randomized trial, these results may stimulate further interest in the clinically relevant efficacy of pemetrexed maintenance in *EGFR* wild-type patients for whom the limited therapeutic options exist.

In conclusion, this study regimen of pemetrexed/carboplatin followed by pemetrexed maintenance is feasible and effective as a first-line treatment for advanced nonsquamous NSCLC patients. Our findings have strengthened the rationale for the ongoing randomized phase III trial comparing this regimen with the carboplatin, paclitaxel and bevacizumab combination in patients with advanced, nonsquamous NSCLC [22].

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Brain metastases after definitive concurrent chemoradiotherapy in patients with stage III lung adenocarcinoma: Carcinoembryonic antigen as a potential predictive factor

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The predictive factors for the development of brain metastases in patients with stage III non-small-cell lung cancer receiving concurrent chemoradiotherapy remain unclear. Several studies have suggested adenocarcinoma as a predictive factor of brain relapses. In the current analysis, we tried to identify the factors associated with brain metastases in stage III lung adenocarcinoma. The demographic and clinical characteristics, site and date of recurrence, and date of death were reviewed in patients with unresectable stage III lung adenocarcinoma who underwent concurrent platinum-based chemoradiotherapy. In total, 116 patients were identified with a median (range) age of 57 (35–74) years. Of these, 86 (74%) were men, all patients had platinum-based chemotherapy, and 100 (86%) received a total dose of 60 Gy in 30 fractions as definitive thoracic radiotherapy. Of the 95 patients with disease progression or recurrence, 19 (16%) developed brain metastases as the sole site of initial recurrence. A total of 43 (37%) patients developed brain metastases at some time during follow-up. Time to brain metastases was significantly associated with the pretreatment carcinoembryonic antigen (CEA) value, with a hazard ratio (95% confidence interval) of 2.64 (1.39–5.02, $P = 0.003$). Patients who developed brain metastases as the first recurrent site had marginally better survival (log-rank test, $P = 0.066$) than those with metastases other than brain. In conclusion, stage III lung adenocarcinoma patients with an elevated CEA value before treatment had a higher risk of developing brain metastases after chemoradiotherapy. Further effort is mandatory to control brain metastases in this patient population by a therapeutic strategy based on the tumor histology and pretreatment CEA value. (*Cancer Sci* 2012; 103: 756–759)

Recent advances in chemotherapy added to radiotherapy have dramatically improved the prognosis of patients with inoperable stage III non-small-cell lung cancer (NSCLC). The current standard treatment for these patients, concurrent thoracic radiotherapy and platinum-based chemotherapy, yields a 5-year survival rate of 16–23%, with acceptable acute and late toxicity.[1,2] However, many patients still die of recurrent disease. Brain metastases, as well as loco-regional recurrences, are the most frequent types of initial failure. Observational studies in patients with stage III NSCLC who underwent chemoradiotherapy with or without surgery showed that the first recurrent site was the brain in only 8–35% of patients, and brain and other sites in 4–10% of patients, resulting in brain metastases as the first recurrent site in 17–43% of patients.[1,3,4] Prophylactic cranial irradiation (PCI) has been tried to eradicate undetectable micrometastases before they become clinically apparent. Prospective randomized trials comparing PCI and observation in patients with locally advanced NSCLC treated by thoracic radiotherapy with or without chemotherapy showed a significant reduction in the development of brain metastases, but no survival benefit in the PCI arms.[5–8] Thus, PCI is not indicated for all patients with stage III NSCLC treated with chemoradiotherapy, but it would improve prognosis if used to treat selected patients who are more likely to develop brain metastases. Several clinical factors have been identified to predict brain metastases in locally advanced NSCLC patients, but they are inconsistent among studies.[9–11] Of these clinical factors, adenocarcinoma histology was suggested to have a higher risk of brain relapses.[11–16] The objectives of this study were to identify factors associated with development of brain metastases in stage III adenocarcinoma patients who received concurrent chemoradiotherapy and to identify potential candidates for intervention to reduce brain relapses.

Materials and Methods

Patient selection. Patients with unresectable stage III lung adenocarcinoma who underwent concurrent platinum-based chemotherapy and thoracic radiotherapy at the National Cancer Center Hospital (Tokyo, Japan) between 1994 and 2005 were eligible for this study. Patients treated with sequential chemotherapy and thoracic radiotherapy were excluded because we have considered the standard care for the stage III NSCLC patients to be concurrent chemoradiotherapy, and therefore, the sequential treatment was given only to patients with poor general condition or to patients who had a tumor too large for radiotherapy initially but decreasing enough for radiotherapy after chemotherapy. All patients underwent a systematic pretreatment evaluation and standardized staging procedures, which included physical examination, chest X-rays, CT scans of the chest and abdomen, a CT scan or MRI of the brain, a bone scintigram, and blood examinations including tumor markers.

Data collection and statistical analyses. Sex, age, performance status, body weight loss, carcinoembryonic antigen (CEA), clinical stage, nodal status, chemotherapy regimens, total dose of radiotherapy, tumor responses to treatment, sites and date of recurrence, and date of death were obtained from a retrospective medical chart review. As a routine clinical practice, tumor markers including CEA were examined in every patient eligible for chemotherapy and chemoradiotherapy before, during,

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and just after the initiation of treatment. Receiver operator characteristic (ROC) curves and the corresponding area under the curve (AUC) were used to evaluate the cut points of CEA values to predict brain metastasis as the sole, or one of the first, relapse sites. Tumor histological classification was based on the criteria of the World Health Organization.[17] Patients were staged using the 6th edition of Union for International Cancer Control TNM classification for lung cancer.

Time to brain metastases was measured from the start of initial chemoradiotherapy to when the brain metastases were confirmed by a brain CT scan or MRI. Although we monitor brain metastases regularly as a routine follow-up imaging study after chemoradiotherapy, there might be diversity in the frequency and methods of monitoring. Patients who did not develop brain metastases at the last follow-up were censored at that time. Time to brain metastases was evaluated using the Kaplan–Meier method, the log–rank test, and Cox's proportional hazard model.

Sex, age, performance status, body weight loss, smoking status, CEA value, stage, T-factor, and nodal status were included as covariates in the multivariate analyses (Cox's proportional hazard model analyses). All of these analyses were carried out using STATA 11.1 software for Windows (StataCorp, College Station, TX, USA).

This study was approved by the president of the National Cancer Center Hospital. The institutional review board and ethics review committee decided to exempt this study from the usual review process because of its retrospective nature.

Results

In total, 116 patients were identified. Females accounted for 26% of the study group. The median age was 57 years. Almost all patients were in good general condition with a performance status of 0–1. Of the 116 patients, 63% had tumor factor (T-factor) 1–2 disease and 93% had nodal factor (N-factor) 2–3 disease. All patients received platinum-based chemotherapy, and 86% received a total dose of 60 Gy in 30 fractions as definitive thoracic radiotherapy (Table 1). The response rate was 82%, median survival time was 24.5 months, and the 5-year survival rate was 24% in this study group.

Disease progression or recurrence was noted in 95 (82%) patients. Brain metastases as the sole site of initial recurrence were noted in 19 (16%) patients, and both brain and other sites were involved in 17 (15%) patients (Table 2). Of the 19 patients who had isolated brain failure, 10 developed recurrences subsequently at additional sites other than the brain, three died of progressive brain metastases without progression in other sites, and two developed meningitis carcinomatosa. Another two patients also died, but the cause of death was not identified because they were lost to follow-up. Brain metastases were controlled by radiotherapy in the other two patients.

A total of 43 patients (37%) developed brain metastases at some time during the course of follow-up. We examined various cut points of CEA value and found 20 ng/mL gave a relatively better AUC (56.2%) by the ROC analysis. Time to brain metastasis was significantly associated with pretreatment CEA value. The responses of CEA during chemoradiotherapy and the CEA level just after chemoradiotherapy did not have significant correlation with brain relapses. The multivariate analysis using Cox's proportional hazard model showed that the hazard ratio (95% confidence interval [CI], *P*-value) of a CEA value $\geq$20 ng/mL was 2.64 (1.39–5.02, $P = 0.003$, Table 3) compared to a CEA value of < 20 ng/mL. Sex, age, performance status, body weight loss, smoking history, T-factor, nodal status, and stage were not associated with the time to brain metastasis (Table 3). Percentages of patients who developed brain metastases at 12 and 24 months were 37% and 67% in patients with elevated CEA value, and 21% and 32% in the others (log–rank test, $P = 0.01$), respectively (Fig. 1).

Overall survival according to the first relapse site is shown in Figure 2. Patients who developed brain metastases only as the first recurrent site had marginally better survival (log–rank test, $P = 0.066$) compared to those with metastases other than brain.

Table 1. Characteristics of patients with stage III lung adenocarcinoma who participated in this study (*n* = 116)

Characteristic	*n*	%
Sex		
Female	30	26
Male	86	74
Age (years)		
Median (range)	57 (35–74)	NA
Performance status		
0	36	31
1	79	68
2	1	1
Body weight loss		
$\leq$4.9%	95	82
$\geq$5.0%	21	18
Smoking (pack-years)		
$\leq$10	29	25
$\geq$11	87	75
CEA (ng/mL)		
< 20	89	77
$\geq$20	27	23
Stage		
IIIA	57	49
IIIB	59	51
T-factor		
1–2	73	63
3–4	43	37
N-factor		
0–1	8	7
2–3	108	93
Chemotherapy type		
Cisplatin + vinorelbine	75	65
Cisplatin + vindesine + mitomycin	26	22
Nedaplatin + paclitaxel	8	7
Other combinations	7	6
Total radiation dose (Gy)		
60	100	86
<60	16	14

CEA, carcinoembryonic antigen; NA, not applicable; N-factor, nodal factor; T-factor, tumor factor.

Table 2. Sites of first recurrence in patients with stage III lung adenocarcinoma (*n* = 95)

Site of recurrence	*n*	%
Relapses including brain	36	38
Brain only	19	20
Brain and other sites	17	18
Sites other than brain	56	59
Unknown	3	3

Discussion

This study showed that CEA values before treatment were associated with time to brain metastasis in patients with stage III

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Table 3. Time to brain metastases according to clinical factors in patients with stage III adenocarcinoma: Cox proportional hazard model analysis

Characteristic	Cox proportional hazard model (HR [95% CI])			
	Univariate	*P*-value	Multivariate	*P*-value
Sex				
Male	1	0.03	1	0.660
Female	2.00 (1.08–3.69)		1.24 (0.48–322)	
Age (years)				
≤57	1	0.17	1	0.110
≥58	0.65 (0.34–1.21)		0.58 (0.30–1.13)	
Performance status				
0	1	0.96	1	0.830
1–2	0.98 (0.53–1.83)		0.92 (0.44–1.92)	
Body weight loss (%)				
≤4.9	1	0.91	1	0.630
≥5.0	1.05 (0.47–2.36)		1.25 (0.51–3.05)	
Smoking (pack-years)				
≤10	1	0.01	1	0.290
≥11	0.43 (0.23–0.79)		0.58 (0.21–1.59)	
CEA				
<20	1	0.01	1	0.003
≥20	2.17 (1.17–3.99)		2.64 (1.39–5.02)	
T-factor				
1–2	1	0.39	1	0.880
3–4	0.75 (0.39–1.44)		0.84 (0.37–1.90)	
N-factor				
0–1	1	0.33	1	0.520
2–3	2.02 (0.49–8.38)		1.40 (0.50–3.88)	
Stage				
IIIA	1	0.93	1	0.770
IIIB	1.03 (0.57–1.87)		0.85 (0.30–2.46)	

CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; N-factor, nodal factor; T-factor, tumor factor.

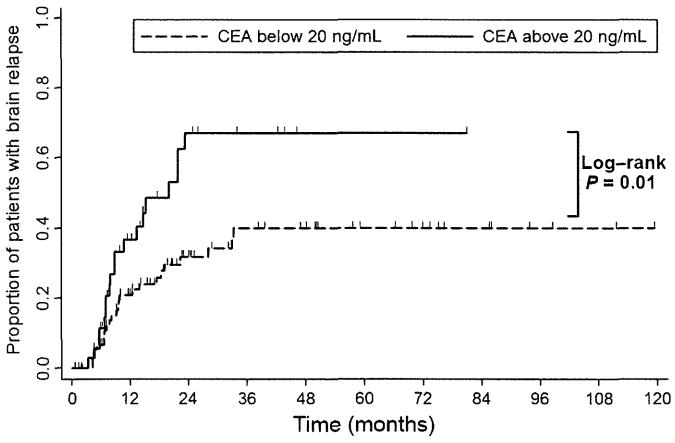

Fig. 1. Cumulative incidence of brain relapse in patients with stage III lung adenocarcinoma by carcinoembryonic antigen (CEA) value (ng/mL). Percentages of patients who developed brain metastases at 12 and 24 months were 37% and 67% in patients with elevated CEA value, and 21% and 32% in the others (log–rank test, $P = 0.01$), respectively.

lung adenocarcinoma who received concurrent platinum-based chemotherapy and thoracic radiotherapy. This is the first report showing that the CEA value might be associated with a higher risk of brain metastases in locally advanced lung adenocarcinoma.

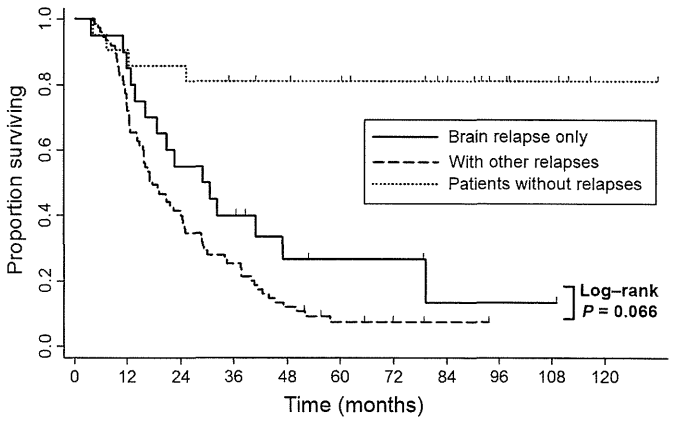

Fig. 2. Overall survival in patients with stage III lung adenocarcinoma according to the first relapse site. Dashed line, patients who developed extracranial recurrence with or without brain metastases; thick line, patients who developed brain relapse only; dotted line, patients who had no relapse. Patients who developed brain metastases as the first recurrent site had marginally better survival (log–rank test, $P = 0.066$) compared to those with metastases other than brain.

The median survival time (24.5 months) in the present study seemed better than the results observed in the study of Cox *et al.* (median survival time, 12.2–18.9 months) that included four clinical trials involving chemoradiotherapy.[12,18–21] The proportion of the participants whose first recurrent sites included brain metastases (38%, Table 2) in this study was substantially higher than the results observed in the analysis of Cox *et al.*[12] (16% with adenocarcinoma). Because the concurrent chemoradiotherapy with better survival failed to improve the proportion of brain relapses, the importance of the prevention of brain metastases has increased in this patient group. Furthermore, overall survival in patients who developed brain metastases as the sole site of the initial recurrence was marginally better than in those with metastases to other sites (log–rank, $P = 0.066$, Fig. 2) in our observation of patients with locally advanced lung adenocarcinoma. In fact, some patients with only brain relapses as the first recurrent site survived without further metastases after local treatment for the brain lesions.

Prospective randomized trials evaluating the effect of PCI in patients with locally advanced NSCLC after chemoradiotherapy showed a significant reduction in the development of brain metastases, but no survival benefit in the PCI arms.[5–8] Thus, it is necessary to identify the clinical factors of patients who are more likely to develop brain metastases and would be good candidates for PCI. In retrospective analyses of patients with locally advanced NSCLC, adenocarcinoma histology was suggested to have a higher risk of brain relapses and be worthy of more attention concerning brain metastases.[11–16] Therefore, locally advanced lung adenocarcinoma was specifically analyzed to identify clinical factors predicting brain metastases.

Among patients with disseminated adenocarcinoma without indications for definitive thoracic radiotherapy, a high CEA value (over 40 ng/mL) before treatment might be associated with a higher risk of brain relapses.[22] The present study involving patients with locally advanced lung adenocarcinoma after chemoradiotherapy showed that the CEA value was significantly associated with the time to brain metastasis on multivariate analysis (Table 3). This result suggested that patients with stage III lung adenocarcinoma and elevated CEA values might be good candidates for interventions to prevent brain metastases.

This study had several limitations. First, the number of patients included in the analysis was relatively small because we selected patients with stage III lung adenocarcinoma who

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underwent concurrent chemoradiotherapy. Second, there might be diversity in the frequency and methods of monitoring brain metastases because of the retrospective nature of the analysis. Third, we could not determine significant factors to predict solitary brain relapses which might be cured by prophylactic brain intervention, mainly because the number of patients with solitary brain relapse was too small for efficient statistical analysis.

In conclusion, the present analysis implies that patients with elevated CEA values before treatment have a higher risk of developing brain metastases after chemoradiotherapy for locally advanced lung adenocarcinoma. Further effort is mandatory to evaluate the clinical relevance of CEA value to predict brain relapses and select candidates for prophylactic interventions in future prospective trials.

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Disclosure Statement

The authors have no conflicts of interest.

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Lung Cancer

Quality of Life with Gefitinib in Patients with *EGFR*-Mutated Non-Small Cell Lung Cancer: Quality of Life Analysis of North East Japan Study Group 002 Trial

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Key Words. Lung carcinoma • Epidermal growth factor receptor • EGFR • Tyrosine kinase inhibitor • TKI • Gefitinib • Quality of life • QoL

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ABSTRACT

Background. **For non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (*EGFR*) mutations, first-line gefitinib produced a longer progression-free survival interval than first-line carboplatin plus paclitaxel but did not show any survival advantage in the North East Japan 002 study. This report describes the quality of life (QoL) analysis of that study.**

Methods. **Chemotherapy-naïve patients with sensitive *EGFR*-mutated, advanced NSCLC were randomized to receive gefitinib or chemotherapy (carboplatin and paclitaxel). Patient QoL was assessed weekly using the Care Notebook, and the primary endpoint of the QoL analysis was time to deterioration from baseline on each of the physical, mental, and life well-being QoL scales. Kaplan–Meier probability curves and log-rank tests were employed to clarify differences.**

Results. **QoL data from 148 patients (72 in the gefitinib arm and 76 in the carboplatin plus paclitaxel arm) were analyzed. Time to defined deterioration in physical and life well-being significantly favored gefitinib over chemotherapy (hazard ratio [HR] of time to deterioration, 0.34; 95% confidence interval [CI], 0.23–0.50; $p < .0001$ and HR, 0.43; 95% CI, 0.28–0.65; $p < .0001$, respectively).**

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Conclusion. **QoL was maintained much longer in patients treated with gefitinib than in patients treated with standard chemotherapy, indicating that gefitinib should be considered as the standard first-line therapy for advanced *EGFR*-mutated NSCLC in spite of no survival advantage.**
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Introduction

Dysregulation of protein kinases is frequently observed in cancer cells. Therefore, protein kinases are attractive targets in the development of anticancer drugs such as small molecule inhibitors that block binding of ATP to the catalytic domain of the tyrosine kinase. In 2004, three groups of researchers reported that activating mutations of the epidermal growth factor receptor gene (*EGFR*) were present in a subset of non-small cell lung cancer (NSCLC) tumors, and that tumors with *EGFR* mutations were highly sensitive to EGFR tyrosine kinase inhibitors (TKIs) [1–3]. Since then, our multiple phase II studies confirmed a striking response to EGFR TKIs in this population [4–8].

In phase III NSCLC trials, EGFR TKIs such as gefitinib or erlotinib were compared with conventional chemotherapies initially in unselected patients [9–11], next on the basis of clinical characteristics [12], and subsequently using molecular selection [13–16]. Among them, the pivotal phase III study North East Japan (NEJ) 002 compared gefitinib with chemotherapy in first-line therapy for patients with NSCLC with mutated *EGFR* and confirmed, as the primary endpoint, that the progression-free survival (PFS) interval in the gefitinib group was significantly longer than that in the carboplatin plus paclitaxel group (10.8 months versus 5.4 months, hazard ratio [HR], 0.30; $p < .001$) [13]. A subgroup analysis of the Iressa® Pan-Asia Study (IPASS) [12] and similar phase III studies—the West Japan Thoracic Oncology Group 3405 trial [14], the OPTIMAL trial [15], and European Randomised Trial of Tarceva versus Chemotherapy [16]—also demonstrated a superior PFS outcome in patients treated with EGFR TKIs than in those treated with standard chemotherapies. However, the IPASS and NEJ 002 trials showed identical overall survival (OS) outcomes using gefitinib and chemotherapy in the first-line treatment of NSCLC patients harboring sensitive *EGFR* mutations [17, 18].

When the OS time is identical in the two arms, improvements in quality of life (QoL) and disease-related symptoms are among the key goals of treatment for NSCLC. However, there has been no prospective report describing QoL in NSCLC patients with sensitive *EGFR* mutations who were treated using an EGFR TKI. This QoL analysis was prospectively conducted as a secondary endpoint in the NEJ 002 study.

Methods

This study was performed in accordance with the Helsinki Declaration (1964, amended in 2000) of the World Medical Association. The participating institutions received approval from their institutional ethics review boards. The details regarding patient eligibility and treatment were described previously [13]. Briefly, eligibility stipulated the presence of advanced NSCLC harboring a sensitive *EGFR* mutation, the absence of the resistant *EGFR* mutation T790M, no history of chemotherapy, and age ≤75 years. *EGFR* mutation status was examined using the peptide nucleic acid-locked nucleic acid polymerase chain reaction (PNA-LNA PCR) clamp method [19]. Eligible patients were randomly assigned to receive either gefitinib (at a dose of 250 mg/day orally) or standard chemotherapy. Standard chemotherapy consisted of paclitaxel (at a dose of 200 mg/m^2 i.v.) and carboplatin (area under the concentration–time curve of 6), both administered on the first day of every 3-week cycle. Randomization was balanced by institution, sex, and stage. The primary endpoint was the PFS interval; secondary endpoints included the OS time, response rate, toxic effects, and QoL.

QoL Assessment

The Care Notebook (supplemental online Fig. 1) [20], which has been previously validated and reported [21, 22], was used to assess QoL. The Care Notebook is a self-administered, cancer-specific questionnaire that asks about cancer patients' conditions during 1 week regarding 24 items that are structured in multidimensional scales. The questionnaire consists of three major scales: physical well-being, mental well-being, and life well-being. These major scales are divided into several subscales. Physical well-being has three multi-item subscales, which are appetite loss (items P3, P4, P7), constipation (P6, P8), and fatigue (P9, P10), and three single-item measures, which are pain (item P1), shortness of breath (item P2), and sleeping trouble (P5). Mental well-being has three multi-item subscales, which are anxiety (M1, M2), irritation (M3, M5), and depression (M4, M6). Life well-being has three multi-item subscales, which are daily functioning (L1, L2), social functioning (L3, L4), and subjective QoL (L5–L8), which consists of peace of mind (L5), feeling of happiness (L6), QoL functioning (L7), and satisfaction with daily life (L8). Each item is asked using one word or a short phrase and employs an 11-point linear analog scale (0–10). A score of 10 in physical well-being and mental well-being indicates the heaviest burden. A score of 10 in life well-being indicates the best possible function or QoL; thus, the polarity of the data for life well-being was reversed before the analysis so that a greater score indicated a poorer QoL in all items of the questionnaire.

Seventy sheets of the Care Notebook were bundled as a booklet. Patients started answering the questionnaire before starting therapy and answered it once a week during first-line treatment. After completion of the questionnaire, the booklets were collected by the patients' doctors and sent to the QoL data center (Saitama Medical University).

Statistical Analyses

The primary endpoint in the QoL analysis, which was prospectively defined in the protocol of the clinical trial, was the time from random assignment of treatment to deterioration in the

following, which are clinically relevant and are frequently observed in patients with advanced NSCLC: (a) pain and shortness of breath (P1 and P2), (b) anxiety (M1 and M2), and (c) daily functioning (L1 and L2). From previous studies [23, 24], deterioration was recognized when the score changed from baseline by one of 11 points (9.1%) in a direction indicating a worse QoL at any timepoint. This primary analysis was performed for 20 weeks after the initiation of first-line therapy. All patients who had a baseline plus at least one follow-up QoL assessment were included in the time-to-deterioration analysis. Patients who had not deteriorated were censored at the time of the last QoL questionnaire completion. Kaplan–Meier curves and the log-rank test were used to compare the time to deterioration in each subscale between the two treatment arms. Also, more severe deterioration was defined as a score change of three of 11 points (27.3%) [23, 24].

In addition, we performed a secondary analysis using QoL data according to the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) standard method [25]. During the initial 20 weeks from the start of treatment, we first checked whether or not the scores showed an improvement at any time in a subscale by ≥9.1% (one point or more) from baseline. In such cases, the response was judged to be "improved" even if the scores were initially or subsequently below the lower boundary, that is, −9.1%. If the response was not classified as improved, we next checked whether or not the scores showed a worsening in a subscale by ≥−9.1% from baseline, resulting in the response being classified as "worsened." In cases that were classified as neither improved nor worsened, the response was classified as "stable." A χ^2 test was used for comparisons between the two arms.

Results

Summary of Clinical Outcomes

In the NEJ 002 study [13], 230 patients who had sensitive *EGFR* mutations were enrolled and were randomly assigned to either gefitinib (n = 115) or carboplatin plus paclitaxel (n = 115), and 114 and 110 patients, respectively, were included in the PFS analysis (Fig. 1). Patients in the gefitinib arm had a significantly longer PFS time (median PFS time, 10.8 months versus 5.4 months; HR, 0.30; 95% CI, 0.22–0.41; $p < .001$) and a higher response rate (73.7% versus 30.7%; $p < .001$) than patients in the chemotherapy arm. Second-line gefitinib was administered to 98.2% of patients in the carboplatin plus paclitaxel arm after disease progression. As a result, the median OS time was 27.7 months in the gefitinib arm and 26.6 months in the chemotherapy arm, with the difference in survival time not statistically significant (p = .48) [18]. The most common adverse events of any grade were rash (71.1%) and aspartate aminotransferase or alkaline phosphatase elevation (55.3%) in the gefitinib arm and neutropenia (77.0%), anemia (64.6%), appetite loss (56.6%), and sensory neuropathy (54.9%) in the chemotherapy arm [13].

Baseline QoL

Of the 224 patients, the QoL booklets of 163 patients (73%) were collected by their doctors and sent to the QoL data center.

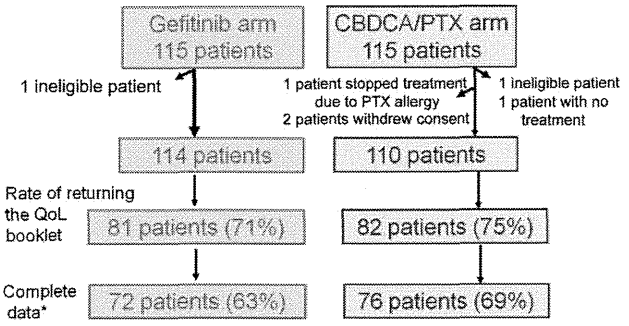

Figure 1. Patient disposition.

*The complete dataset was defined as having both a pretreatment measurement (baseline) and measurement(s) after starting the treatment during first-line therapy.

Abbreviations: CBDCA, carboplatin; PTX, paclitaxel; QoL, quality of life.

The rates of compliance among these 73% of patients were similar in the two arms. Of the 163 patients, 15 patients failed to provide complete information on their QoL prior to first-line therapy (nine patients in the gefitinib arm and six patients in the chemotherapy arm). Seventy-two patients (63%) in the gefitinib arm and 76 patients (69%) in the chemotherapy arm were investigated in this QoL analysis (Fig. 1). Demographics and disease characteristics were found to be well balanced in the two arms and were similar to those for the primary PFS analysis [13] (Table 1). Most patients had an Eastern Cooperative Oncology Group performance status (PS) score of 0 or 1 at the time of enrollment. Toxicity profiles for the patients in the QoL analysis were also similar to those for the patients in the PFS analysis [13].

Before the initiation of treatment, patients in both arms had similar baseline QoL scores on all subscales (Table 2). They had a low burden of physical well-being, but impairment was seen in the anxiety subscale (mean score, 40.5 and 40.8 in the gefitinib and carboplatin plus paclitaxel arms, respectively).

Time to Deterioration in QoL

In terms of the minimal clinically important difference in QoL, previous studies indicated that patients perceived a 5%–7% change in the scores on QoL questionnaires as clinically significant [23, 24]. The NCIC CTG recommends a 10% change as the value for clinical significance [25]. In the primary analysis of QoL in the NEJ 002 trial, deterioration was recognized when the score changed from baseline by one in 11 points (9.1%) or more in a direction indicating worse QoL at any timepoint. This criterion was chosen on the basis of our previous study, which estimated content validity by performing interviews with cancer patients (unpublished results). The times to 9.1% deterioration for pain and shortness of breath, anxiety, and daily functioning are summarized in Figure 2A. Significant differences between treatment arms were observed in deterioration of pain and shortness of breath (HR, 0.34; 95% CI, 0.23–0.50; $p < .0001$) and daily functioning (HR, 0.43; 95% CI, 0.28–0.65; $p < .0001$). There was no significant difference in anxiety between arms (HR, 0.72; 95% CI, 0.46–1.13; p = .14).

Table 1. Characteristics of patients in QoL analysis

Characteristic	Gefitinib (n = 72), n (%)	CBDCA/PTX (n = 76), n (%)	p-value
Gender			
Male	24 (33%)	29 (38%)	.608[a]
Female	48 (67%)	47 (62%)	
Mean age (range), yrs	63.0 (43–75)	62.2 (35–74)	.576[b]
Smoking status			
Never	51 (71%)	46 (61%)	.227[a]
Ever	21 (29%)	30 (39%)	
Performance status score, 0/1/2	40/32/0	43/32/1	.959[c]
Histology, adenocarcinoma/other	67/5	74/2	.495[a]
Stage, IIIB/IV/postoperative	10/52/10	15/52/9	.621[a]
Type of mutation			
Deletion	37 (51%)	36 (47%)	.616[a]
L858R	31 (43%)	36 (47%)	
Other	4 (6%)	4 (6%)	

Characteristics of patients investigated in the QoL analysis had no significant differences between arms.
[a]Fisher's exact test.
[b]t-test.
[c]Wilcoxon test.
Abbreviations: CBDCA, carboplatin; PTX, paclitaxel; QoL, quality of life.

Table 2. Baseline QoL scores

	Gefitinib		CBDCA/PTX	
Measure	Mean points	SD	Mean points	SD
Physical well-being	11.2	13.5	10.4	12.0
Appetite loss	6.8	13.0	5.9	11.5
Constipation	7.5	14.1	8.0	12.3
Pain and shortness of breath	13.5	23.2	10.5	18.5
Mental well-being	27.6	26.2	25.0	20.6
Anxiety	40.8	31.3	40.5	24.6
Irritation	18.3	25.2	14.3	20.4
Depression	23.5	27.9	20.0	24.3
Life well-being	26.4	19.3	22.9	17.1
Daily functioning	31.1	27.0	25.5	22.8
Social functioning	13.4	18.4	10.4	13.8
Subjective QoL	30.5	23.0	29.4	21.2

A 0–10 linear analog rating was changed to 0–100 points. For physical and mental well-being, a score of 100 represents the highest burden of symptoms. For life well-being, a score of 100 represents the worst possible function or QoL by changing the score polarity. There were no significant differences in scale and subscale scores between arms before starting first-line therapies.
Abbreviations: CBDCA, carboplatin; PTX, paclitaxel; QoL, quality of life; SD, standard deviation.

From previous reports [23, 24], a change in QoL score >20%, indicating more severe QoL deterioration, was also investigated. Figure 2B summarizes the time to a 27.3% (three of 11 points) deterioration in pain and shortness of breath, anxiety, and daily functioning. Patients who received gefitinib had a significantly longer time to deterioration than patients who received carboplatin plus paclitaxel for pain and shortness of breath (HR, 0.28; 95% CI, 0.17–0.46; $p < .0001$) and daily functioning (HR, 0.32; 95% CI, 0.17–0.59; $p < .0001$) as well as anxiety (HR, 0.44; 95% CI, 0.22–0.87; $p = .01$), for which a significant difference was not observed in the analysis of a 9.1% deterioration (see above).

Proportion of Patients with Improved, Stable, or Worsened QoL

Table 3 details the QoL responses according to three categories (improved, stable, worse) defined in Methods. The χ^2 test indicated that the QoL subscales of appetite loss ($p = .014$), constipation ($p < .0001$), and pain and shortness of breath ($p < .0001$) favored gefitinib over standard chemotherapy, leading to superiority of the gefitinib group on the physical well-being scale ($p < .0001$). A similar trend was observed for the QoL subscales of daily functioning ($p = .007$), social functioning ($p = .035$), and subjective QoL ($p = .042$), leading to superiority of the gefitinib group on the life well-being scale ($p < .0001$). The subscale of the mental well-being scale did not show any significant difference between the treatment arms ($p = .458$).

Discussion

This QoL analysis clearly demonstrated superior QoL in NSCLC patients with mutated *EGFR* receiving gefitinib, com-

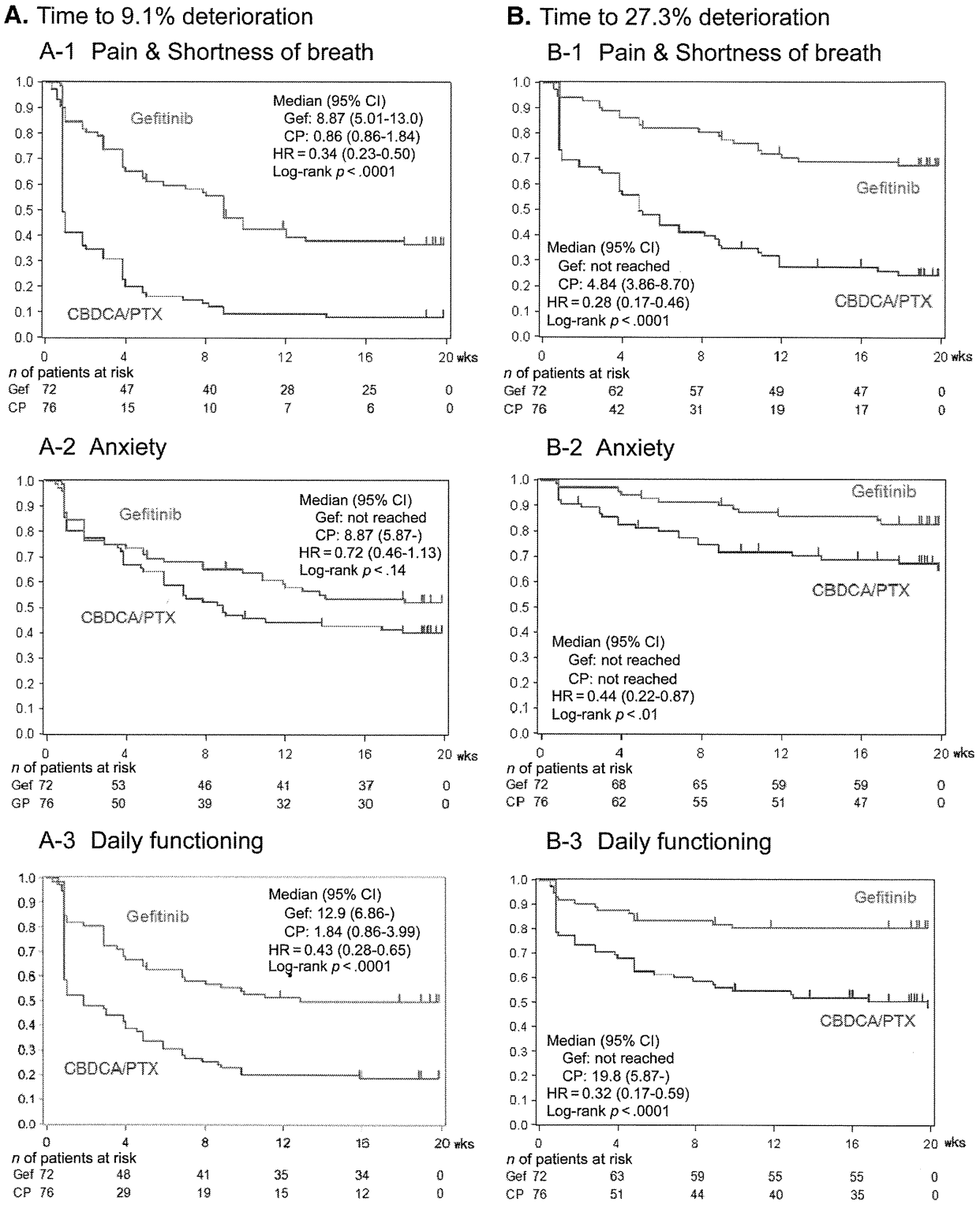

Figure 2. Time to deterioration of QoL. **(A):** Time to a 9.1% QoL deterioration for pain and shortness of breath **(A-1)**, anxiety **(A-2)**, and daily functioning **(A-3)** **(B):** Time to a 27.3% QoL deterioration for pain and shortness of breath **(B-1)**, anxiety **(B-2)**, and daily functioning **(B-3)**.

Abbreviations: CBDCA, carboplatin; CI, confidence interval; CP, carboplatin plus paclitaxel; Gef, gefitinib; HR, hazard ratio; PTX, paclitaxel; QoL, quality of life.

Table 3. QoL response

	Gefitinib, *n*			CBDCA/PTX, *n*			
Measure	**Improved**	**Stable**	**Worse**	**Improved**	**Stable**	**Worse**	***p*-value**
Physical well-being	18	28	26	16	10	50	<.0001
Appetite loss	13	21	38	14	8	54	.014
Constipation	16	24	32	23	6	47	<.0001
Pain and shortness of breath	21	18	33	16	3	57	<.0001
Mental well-being	33	16	23	40	11	25	.458
Anxiety	48	8	16	57	6	13	.535
Irritation	27	18	27	27	11	38	.181
Depression	35	15	22	36	10	30	.346
Life well-being	38	22	12	32	8	36	<.0001
Daily functioning	40	10	22	30	4	42	.007
Social functioning	23	28	21	16	22	38	.035
Subjective QoL	41	15	16	38	8	30	.042

In a secondary analysis of QoL responses, patients were classified as improved (>9.1%), stable (<9.1%, >−9.1%), or worsened (<−9.1%) for all scales and subscales according to the National Cancer Institute of Canada Clinical Trials Group standard QoL analysis framework.
The χ^2 test was used to compare the distributions of these three categories between two treatment arms.
Abbreviations: CBDCA, carboplatin; PTX, paclitaxel; QoL, quality of life.

pared with patients receiving chemotherapy. Better QoL in patients receiving gefitinib further endorses the preference of gefitinib as the first-line therapy for patients with NSCLC with mutated *EGFR* despite a lack of difference in OS outcomes. Accordingly, integration of QoL analyses into a clinical trial should be considered, because maintenance of a good QoL solidifies the clinical efficacy of the treatment being investigated. In addition, this analysis also highlights the importance of QoL endpoints in randomized trials analyzing PFS outcomes, because OS outcomes may be affected by subsequent therapies.

QoL recorded by patients in a self-reported form accurately demonstrated how the patients felt about their QoL during treatment. As soon as chemotherapy with carboplatin plus paclitaxel was started, a striking difference in QoL was observed (Fig. 2A). It seems reasonable that physical well-being deteriorated with chemotherapy in a high proportion of patients, considering that >95% of patients had a PS score of 0–1, a fact that is probably reflected by the low scoring in the baseline scores of physical well-being and daily functioning, with the majority of patients scoring <30. The NCIC CTG recommended matrix (Table 2) also showed that physical well-being was stable or improved in 60% of patients in the gefitinib group. In sharp contrast, scores for physical well-being deteriorated in 75% of patients in the chemotherapy group. This better QoL in the gefitinib group will help patients to maintain social activities, continue to work, and enjoy spending time with their families.

When patients were treated with gefitinib monotherapy in other trials, QoL and symptom improvement were rapid and were correlated with tumor response and survival [26, 27]. In the BR.21 study using unselected patients, another EGFR TKI, erlotinib, also improved tumor-related symptoms and important aspects of QoL such as physical functioning [28]. Post hoc investigations in the IPASS study employing selection by background indicated that QoL was better in the gefitinib group than in the chemotherapy group for patients with *EGFR*-mutated NSCLC [29]. Taken together with our first prospective QoL analysis of patients with *EGFR*-mutated NSCLC, EGFR TKI therapy provides an advantage in terms of improving QoL and symptoms over conventional cytotoxic agents.

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) [30] and Functional Assessment of Cancer Therapy (FACT)–General [31] have been used in many clinical trials to assess the QoL of patients worldwide, and we have developed and validated Japanese versions of these tests for use mainly in clinical studies with the original developers [32, 33]. The Care Notebook [20–22] was originally developed in the 1990s for clinical practice and has a notebook-style format to collect valid and reliable QoL information repeatedly. The NEJ 002 study lacked sufficient support from clinical research coordinators, and doctors had to personally administer QoL questionnaires to patients and pick them up after the answers were completed. Therefore, we chose the Care Notebook, which has good results concerning concurrent validity with the EORTC QLQ-C30 and FACT–Spiritual Well-being [22], for QoL investigation on a weekly basis instead of the above gold standard questionnaires. More than 3,000 Care Notebooks were collected during the initial 20 weeks of treatment in this study, and this method might be the first success of a QoL investigation on a weekly basis for advanced cancer patients in a phase III trial.

This study has some limitations. First, compliance with the QoL survey was modest. Missing data in the QoL investigation

were found to be institution dependent. Namely, the doctors in some institutions did not give the Care Notebook to patients or did not pick it up after the answers were completed. However, randomization of the study treatments was stratified by institution, and therefore, the effects of selection bias might not be large. Both arms had similar patient characteristics (Table 1) and similar baseline QoL scores (Table 2). Although compliance was modest, this QoL difference between arms may represent that in the overall population. Secondly, because the primary endpoint of the NEJ 002 study focused on the PFS interval after first-line treatment, the QoL analysis also focused on patients treated during first-line treatment, and, therefore, the investigation period for the primary QoL analyses was relatively short (20 weeks) to reduce the effects of second-line treatment. Finally, the patients in this QoL analysis were a selected population—patients with a PS score of 0–1 whose tumor had *EGFR* mutation—which might potentially influence the QoL outcomes. However, in another study, namely the NEJ 001 study [7], which employed *EGFR* mutation-positive patients with an extremely poor PS, 68% of the patients improved from a PS score ≥3 at baseline to a PS score ≤1 with gefitinib therapy. Although no QoL investigation was conducted in the NEJ 001 study because of the patients being in extremely poor condition, the striking PS score improvement might have been related to improved QoL. This indicates that EGFR TKIs might universally ameliorate the QoL of patients with *EGFR*-mutated NSCLC, irrespective of their PS scores or symptomatic burdens.

Summary

The QoL analysis of the NEJ 002 study clearly demonstrated that gefitinib maintained patient QoL longer than carboplatin plus paclitaxel during first-line treatment. A longer PFS interval with a better QoL during first-line treatment is valuable for advanced NSCLC patients with limited survival times. Although the OS time for patients first treated using gefitinib was not significantly different from that of patients treated using chemotherapy, the first-line use of gefitinib for advanced NSCLC harboring *EGFR* mutations is strongly recommended.

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This study is registered in University Hospital Medical Information (UMIN) Network Clinical Trial Registry (identification number, UMIN C000000376).

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First-Line Gefitinib in Patients Aged 75 or Older With Advanced Non–Small Cell Lung Cancer Harboring Epidermal Growth Factor Receptor Mutations

NEJ 003 Study

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Introduction: Recent studies have demonstrated that first-line treatment with gefitinib, an epidermal growth factor receptor (EFGR)–targeted tyrosine kinase inhibitor, is significantly superior to standard chemotherapy for advanced non–small-cell lung cancer (NSCLC) harboring EGFR sensitive mutations. Meanwhile, the efficacy of gefitinib therapy among elderly populations diagnosed with EGFR-mutated NSCLC has not yet been elucidated. The purpose of this study was to investigate the efficacy and feasibility of gefitinib for chemotherapy-naive patients aged 75 or older with NSCLC harboring EGFR mutations; generally, these patients have no indication for treatment with platinum doublets.

Methods: Chemotherapy-naive patients aged 75 years or older with performance status 0 to 1 and advanced NSCLC harboring EGFR mutations, as determined by the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method, were enrolled. The enrolled patients received 250 mg/day of gefitinib orally.

Results: Between January 2008 and May 2009, 31 patients were enrolled, all of whom were eligible. The median age was 80 (range, 75–87) years. Twenty-five patients (81%) were women, and 30 patients (97%) had adenocarcinoma. The overall response rate was 74% (95% confidence interval, 58%–91%), and the disease control rate was 90%. The median progression-free survival was 12.3 months. The common adverse events were rash, diarrhea, and liver dysfunction. One treatment-related death because of interstitial lung disease occurred.

Conclusions: This is the first study that verified safety and efficacy of first-line treatment with gefitinib in elderly patients having advanced NSCLC with EGFR mutation. Considering its strong antitumor activity and mild toxicity, first-line gefitinib may be preferable to standard chemotherapy for this population.

Key Words: Non–small cell lung cancer, Epidermal growth factor receptor mutation, Gefitinib

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Non–small-cell lung cancer (NSCLC), which accounts for 80% of lung cancer, remains the major cause of cancer-related death in both Western and Asian countries. With prolongation of life expectancy, both the incidence and mortality of lung cancer in the elderly are rising. In Japan, 48 500 individuals aged 70 years or older were estimated to die of lung cancer in 2009[1]; moreover, the ratio of elderly patients dying from lung cancer increased from 57% in 1989 to 72% in 2009. Treatment strategy in elderly patients with lung cancer has, thus, become an important issue.

About half of the newly diagnosed NSCLC patients have advanced disease, with no indication for local therapy such as surgery and radiotherapy. Chemotherapy for the elderly shows similar efficacy to that observed in younger

patients. However, it is generally more toxic, in terms of both incidence and severity, because of age-related weakening of organ function.[2] Consequently, standard chemotherapy for elderly NSCLC patients, especially those aged 75 years or older, is performed as monotherapy with vinorelbine, gemcitabine, or docetaxel instead of platinum doublets, which are the standard for younger patients.[3–7] Although a recent phase III study suggested that the platinum doublet of monthly carboplatin and weekly paclitaxel may be superior to the gemcitabine or vinorelbine monotherapy in the elderly population, the treatment-related death rate of the doublet group was determined to be 7%.[8] Thus, investigation into safer and more effective treatments for elderly NSCLC patients is required.

Gefitinib, an orally administered tyrosine kinase inhibitor (TKI) of the epidermal growth factor receptor (EGFR), is a key molecularly targeted drug used for the treatment of advanced NSCLC. In May 2004, seminal studies showed that the presence of somatic mutations in the kinase domain of EGFR strongly correlated with increased responsiveness to EGFR TKIs in patients with NSCLC.[9,10] Before this observation, it had been known that subgroups of NSCLC patients, including those of Asian race, female sex, nonsmoking status, and having adenocarcinoma, displayed significant responses to gefitinib.[11,12] These subgroups turned out to have a high incidence of EGFR mutations.[13] Recently, two phase III studies comparing gefitinib treatment with chemotherapy in chemo-naive patients selected on the basis of EGFR mutations were reported from Japan.[14,15] These studies revealed the superiority of gefitinib treatment over standard chemotherapy by demonstrating that first-line gefitinib administration doubled progression-free survival (PFS) as compared with standard chemotherapy. One of two studies we conducted, namely the NEJ002 study, demonstrated that treatment with gefitinib provided patients with a better quality of life as compared with chemotherapy.[16] The eligibility criteria in these studies was limited to patients aged 75 years or younger, as the treatments with platinum doublets were considered to be inappropriate for more elderly populations because of increased toxicity. Moreover, it has been reported in Japan that this more elderly group of patients develop interstitial lung disease (ILD) frequently when treated with gefitinib.[17] In previous studies, we demonstrated that patient selection by EGFR mutation can dramatically improve the risk–benefit balance of gefitinib treatment; however, no study thus far has investigated the efficacy and feasibility of first-line gefitinib treatment in elderly NSCLC patients with EGFR mutation. Thus, the current phase II study was conducted.

METHODS

Patient Selection

This multicentric phase II study was approved by the institutional review board of each participating institute. The main eligibility criterion was to select chemotherapy-naive patients with NSCLC harboring sensitive EGFR mutations. Namely, patients with exon 19 deletions, L858R, L861Q, G719A, or G719S were included, but those with a resistant T790M mutation were excluded. Patients who were 75 years of age or older with Eastern Cooperative Oncology Group performance status (PS) 0 to 2 were also deemed eligible. Other eligibility requirements were stage IIIB to IV or postoperative recurrent NSCLC, presence of a measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST), adequate organ function including liver function (aspartate transaminase and alanine aminotransferase ≤100 U/liter, total bilirubin <2.0 mg/dL), and written informed consent.

EGFR Mutation

Cytological or histological specimens were examined for EGFR mutation by the peptide nucleic acid-locked nucleic acid polymerase chain reaction (PCR) clamp method.[18] Briefly, genomic DNA fragments containing mutation hot spots of the EGFR gene were amplified via PCR in the presence of a peptide nucleic acid clamp primer synthesized from a peptide nucleic acid with a wild-type sequence. This method leads to 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, the 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 peptide nucleic acid-locked nucleic acid PCR clamp method are 97% and 100%, respectively.

Drug Administration

Gefitinib was administered orally once a day at a dose of 250 mg. Patients continued to receive gefitinib until progression of disease, occurrence of intolerable severe toxicity, or withdrawal of consent. When severe toxicity was observed, patients were allowed to receive a reduced dose of gefitinib in accordance with the protocol.

Treatment Assessment

Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were determined based on RECIST version 1.0. The primary end point of this study was overall objective response rate (ORR), which was the rate of patients with CR + PR; secondary end points were PFS, overall survival (OS), and toxicities. Computer

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tomography (CT) scans were taken every month until CR or PR was observed. CR and PR required confirmation via reassessment no earlier than 4 weeks after the first assessment meeting the criteria for response. After the confirmation, CT scans were taken every other month until PD was observed. The CT films of all patients were extramurally reviewed for confirmation of response. PFS was defined as the time from the date of randomization to the first observation of disease progression or death. OS was defined as the time from the date of randomization to the date of death or the most recent follow-up. Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0.

Statistical Consideration

Sample size was determined using the data as follows. Response rates greater than 70% had been previously observed in nonage-restricted patients with EGFR-mutated NSCLC.[15] Meanwhile, clinical studies with elderly patients that investigated the efficacy of first-line chemotherapies in Japan showed ORR of 28% to 55%.[7,19] Thus, we assumed that an ORR of more than 55% was clinically useful, whereas an ORR of less than 30% was not clinically useful. With $\alpha = 0.05$ and $\beta = 0.1$, the number of patients required was 27. Allowing 10% loss in follow-up, a total of 30 patients were planned for enrollment.

All enrolled patients were evaluated for efficacy of received regimen. All patients treated with gefitinib, even for a short period of time, were entered into safety analysis.

RESULTS

Patient Characteristics

Between January 2008 and May 2009, a total of 31 patients were enrolled. Baseline characteristics are described in Table 1. The median age at the time of enrollment was 80.3 years (range, 75–89 years); 52% of the patients were over the age of 80. Of the 31 patients enrolled, 25 (81%) were women and 2 (6%) had a PS of 2. Histological types were all adenocarcinoma except for one adenosquamous carcinoma. There were 7 patients (23%) with stage IIIB, 22 (71%) with stage IV, and 2 (6%) with postoperative recurrence.

Efficacy

The ORR was 74.2% (95% confidence interval [CI], 57.9%–90.5%); one patient had CR, and 22 patients had PR. Five of the remaining 8 patients (16.1%) had SD, with the resulting disease control rate (CR + PR + SD) reaching 90.3% (Table 2). This result attained the primary end point by a wide margin. The median follow-up period at the time of analysis was 27.5 months. Of all 31 patients enrolled, 15 (48.3%) were alive and free from progression for at least 6 months. The median PFS was 12.1 months (Fig. 1*A*), the 1-year OS was 83.9% (95% CI, 70.2%–97.6%), and 2-year OS was 58.1% (95% CI, 45.2%–70.9%). At the data cutoff point (December 2010), 13 patients (41.9%) had died, and the median OS was 33.8 months (Fig. 1*B*).

TABLE 1. Character

	N = 31	(%)
Sex		
Women	6	19
Men	25	81
Age		
Mean (SD)	80.3	(4.1)
Range	75–89	
Smoking status		
Nonsmoker	23	74
Smoker	8	26
Performance status		
0	16	55
1	13	39
2	2	6
Stage		
IIIB	7	23
IV	22	71
Postop	2	6
Histology		
Adenocarcinoma	30	97
Adenosquamous	1	3

Safety and Toxicity

Toxicity data for all 31 patients are presented in Table 3. Nine patients (29%) had a grade 3 adverse event (AE); 1 had a grade 5 AE ILD, and died of respiratory failure. The most common hematologic AE was elevation of transaminases; grade 3 to 4 elevation occurred in three patients (19%). The most common nonhematologic AEs were rash in 21 patients (71%), diarrhea in 10 patients (32%), and appetite loss in 9 patients (29%). Dose reduction was seen in 14 patients (45%). Incidence and severity of AEs were acceptable and comparable with previous reports.[13–15]

Treatment After Progression of Disease

Patient management after the protocol treatment was retrospectively investigated. Any treatment was allowed after confirmation of PD. Gefitinib was continued in 10 of 20 patients confirmed to have PD. Three patients were treated with monotherapies of cytotoxic agents, including vinorelbine, gemcitabine, or docetaxel, and one patient was given

TABLE 2. Response Rate of Treatment With Gefitinib

Response	N = 31	(%)
CR	**1**	**3**
PR	**22**	**71**
Stable disease	**5**	**16**
Progressive disease	**3**	**10**
Overall response rate (CR + PR)	**23**	**74**
95% confidence interval		(57.9–90.5)

CR, complete response; PR, partial response.

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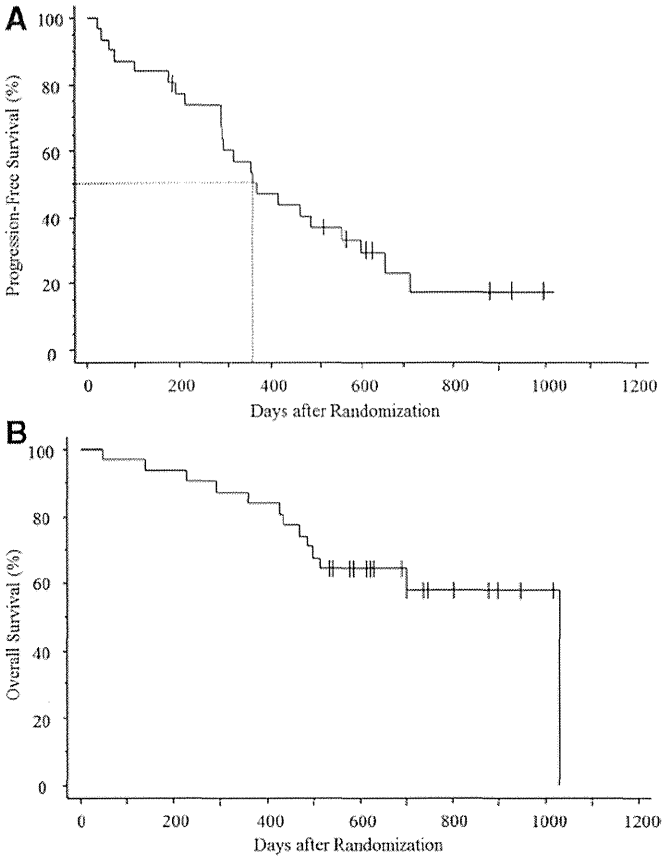

FIGURE 1. Progression-free survival and overall survival. Kaplan–Meier curves for progression-free survival are shown for the progression-free survival population (*A*), and Kaplan–Meier curves for overall survival are shown in (*B*). In (*A*) and (*B*), tick marks indicate patients for whom data were censored.

TABLE 3. Safety—Hematologic and Nonhematologic Toxicity

	NCI-CTC Grade					Grade
	1	2	3	4	5	3–4 (%)
Hematologic adverse events						
Leukocytopenia	2	1	0	0	0	0
Neutropenia	0	1	0	0	0	0
Anemia	6	4	0	0	0	0
Thrombocytopenia	2	1	0	0	0	0
AST/ALT	7	2	6	0	0	19
T-Bil	3	1	0	0	0	0
Creatinine	5	1	0	0	0	0
Hyperkalemia	7	0	0	0	0	0
Nonhematologic adverse events						
Pneumonitis	0	0	0	0	1[a]	3
Rash	12	10	1	0		3
Nail change	4	2	0	0		0
Stomatitis	3	0	0	0		0
Alopecia	3	0	0	0		0
Appetite loss	7	2	1	0		3
Nausea/vomiting	1	0	0	0		0
Diarrhea	9	2	1	0		3
Constipation	2	0	0	0		0
Fatigue	4	1	0	0		0

NCI-CTC, National Cancer Institute Common. Terminology Criteria; AST, androgen suppression therapy; ALT, alanine aminotransferase; T-Bil, total bilirubin.
[a]Treatmant-related death.

erlotinib. No patient was treated with platinum doublets. Six patients did not receive any second-line treatment.

DISCUSSION

This is the first study targeting elderly patients with EGFR-mutated NSCLC. In this study, gefitinib displayed remarkable efficacy without increased toxicity.

We have previously reported a single-arm phase II study in which gefitinib was administered to frail patients with poor PS or elderly patients who were unfit to undergo treatment with cytotoxic agents.[20] In that study, the patients enrolled were 20 to 74 years old with a PS of 3 to 4, 75 to 79 years old with a PS of 2 to 4, and aged 80 years or older (super-elderly) with a PS of 1 to 4. Patients older than 74 years of age accounted for 39% of the total enrolled patients but, nevertheless, OS was 17.8 months (Table 4). The current study strengthened the conclusion of the previous one and provided more information with respect to the efficacy of gefitinib in elderly NSCLC patients with EGFR mutation.

We defined elderly patients as those who were 75 years old and older. Many studies and subgroup analyses were performed by considering elderly cases as 70 years of age or older, especially in Western countries. We have regarded patients aged 70 to 75 years as being treatable with platinum-based chemotherapy. In fact, patients in this age group were enrolled in the NEJ002 study and were able to withstand treatment with platinum doublet. Accordingly, we excluded this group of patients from enrollment in the present study. Considering the aging of population structures and the increased longevity in Japan, we thought that the candidate selection for this study was reasonable.

Currently, in elderly patients, single-agent chemotherapy with a third generation agent (vinorelbine, gemcitabine, or taxanes) is the recommended approach according to the American Society of Clinical Oncology guidelines.[2–7] Gefitinib, which is considered minimally toxic, is often selected for the treatment of advanced NSCLC in elderly patients. Crino et al. performed a randomized phase II study (Gefitinib Versus Vinorelbine in Chemotherapy-Naïve Elderly Patients With Advanced Non-Small-Cell Lung Cancer [INVITE]) of gefitinib versus vinorelbine treatment in 196 chemotherapy-naive unselected elderly patients.[21] There were no statistical differences between gefitinib and vinorelbine in terms of PFS, OS, and ORR. Their study showed obviously lower efficacy of gefitinib in nonselected patients, as compared with the results shown from our study of EGFR-mutated patients.[22–24] These differences in effectiveness among studies highlight the importance of selection of patients by EGFR mutation analysis when administrating gefitinib. Furthermore, in another study of gefitinib treatment in Japanese patients aged

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TABLE 4. Pivotal Clinical Trials of Cytotoxic Agents or EGFR-TKIs in Elder Patients With NSCLC and Recent Trials of Gefitinib in Patients selected by EGFR Mutation

Trial	Treatment	*n*	ORR (%)	PFS (mo)	MST (mo)	*p* Value
Cytotoxic agent in unselected elder patients						
ELVIS[3]	VNR	76	19.7		6.4	0.04
	BSC	78	—		4.8	
MILES[5]	VNR + GEM	232	21	4.1	6.9	NS
	GEM	233	16	4.4	6.5	
	VNR	233	18	4.4	8.3	
WJTOG9904[7]	DTX	89	22.7	5.5	14.3	$p = 0.138$
	VNR	91	9.9	3.1	9.9	
EGFR-TKI in unselected elder patients						
Ebi N.[25]	Gefitinib	49	25	4	10	—
Crino L.[21]	Gefitinib	97	3.1	2.7	5.9	NS
	VNR	99	5.1	2.9	8.0	
Jackman D. M.[27]	Erlotinib	80	10	3.5	10.9	—
Chen Y. M.[28]	Erlotinib	57	22.8	4.6	11.7	$p = 0.70$
	VNR	56	8.9	2.5	9.3	
EGFR-TKI in selected younger patients						
WJTOG3405[14]	Gefitinib	86	62.1	9.2	Immature	$p < 0.001$ (PFS)
	CDDP + DTX	86	32.2	6.3		
NEJ002[15]	Gefitinib	114	73.7	10.8	30.5	$p < 0.001$ (PFS)
	CBDCA + PTX	110	30.7	5.4	23.6	
EGFR-TKI in selected elder patients (current study)						
NEJ003	Gefitinib	31	74.2	12.1	33.8	—

ELVIS, Elderly Lung Cancer Vinorelbine Italian Study; MILES, Multicenter Italian Lung Cancer in the Elderly Study; ORR, overall response rate; PFS, progression-free survival; MST, median survival time; VNR, vinorelbine; BSC, best supportive care; NS, not significant; GEM, gemcitabine; DTX, docetaxel; EGFR-TKI, epidermal growth factor receptor–tyrosine kinase inhibitors; CDDP, cisplatin; CBDCA, carboplatin; PTX, paclitaxel.

75 or older, which included about 40% of the patients who were examined for EGFR mutations and 14% of the patients with EGFR-mutated tumors, the response rate was only 25%.[25] Meanwhile, there have been a few studies of treatment for elderly unselected patients with erlotinib, which is supposed to be more toxic than gefitinib as the administered dose was set near the maximum tolerance dose.[26,27] The response rates in these studies were 10% or less, which were similar to those from the gefitinib studies conducted in Western populations (Table 4). In the other Asian study, erlotinib was compared with vinorelbine treatment in patients aged 70 or older.[28] That study demonstrated that erlotinib yielded a higher response rate and PFS than vinorelbine. The percentage of mutation-positive patients was 30% of those who were examined for EGFR mutations in the erlotinib group. This high proportion might have contributed to the better results of the erlotinib group. The treatment of unselected NSCLC patients with erlotinib was also as ineffective as with gefitinib. Efficacy results in patients selected by EGFR mutation in the current study were substantially superior to those observed in the studies of gefitinib or erlotinib with unselected cases. Surprisingly, the median PFS and 2 year-survival rate here were comparable with results obtained in NEJ002 (12.3 versus 10.8 months, 58% versus 61%, respectively) despite the limited enrollment of an elderly population in this study. These two studies, namely NEJ002 and NEJ003, have very similar backgrounds as they were performed during almost the same time period at identical institutions. It was suggested that gefitinib displayed similar efficacy in elderly patients when compared with their younger counterparts (Table 4). Although the current phase II study could not verify whether gefitinib prolonged PFS in elderly patients in comparison with younger patients, gefitinib might still prove to be the most suitable agent for elderly patients with EGFR-mutated NSCLC.

Elderly patients generally have more comorbidities and lower organ function than younger patients. Treatment-related toxicity in the elderly is a more significant issue than for younger patients. A subgroup analysis of BR.21 showed that elderly patients treated with erlotinib displayed similar efficacy with respect to survival and quality of life as their younger counterparts but experienced greater toxicity.[27] In the current study, toxicity was generally mild and predictable. Rash, diarrhea, and elevation of transaminase were observed frequently, similar to other studies with EGFR-TKIs. The single case of treatment-related death that occurred in our study was because of ILD, although this condition was not found in other patients. The frequency of ILD in the current study was comparable with that previously reported in Japan. Unfortunately, this patient did not respond to treatment with a large dose of corticosteroid, which is generally used for such conditions.[17,29] Advanced age and smoking, preexisting ILD, and poor performance status have been reported as risk factors for ILD during treatment with gefitinib.[17] Elderly patients treated with EGFR-TKIs should be monitored with further caution for ILD. On the whole, gefitinib was found to be a well-tolerated therapy for elderly patients with mutated NSCLC.

In conclusion, first-line gefitinib treatment is highly effective with acceptable toxicity for elderly patients with advanced NSCLC harboring EGFR mutations. Together with our previous studies (NEJ001, NEJ002), gefitinib is shown to be an ideal therapy for all types of NSCLC patients with EGFR mutation.

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PHASE I STUDIES

Phase I dose-escalating study of panobinostat (LBH589) Administered intravenously to Japanese patients with advanced solid tumors

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Summary Panobinostat (LBH589) is a potent pan-histone deacetylase inhibitor. As a result of promising preclinical data, Phase I and II clinical trials of intravenous and oral panobinostat have been conducted in patients with a wide variety of hematologic and solid tumors. This is the first report of a phase I study to evaluate intravenous panobinostat given on days 1 and 8 of a 21-day cycle in patients with solid tumors. The primary objective was to characterize the safety and tolerability of panobinostat by evaluating the occurrence of dose-limiting toxicity (DLT) and determining the maximum tolerated dose (MTD) in Japanese patients with advanced solid tumors. Secondary objectives included characterizing the pharmacokinetics and assessing antitumor activity. Fourteen patients were assigned to three dose levels (Cohort 1: 10 mg/m^2 [three patients], Cohort 2: 15 mg/m^2 [three patients], Cohort 3: 20 mg/m^2 [eight patients]), according to a standard "3+3" design. One patient who received 20 mg/m^2 had a DLT (grade 3 elevation of γ-glutamyl transpeptidase for >7 days). Thrombocytopenia was observed in all patients (grade 3 or 4 in 8), the severity of which was dependent on the dose and platelet count at baseline. The thrombocytopenia rapidly resolved within 8 days. Plasma panobinostat levels increased dose dependently, without clinically significant drug accumulation. Stable disease for ≥4 months was observed in six patients; however, there were no complete or partial responses. It is feasible to conclude that 20 mg/m^2 was the MTD and recommend as the starting dose for phase II clinical trials.

This trial is registrated at www.clinicaltrials.gov as NCT00739414.

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