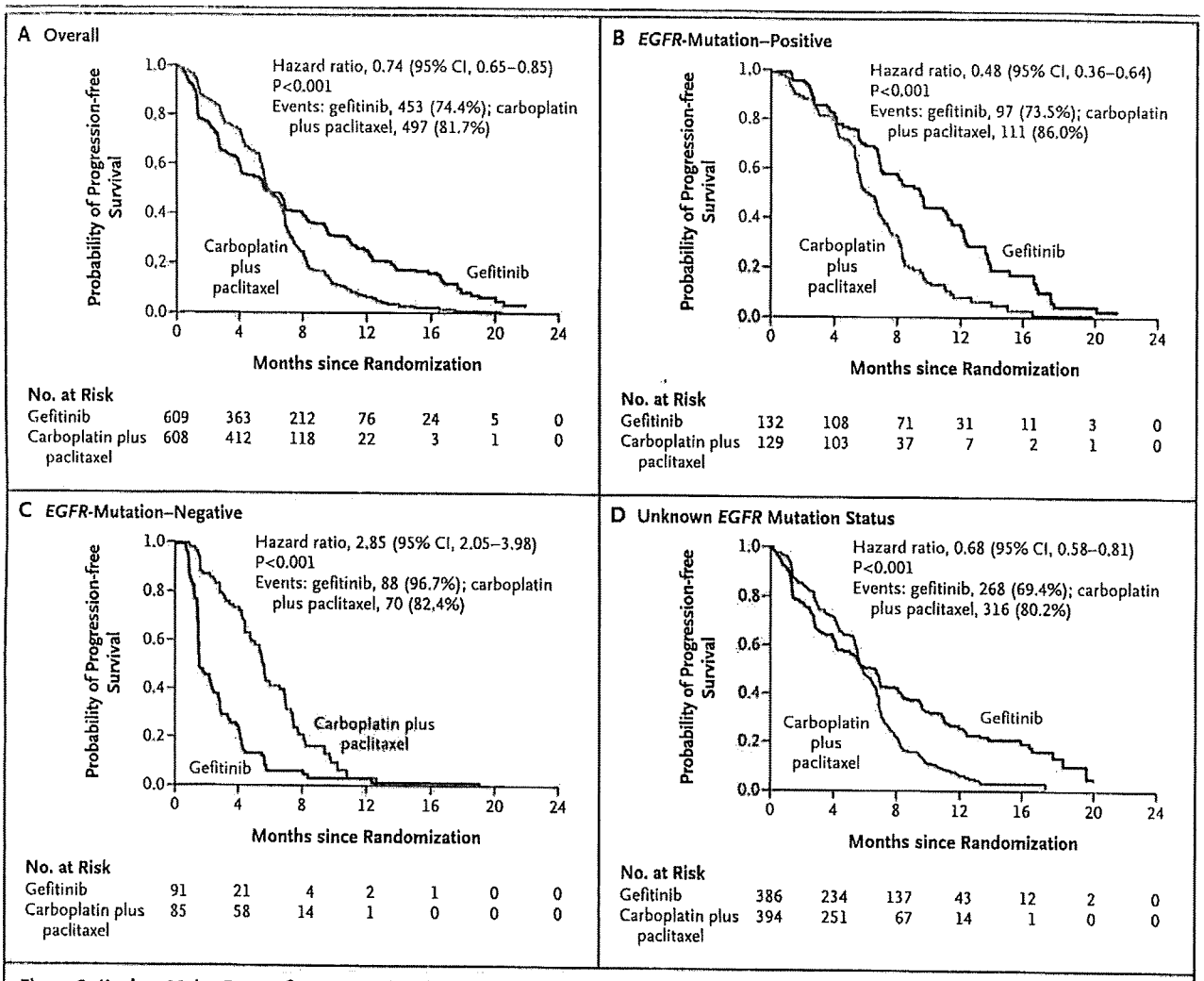

Figure 2. Kaplan–Meier Curves for Progression-free Survival.

Kaplan–Meier curves for progression-free survival are shown for the overall population (Panel A), patients who were positive for the *EGFR* mutation (Panel B), patients who were negative for the *EGFR* mutation (Panel C), and patients with unknown *EGFR* mutation status (Panel D). Analyses were performed on the basis of the intention-to-treat population. With respect to the overall population, results of the supportive secondary analyses (including a log-rank test, which is valid under the null hypothesis even when hazards are not proportional, and analysis in the per-protocol population) were consistent with the result of the primary analysis. Hazard ratios were calculated with the use of a Cox proportional-hazards model, with the WHO performance status (0 or 1, or 2), smoking history (nonsmoker or former light smoker), and sex as covariates. EGFR denotes epidermal growth factor receptor.

adverse events, as defined according to the Common Terminology Criteria for Adverse Events (28.7% vs. 61.0%), a lower rate of adverse events leading to discontinuation of the drug (6.9% vs. 13.6%), and a lower rate of dose modification due to toxic effects (16.1% vs. 35.2% for carboplatin and 37.5% for paclitaxel). Adverse events leading to death occurred in 3.8% of the patients treated with gefitinib and in 2.7% of the patients treated with paclitaxel–carboplatin; serious adverse events, including death, occurred in 16.3% and 15.6% of patients in the two groups, respectively; and serious adverse events leading to hospitalization occurred in 13.8% and 13.1% of patients in the two groups, respectively. The incidences of rash or acne, diarrhea, and elevated liver aminotransferase levels were significantly higher with gefitinib than with carboplatin–paclitaxel, whereas the incidences of neurotoxic effects, nausea and vomiting, and hematologic toxic effects were significantly higher with carboplatin–paclitaxel (Table 4 in the Supplementary Appendix). Interstitial-lung-disease events (i.e., the acute respiratory distress syndrome, interstitial lung disease, pneumonitis, or radiation

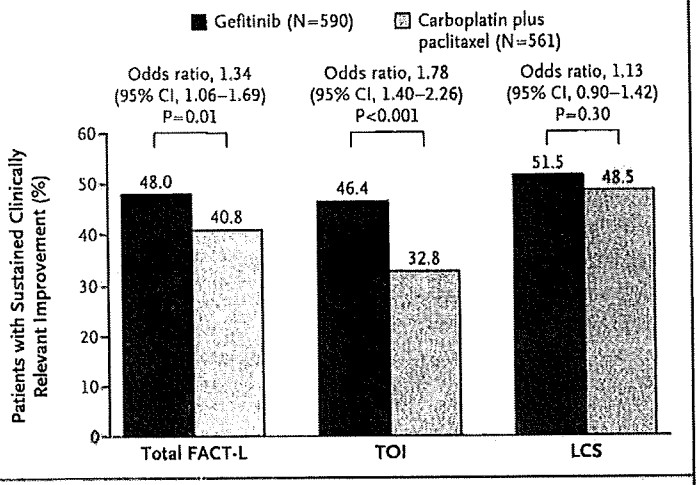

Figure 3. Rates of Improvement in Scores for Quality for Life and Symptoms.

Calculations were performed on the basis of all patients with a baseline and at least one post-baseline quality-of-life assessment that could be evaluated. P values were calculated with the use of logistic regression, with the WHO performance status (0 or 1, or 2), smoking history (nonsmoker or former light smoker), and sex as covariates. Clinically relevant improvement was predefined as an improvement of six points or more in scores on the Functional Assessment of Cancer Therapy–Lung (FACT–L, in which scores range from 0 to 136, with higher scores indicating better quality of life) and Trial Outcome Index (TOI, in which scores range from 0 to 84, with higher scores indicating better quality of life) or an improvement of two points or more in scores on the lung-cancer subscale (LCS) of the FACT–L (in which scores range from 0 to 28, with higher scores indicating fewer symptoms), with the higher scores maintained for at least 21 days.

pneumonitis) occurred in 16 patients treated with gefitinib (2.6%), 3 of whom died, and in 8 patients treated with carboplatin-paclitaxel (1.4%), 1 of whom died.

DISCUSSION

Platinum-based combination chemotherapy, such as carboplatin–paclitaxel, is the standard first-line therapy for advanced non–small-cell lung cancer.[25,26] The results of this trial showed that gefitinib by itself is superior to carboplatin–paclitaxel in a selected population of East Asian patients.

As initial treatment of non–small-cell lung cancer in East Asian nonsmokers or former light smokers with pulmonary adenocarcinoma, gefitinib, as compared with carboplatin–paclitaxel, prolonged progression-free survival, increased the objective response rate, reduced toxic effects, and improved quality of life. The overall benefit was driven primarily by the subgroup of patients with *EGFR* mutations; in this subgroup, patients treated with gefitinib, as compared with those treated with carboplatin–paclitaxel, had a remarkably high objective response rate (71.2%) and prolonged progression-free survival (hazard ratio for progression or death, 0.48; 95% CI, 0.36 to 0.64; P<0.001). In the subgroup of patients without *EGFR* mutations, the objective response rate with gefitinib was 1.1%, and progression-free survival favored chemotherapy (hazard ratio with gefitinib, 2.85; 95% CI, 2.05 to 3.98; P<0.001). These contrasting outcomes probably explain the change over time in treatment effect for progression-free survival in the overall population. The initial superiority of carboplatin–paclitaxel was attributed to the benefit that the *EGFR*-mutation–negative subgroup received from chemotherapy but not from gefitinib, whereas prolonged progression-free survival in the *EGFR*-mutation–positive subgroup explained the subsequent improvement favoring gefitinib. Crossing of the Kaplan–Meier curves did not occur in the mutation-positive subgroup or the mutation-negative subgroup.

Lynch et al. found specific *EGFR* mutations that correlated with tumor response to gefitinib.[7] In the Iressa Survival Evaluation in Lung Cancer trial (ISEL; ClinicalTrials.gov number, NCT00242801), the objective response rate for gefitinib-treated patients was 37.5% among the 16 patients with a tumor bearing an *EGFR* mutation as compared with 2.6% among the 116 patients without a mutation.[27] Our trial confirms the predictive value of *EGFR* mutations for the responsiveness of pulmonary adenocarcinoma to gefitinib as compared with carboplatin–paclitaxel. The difference in the rates of objective response between gefitinib-treated patients with an *EGFR* mutation and those without an *EGFR* mutation (71.2% vs. 1.1%) was remarkable. The rate of an objective response to first-line gefitinib in our study is similar to rates reported in other studies in which patients were selected according to *EGFR*-mutation status, including patients in Western countries.[10,12,28] Sequist et al. screened patients (who were selected on the basis of clinical characteristics) for an *EGFR* mutation and reported an objective response rate of 54.8% among 31 gefitinib-treated patients who were positive for an *EGFR* mutation, only 2 of whom were Asian.[12] However, in our study, objective response rates among patients without an *EGFR* mutation were lower than expected, given the results of previous studies.[16,29] One possible explanation is our use of ARMS, a more sensitive technique for detecting *EGFR* mutations.[21,22] When Zhu et al. used ARMS to reanalyze 148 samples

Table 2. Adverse Events.*

Adverse Event	Gefitinib (N=607)		Carboplatin–Paclitaxel (N=589)	
	All Adverse Events	CTC Grade 3, 4, or 5	All Adverse Events	CTC Grade 3, 4, or 5
	number (percent)			
Rash or acne†	402 (66.2)	19 (3.1)	132 (22.4)	5 (0.8)
Diarrhea	283 (46.6)	23 (3.8)	128 (21.7)	8 (1.4)
Dry skin	145 (23.9)	0	17 (2.9)	0
Anorexia†	133 (21.9)	9 (1.5)	251 (42.6)	16 (2.7)
Pruritus†	118 (19.4)	4 (0.7)	74 (12.6)	1 (0.2)
Stomatitis†	103 (17.0)	1 (0.2)	51 (8.7)	1 (0.2)
Asthenic conditions†	102 (16.8)	2 (0.3)	259 (44.0)	11 (1.9)
Nausea	101 (16.6)	2 (0.3)	261 (44.3)	9 (1.5)
Paronychia	82 (13.5)	2 (0.3)	0	0
Vomiting	78 (12.9)	1 (0.2)	196 (33.3)	16 (2.7)
Constipation	73 (12.0)	0	173 (29.4)	1 (0.2)
Alopecia	67 (11.0)	0	344 (58.4)	0
Neurotoxic effects†	66 (10.9)	2 (0.3)	412 (69.9)	29 (4.9)
Myalgia	47 (7.7)	3 (0.5)	186 (31.6)	10 (1.7)
Arthralgia	39 (6.4)	1 (0.2)	113 (19.2)	6 (1.0)
Neutropenia‡				
Any	NA	22 (3.7)	NA	387 (67.1)
Febrile	1 (0.2)	1 (0.2)	17 (2.9)	17 (2.9)
Anemia‡	NA	13 (2.2)	NA	61 (10.6)
Leukopenia‡	NA	9 (1.5)	NA	202 (35.0)

* Calculations were based on 1196 patients who received at least one dose of the study treatment. The Common Terminology Criteria (CTC) grade is defined on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Events are included if they occurred in at least 10% of patients in either treatment group, either while the patients were receiving treatment or during the 28-day follow-up, and if there was at least a 5% difference between groups. There were other adverse events that occurred in few patients and that may or may not have been related to the study drug. NA denotes not available.

† This is a group term (sum of high-level and preferred terms, according to the definitions in the *Medical Dictionary for Regulatory Activities*).

‡ Data are from the laboratory reports of 599 patients who were taking gefitinib and 577 who were taking carboplatin–paclitaxel. Events were included if there was a worsening in the laboratory value (absolute neutrophil count in the case of neutropenia, hemoglobin in the case of anemia, and white-cell count in the case of leukopenia) from baseline to CTC grade 3 or 4.

that had previously been classified as negative for an *EGFR* mutation, they found 11 new samples with exon 19 mutations.[30] Another possible explanation is that studies that showed higher response rates among mutation-negative patients were not always conducted in previously untreated patients. Mutation-negative status that is determined in a diagnostic sample obtained at the time of the initial presentation may change during subsequent tumor progression or during the course of chemotherapy.[31]

Our findings suggest that, whenever possible, *EGFR*-mutation status should be determined before the initial treatment of pulmonary adenocarcinoma. Ethnic origin, smoking status, and histologic findings help to identify patients who have a high likelihood of having an *EGFR* mutation; in this study, 59.7% of the tumors in a clinically selected population had *EGFR* mutations, as compared with 12.1% and 14.8% in the unselected populations in the ISEL and Iressa in NSCLC Trial Evaluating Response and Survival versus Taxotere (INTEREST; NCT00076388) studies, respectively.[2,27]

The efficacy of gefitinib seen in this study was coupled with lower incidences of alopecia, nausea, vomiting, neurotoxic symptoms, and myelosuppression than those seen with carboplatin–paclitaxel. Among 607 patients who received gefitinib

and who were included in the safety analysis, interstitial-lung-disease events developed in only 16 (2.6%), 3 of whom (0.5%) died.

In summary, this study shows that first-line therapy with gefitinib as compared with carboplatin–paclitaxel prolongs progression-free survival, increases the objective response rate, and improves quality of life among clinically selected patients with non–small-cell lung cancer. The presence of an *EGFR* mutation was a robust predictor of improved progression-free survival with gefitinib, as compared with carboplatin–paclitaxel, and of the benefit of gefitinib with respect to the objective response rate, indicating that patients in whom an *EGFR* mutation has been identified will benefit most from first-line therapy with gefitinib.

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APPENDIX

Members of the First Line Iressa versus Carboplatin/Paclitaxel in Asia (Iressa Pan-Asia Study [IPASS]) Study Organization were as follows: **Steering Committee:** T.S. Mok, M. Fukuoka, S. Thongprasert, Y.-L. Wu, C.-H. Yang, D.-T. Chu, N. Saijo, H. Jiang, C.L. Watkins, A.A. Armour (K.F. To, pathologist, advisor to steering committee). **Independent Data and Safety Monitoring Committee:** A. Chang, K. Eguchi, M. Buyse, S. Zuckerman. **International Coordinating Investigators:** T.S. Mok, M. Fukuoka. **Study Personnel:** S. Rigby, study coordinator and study delivery leader; H. Jiang, study physician; P. Magill, study physician; E.L. Duffield, biostatistician. **Investigators:** *China* — C. Bojun, X. Cai, X. Cai, Q. Chen, X. Chen, Y. Chen, Z. Chen, W. Cheng, X. Chongrui, D. Chu, T. Chu, J. Dai, Z. Ding, J. Duan, M. Fan, Y. Fan, J. Feng, X. Fu, M. Gao, A. Gu, J. Gu, Z. Guan, B. Han, A. Hao, Z. He, W. Hong, X. Hong, M. Hou, C. Huang, J. Huang, P. Huang, Y. Huang, Y. Huang, Y. Huang, W. 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A Phase I Study of Gemcitabine and Carboplatin in Patients with Advanced Non-small Cell Lung Cancer and a Performance Status of 2

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Objective: The aim of this study was to determine the maximum-tolerated dose (MTD) and the recommended dose of combination chemotherapy with gemcitabine (GEM) and carboplatin (CBDCA) in non-small cell lung cancer (NSCLC) patients with a performance status (PS) of 2.
Methods: Chemotherapy-naïve NSCLC patients with PS 2 were enrolled. Chemotherapy consisted of an escalated dose of GEM on days 1 and 8 and CBDCA on day 1 every 3 weeks. Patients were scheduled to receive GEM (mg/m^2)/CBDCA (area under the curve: AUC) at four dose levels: 800/4 (level 1), 1000/4 (level 2), 1000/4.5 (level 3) and 1000/5 (level 4), respectively.
Results: Between February 2004 and August 2006, 13 patients were enrolled in this study. Dose-limiting toxicities (DLTs) were thrombocytopenia, febrile neutropenia and hyponatremia. DLTs were observed in two of six patients at dose level 1 and in three of six patients at dose level 2. Dose level 2 was thus determined to be the MTD. Among 12 evaluable patients, 7 patients had stable diseases and 5 patients had progressive diseases, and the median survival time was 3.8 months.
Conclusions: The MTD and the recommended dose for Phase II studies of this regimen were determined to be GEM 1000 mg/m^2 and CBDCA AUC of 4. Additional objective measures are needed to evaluate patients' risk and benefit in future clinical trials for PS 2 patients.

Key words: non-small cell lung cancer – performance status 2 – gemcitabine – carboplatin – Phase I

INTRODUCTION

Platinum-based combination chemotherapy has been shown to improve survival and quality-of-life (QOL) in patients with advanced non-small cell lung cancer (NSCLC) (1,2). In the 1990s, new chemotherapeutic agents, such as gemcitabine (GEM), vinorelbine, docetaxel, paclitaxel (PTX) and irinotecan, were developed. Currently, platinum-based chemotherapy employing these new agents is accepted as the standard chemotherapy worldwide (3,4). In addition, a meta-analysis demonstrated significant longer progression-free survival of GEM and platinum combination compared with other new agents and platinum combinations (5). Thus, combination chemotherapy with GEM and platinum is now considered as one of the most active regimens for advanced NSCLC.

Like in other types of cancers, performance status (PS) has been shown to be one of the most important prognostic factors for survival in advanced NSCLC (6–8). Patients with impaired PS generally have lower response rate and shorter survival in spite of high risk for severe toxicities (9,10). Historically, clinical trials have excluded patients with Eastern Cooperative Oncology Group (ECOG) PS of 2 or worse. To date, it has not been fully elucidated whether platinum-based combination chemotherapy is feasible and effective in patients with PS 2.

Carboplatin (CBDCA), an analog of cisplatin (CDDP), has lower nephro- and gastrointestinal toxicity and has been widely used as a substitution of CDDP. Several randomized

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trials have shown the equivalence between GEM + CBDCA (GC) and GEM + CDDP (GP) in terms of response rate and survival (11,12). In those trials, toxicities, such as emesis, nephropathy and neuropathy were significantly mild in GC. Although recent meta-analysis disclosed slightly but significant survival advantage of CDDP (13,14), GC can be one of the treatment options, especially for patients who are not suitable to receive CDDP. In a randomized Phase III trial comparing GC with vinblastine + CDDP, GC showed better response rate and survival, and toxicities were similar between the two arms (15). Although 70% of all enrolled patients in the study had PS 2, overall response rate and median survival time (MST) were 27% and 11.6 months in GC arm. These survival data were comparable to those in patients with PS 0 or 1 who treated with platinum-based chemotherapy.

These results suggest the potential benefit of GC in patients with PS 2; however, the optimal dose of GC has not been investigated in patients with impaired PS. Therefore, we conducted a Phase I study to determine the maximum-tolerated dose (MTD) and the recommended dose for Phase II studies of GC in advanced NSCLC patients with PS 2.

PATIENTS AND METHODS

Eligibility

Patients with histologically or cytologically proven advanced NSCLC were eligible for the study. Each patient was required to meet the following criteria: (i) clinical stage IIIB or IV; (ii) ECOG PS of 2; (iii) aged 20–75 years; (iv) measurable lesion; (v) no prior chemotherapy; (vi) adequate hematological function (white blood cell $\geq$3500/mm^3, hemoglobin $\geq$9.5 g/dl and platelets $\geq$100 000/mm^3); (vii) adequate hepatic and renal function (total bilirubin $\leq$1.5 mg/dl, AST and ALT$<$100 IU/l and creatinine $\leq$1.5 mg/dl); (viii) PaO_2 $\geq$60 mmHg; and (ix) written informed consent. Patients with active concomitant malignancy, radiologically apparent interstitial pneumonia or pulmonary fibrosis, serious concurrent illness (e.g. uncontrolled diabetes mellitus, hypertension, angina pectoris, myocardial infarction within 3 months after onset or severe infection), history of severe drug allergy or pregnant/lactating women were excluded. The study protocol was approved by the institutional review board of the National Cancer Center.

Treatment Schedule

This was a Phase I, dose-escalation study planned for GEM on days 1 and 8 and CBDCA on day 1 of a 21-day course. The initial dose level of GEM was 800 mg/m^2 and CBDCA was an area under the concentration–time curve (AUC) of 4 mg min/ml. The actual dose of CBDCA was calculated based on Cockcroft–Gault equation (16) and Calvert formula (17) every course. CBDCA was infused over 60 min, and 60 min after the completion of CBDCA infusion, GEM was administered over 30 min. Prophylactic administration of granulocyte colony-stimulating factor (G-CSF) was not permitted. Administration of G-CSF was permitted for patients with grade 4 neutropenia and/or leukopenia and grade 3 febrile neutropenia. The administration of GEM was omitted on day 8 if patients met one of the following criteria: white blood cell $<$2000/mm^3, neutrophil $<$1000/mm^3, platelets $<$50 000/mm^3 and PS $\geq$3. No dose modification of GEM was permitted on day 8. If dose-limiting toxicity (DLT) was observed, the dose of each drug was reduced to 80% in the next course of chemotherapy. Treatment was to be performed for at least two courses, unless unacceptable toxicity or disease progression occurred.

The DLT was defined as follows: grade 4 thrombocytopenia, grade 3 or grade 4 febrile neutropenia, grade 3 non-hematological toxicity (except for nausea/vomiting and alopecia) and omission of the treatment on day 8. Dose-escalation schedule is shown in Table 1. Initially, three patients were treated at each dose level. If DLT was not observed in any of three patients, dose escalation was made. If DLT was observed in one or two of three patients, an additional three patients were entered in the same dose level. If DLT was observed in three or more of six patients or all of the initial three patients, we considered that the dose was the MTD. If DLT was observed in one or two of six patients, dose escalation was also made. Dose escalation was decided by the toxic data only in the first course of chemotherapy.

Baseline and Treatment Assessment

Pre-treatment evaluation consisted of complete medical history and physical examination, complete blood cell counts, blood chemistry studies, electrocardiograph, arterial blood gas analysis, chest radiography, computed tomography (CT) of the chest, CT or ultrasound study of the abdomen, CT or magnetic resonance imaging of the brain, and bone scintigraphy. Complete blood cell counts, blood chemistry studies and chest radiography were repeated every week. Creatinine clearance was estimated by the Cockcroft–Gault equation every course. Tumor response was assessed with the Response Evaluation Criteria in Solid Tumor (RECIST) criteria (18). Toxicity was evaluated according to the National Cancer Institute-Common Toxicity Criteria (version 2.0).

Table 1. Dose-escalation schedule

Dose level	Gemcitabine (mg/m^2)	Carboplatin (AUC)	No. of patients
1	800	4	3–6
2	1000	4	3–6
3	1000	4.5	3–6
4	1000	5	3–6

AUC, area under the curve.

RESULTS

Patient Characteristics

Between February 2004 and August 2006, 13 patients were enrolled in this study. However, one patient was excluded from the analysis because of the error in dose calculation. Table 2 shows the characteristics of 12 evaluable patients. Eleven patients were male and one was female. The median age of the patients was 68 years (range, 51–72 years). There were five adenocarcinomas, four squamous cell carcinomas, two large cell carcinomas and one pleomorphic carcinoma. Stage IIIB and IV patients were five and six, respectively, and one patient was a relapse after surgical resection.

Dose Escalation

At the dose level 1, DLT was observed in two of the first three patients: one experienced grade 3 hyponatremia and the other experienced grade 3 febrile neutropenia. Thereafter, we amended the protocol, and grade 3 hyponatremia was excluded from DLT criteria after that. Another three patients were treated at the same dose. Since these patients did not show any additional DLT, the dosage was then escalated to the next step. At the dose level 2, DLT was observed in two of the first three patients: one experienced grade 3 nausea/vomiting and omission on day 8 and the other experienced grade 3 febrile neutropenia and anorexia. Therefore, another three patients were assigned to receive the treatment at the same dose. Out of those three patients, one patient developed grade 4 febrile neutropenia and grade 3 anorexia. Thus, DLT was observed in three of six patients at the dose level 2. As a result, the dose level 2 (GEM, 1000 mg/m^2 and CBDCA, AUC of 4) was determined to be the MTD.

Table 2. Characteristics of evaluable patients ($n = 12$)

Characteristics	No. of patients
Gender	
Male	11
Female	1
Age (years)	
Median	68
Range	51–72
Histology	
Adenocarcinoma	5
Squamous cell carcinoma	4
Large cell carcinoma	2
Pleomorphic carcinoma	1
Stage	
IIIB	5
IV	6
Relapse after surgery	1

Toxicity

The worst grades for each patient in the first cycle are listed in Table 3. Grade 3/4 leukopenia or neutropenia was observed in one patient at level 1 and two patients at level 2. Febrile neutropenia was observed in one patient at level 1 and two patients at level 2. Two patients had grade 3/4 anemia at level 1 and one patient required red blood cell transfusion. No grade 3/4 anemia occurred at level 2. Thrombocytopenia was the principal toxicity of this combination chemotherapy. At level 1, grade 3/4 thrombocytopenias were observed in three patients, and two patients received platelet transfusion. At level 2, two patients experienced grade 3/4 thrombocytopenia requiring no platelet transfusions. Non-hematologic toxicities were generally mild at level 1, however, one patient experienced grade 3 nausea/

Table 3. Toxicities during the first cycle

NCI-CTC grade	Level 1 ($n = 6$)		Level 2 ($n = 6$)	
	G1/2	G3/4	G1/2	G3/4
Hematologic				
Leukopenia	1/2	0/1	2/1	2/0
Neutropenia	1/1	1/0	1/1	2/0
Febrile neutropenia	0/0	1/0	0/0	1/1
Anemia	1/3	1/1	2/3	0/0
Thrombocytopenia	1/2	2/1	1/1	4/0
Transaminase	2/0	0/0	4/2	0/0
Bilirubin	0/0	0/0	0/0	1/0
Creatinine	0/0	0/0	0/0	0/0
Hyponatremia	4/0	2/0	5/0	0/0
Non-hematologic				
Nausea/vomiting	2/0	0/0	3/1	1/0
Anorexia	4/1	0/0	2/1	3/0
Fatigue	1/0	0/0	1/2	1/0
Diarrhea	0/0	0/0	2/0	0/0
Constipation	0/0	0/0	0/1	0/0
Mucositis	0/0	0/0	0/0	0/0
Pneumonitis	0/0	0/0	0/0	0/0
Infection	0/0	0/0	0/0	0/0
Skin rash	1/0	0/0	1/0	0/0
Omission on day 8	0		1	
No. of patients with DLT	2		3	

NCI-CTC, National Cancer Institute-Common Toxicity Criteria; DLT, dose-limiting toxicity.

vomiting and omission of day 8 at level 2. This patient also presented grade 3 hyperbilirubinemia suspected to be drug-induced hepatitis, and died 16 days after the start of the treatment. The worst value of his laboratory data was 6.6 mg/dl in total bilirubin on day 12, 40 IU/l in AST on day 7 and 103 IU/l in ALT on day 7. He had a past history of drug-induced hepatitis related to aspirin. The excluded patient was administered GEM at 800 mg/body. Despite the dose was approximately two-thirds of the planned dose, he experienced grade 3 nausea/vomiting and the treatment was discontinued. The median number of administered cycle was 1. The actual administered cycles were one in seven patients, two in one patient, three in two patients and four in two patients. The reasons for the discontinuation in seven patients who terminated the treatment at one cycle were toxicity for three patients, patient refusal for two patients, treatment delay for one patient and both toxicity and disease progression was for one patient.

Anti-tumor Activity

There were seven stable diseases and five progressive diseases (PD). No partial or complete response was observed (Table 4). Four patients received second-line chemotherapy after GC: docetaxel for two patients and gefitinib for two patients. One patient received gefitinib experienced partial response; however, remaining three patients had PD also in the second-line treatment. The MST was 3.8 months (Fig. 1).

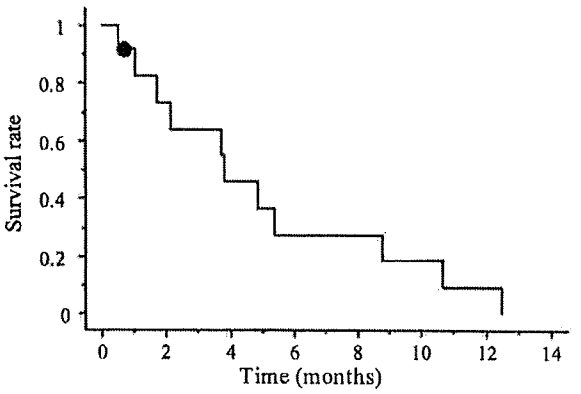

Figure 1. Kaplan Meier curve of overall survival. Median overall survival time was 3.8 months.

DISCUSSION

This is the first PS 2-specific Phase I study of GC in Japanese patients, and the MTD and recommended dose were determined to be GEM 1000 mg/m^2 and CBDCA AUC of 4.

The recommended dose of CBDCA was lower than other studies conducted in the USA (19,20). With respect to the dose of CBDCA, the method of measuring serum creatinine values is critical. In Japan, most institutions use the enzymatic method, whereas the Jaffe method remains the mainstream in the USA (21). According to the study comparing these two methods, serum creatinine values are higher in the Jaffe method than in the enzymatic method by ~0.2 mg/dl (21). Therefore, at the same AUC, higher CBDCA dose is administered in Japan than in the USA. Incidentally, based on the Calvert formula, a difference of 0.2 mg/dl of creatinine leads to the difference of AUC = 1. In short, the AUC = 4 in Japan roughly corresponds to the AUC = 5 in the USA. For global clinical trials, the difference of methods for measurement of laboratory data also should be paid attention to.

PS is one of the most powerful and reliable prognostic factors in advanced NSCLC (6–8), and a worse PS is characterized by lower response rate to chemotherapy and shorter survival (9,10). Median survival of patients with PS 2 is substantially shorter than that of patients with PS 0 or 1. Moreover, patients with PS 2 are at higher risk for severe toxicity than those with better PS. According to the population-based surveys, up to 30–40% of all advanced NSCLC is characterized PS 2 (22,23). Namely, patients with PS 2 constitute a distinctive, non-trivial subgroup in NSCLC. However, little attention has been paid to this special patient population until recently.

The guidelines from the American Society of Clinical Oncology support the single use of third-generation non-platinum agents for patients with PS 2 (24). This recommendation is mainly based on the results of Phase III trials comparing single-agent chemotherapy with best supportive care alone, in which good tolerability and significant survival benefit or improvement of QOL with single-agent chemotherapy have been demonstrated (25–28). However, PS 2 patients accounted for a small proportion of patients in those trials and any conclusive evidence cannot be drawn for the treatment of patients with PS 2. At present, available data from PS 2-specific clinical trials are quite limited. In this context, no consensus has been developed on the standard chemotherapy in patients with PS 2.

The role of adding platinum to third-generation single agents is still unclear. Recently, the Norwegian Lung Cancer Study Group reported the results of a retrospective study that compared the outcome of patients with PS 2 to that of patients with PS 0 or 1 who had participated in randomized trials comparing two third-generation, CBDCA-based

Table 4. Drug delivery and anti-tumor efficacy

Dose level	Number of patients	Median course (range)	Overall response			
			CR	PR	SD	PD
1	6	1 (1–4)	0	0	4	2
2	6	2 (1–4)	0	0	3	3

CR, complete response; PR, partial response; SD, stable diseases; PD, progressive diseases.

regimens (29). According to the retrospective study, although MST of patients with PS 2 was significantly shorter than that of patients with PS 0 or 1 (4.5 vs. 8.9 months; $P < 0.01$), toxicity was acceptable for patients with PS 2 and they achieved better symptom improvement compared with patients with PS 0 or 1. ECOG conducted the first PS 2-specific randomized trial (19). In the randomized Phase II trial, two platinum-based chemotherapy regimens, PTX + CBDCA (PC) and GP, have been compared, and both regimens were proved feasible with acceptable toxicity. However, survival time was quite limited in both treatment arms: MST was 6.2 months for PC and 6.9 months for GP, respectively. A Greece Group performed a randomized Phase II trial comparing non-platinum single-agent chemotherapy with CBDCA-based chemotherapy (30). In the study, patients were randomly assigned to either GC or GEM alone and MST was 6.7 months for GC and 4.8 months for GEM alone, respectively ($P = 0.49$), whereas neutropenia ($P = 0.007$) and thrombocytopenia ($P < 0.001$) were more common in GC arm. In contrast, according to a subgroup analysis of the Cancer and Leukemia Group B study 9730 comparing PC with PTX alone, patients with PS 2 (107 patients, 18% of the population) achieved significantly better survival when they were treated with PC than those treated with PTX alone (20). Thus, the role of platinum-based chemotherapy for patients with PS 2 is still controversial.

The results could vary even between PS 2-specific trials due to two major reasons. First, determining PS score is inevitably subjective, there is considerable inter-observer variation even between healthcare professionals (31). Second, there can be significant heterogeneity in the PS 2 patient population: the reasons for impaired PS may be due to tumor-related (such as pain, fatigue and weight loss), to pre-existing co-morbidities (such as chronic obstructive pulmonary disease, cardiovascular disease and age-related decline in functional status) or both, furthermore (32). There is a clear need for a more objective classification system that takes into account the individual effects of disease-related symptoms and co-morbidities. The common co-morbidity scales are the Cumulative Illness Rating Scale-Geriatric (CIRS-G) and the Charlson scale. Their prognostic impacts have been validated prospectively (33,34). Moreover, they are more objective than PS. Although our study did not, all future studies for PS 2 patients should use such co-morbidity scales to stratify patients more accurately.

Recently, molecular-targeted agents, especially epidermal growth factor receptor tyrosine kinase inhibitors such as gefitinib or erlotinib, have been tested in clinical trials for patients with poor PS. Inoue et al. (35) conducted a Phase II trial of gefitinib in patients with NSCLC whose tumor harboring EGFR gene mutation. In the study, all patients were not feasible for cytotoxic chemotherapy due to poor PS: 26 of 29 patients were PS 2–4. Overall response rate and MST were 66% and 6.5 months, respectively. In addition, PS improvement rate was 79%, and no treatment-related deaths were observed. These excellent results strongly suggest that stratification with molecular status should be required in the future trial of PS 2 or more.

In this study, we determined the MTD and the recommended dose of GC in Japanese patients with PS 2. Response rate and overall survival of the regimen were disappointing. However, some previous studies clearly support the use of platinum agent in PS 2 patients (19,20). Future clinical trials for PS 2 patients should use more objective criterion such as co-morbidity scales in addition to PS in order to measure patients' risk more accurately. Such studies may reveal that which patients should be treated and not be treated with platinum-based chemotherapy among PS 2 patients.

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Conflict of interest statement

None declared.

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