utilized based on results of a study that had shown that a combination of pemetrexed 500 mg/m$^2$ plus carboplatin (AUC = 6), followed by pemetrexed maintenance therapy, had been generally tolerated in a Japanese population [24]. The incidence of hematological adverse events in this study was similar with those previously reported following carboplatin (AUC = 6) and pemetrexed treatment [25]. Additionally, interstitial lung diseases were not frequent in this study when compared with the reported incidence following gefitinib monotherapy [26, 27], and these events were reversible. Thus, the combination of gefitinib and carboplatin/pemetrexed does not appear to have additive toxicity. However, 41.5% of patients in the concurrent regimen group required dose reductions of carboplatin/pemetrexed. A lower incidence of adverse hematological events is preferred, as such, an AUC of 5 has been adopted in the NEJ009 study.

One limitation of this study is related to the nature of a phase II evaluation; specifically, this study was not designed to formally identify a difference in the efficacy and safety between the two regimens. Therefore, the findings obtained in this study should not be considered definitive.

In conclusion, this study demonstrated that both concurrent and sequentially alternating regimens with a combination of gefitinib and carboplatin/pemetrexed had promising efficacy with predictable toxicities for patients with NSCLC harboring *EGFR* mutations. The concurrent regimen was chosen as an experimental arm in an ongoing phase III NEJ009 study. The NEJ009 study will clarify whether this combinational strategy can be implemented into routine clinical practice.

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## DISCLOSURE

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## FIGURE LEGENDS

Figure 1. CONSORT diagram showing patients disposition. Adverse events causing early discontinuation of the protocol treatment are summarized in Supplementary Table S3.

Figure 2. Kaplan-Meier curve of progression-free survival (A) and overall survival (B) for all randomly assigned patients.

Figure 3. Response to the concurrent and the sequential alternating regimens. In this waterfall plot, the bars indicate the largest percentage change in target lesions from baseline. The dashed line indicates a 30% reduction from baseline.

Figure 1

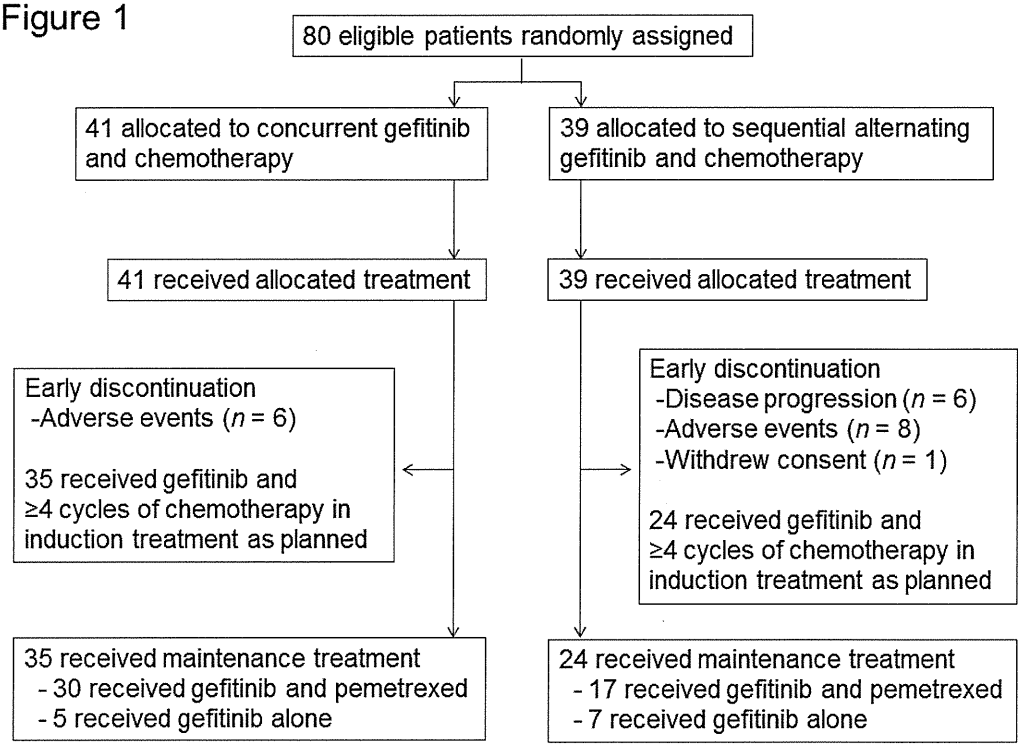
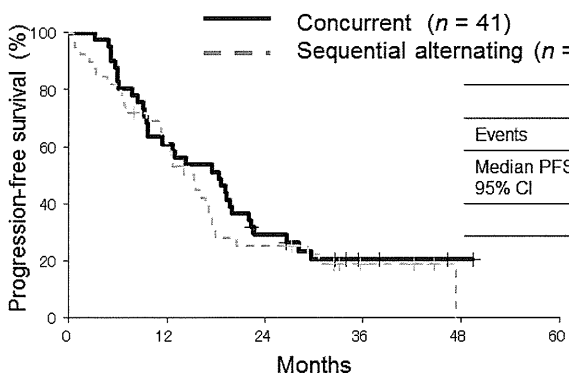


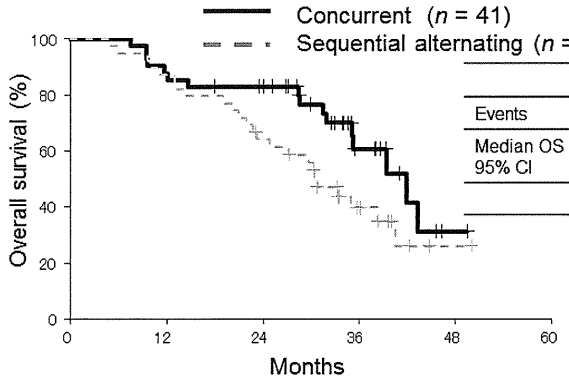
Figure 2

A




| | Concurrent | Sequential |
|---|---|---|
| Events | 32 (78.0%) | 31 (79.5%) |
| Median PFS (months)<br>95% CI | 18.3<br>9.7-21.9 | 15.3<br>11.3-17.4 |
| | $p$ = 0.20, HR 0.80 | |

B




| | Concurrent | Sequential |
|---|---|---|
| Events | 16 (39.0%) | 24 (61.5%) |
| Median OS (months)<br>95% CI | 41.9<br>35.1-NR | 30.7<br>23.2-40.5 |
| | $p$ = 0.042, HR 0.55 | |

Figure 3

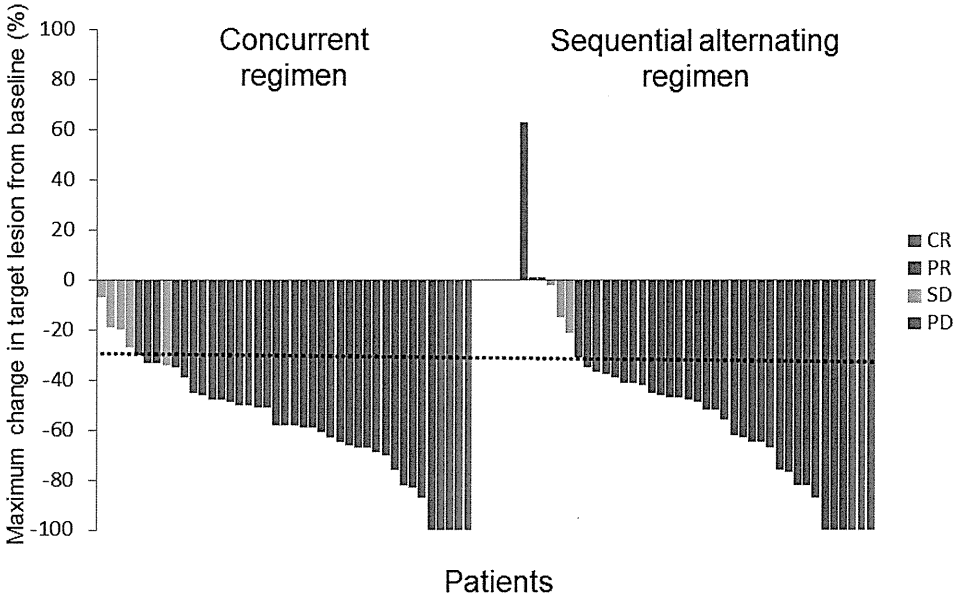


Table 1. Baseline characteristics of patients

| | Concurrent regimen *n* = 41 | Sequential alternating regimen *n* = 39 |
|---|---|---|
| Characteristics | No. of patients (%) | No. of patients (%) |
| Gender | | |
| Male | 15 (36.6%) | 13 (33.3%) |
| Female | 26 (63.4%) | 26 (66.7%) |
| Age (years) | | |
| Median | 62 | 61 |
| Range | 41-75 | 39-75 |
| Smoking status | | |
| Never smoked | 22 (53.7%) | 22 (56.4%) |
| Previous or current smoker | 19 (46.3%) | 17 (43.6%) |
| ECOG performance status score | | |
| 0 | 21 (51.2%) | 17 (43.6%) |
| 1 | 19 (43.9%) | 22 (56.4%) |
| 2 | 1 (2.4%) | 0 (0%) |
| Histologic diagnosis | | |
| Adenocarcinoma | 41 (100.0%) | 39 (100.0%) |
| Clinical stage | | |
| IIIB | 2 (4.9%) | 1 (2.6%) |
| IV | 37 (90.2%) | 36 (92.3%) |
| Postoperative relapse | 2 (4.9%) | 2 (5.1%) |
| Type of *EGFR* mutation | | |
| Exon 19 deletion | 24 (58.5%) | 17 (43.6%) |
| L858R | 17 (41.5%) | 20 (51.3%) |
| Others | 0 (0%) | 2 (5.1%) |

ECOG: Eastern Cooperative Oncology Group; *EGFR*: epidermal growth factor receptor.

Table 2. Most commonly reported adverse events

| Toxicity | Concurrent regimen ($n$ = 41) | | | | | Sequential alternating regimen ($n$ = 39) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Grade* | 1 | 2 | 3 | 4 | ≥ Grade 3 | 1 | 2 | 3 | 4 | ≥ Grade 3 | $p$ value for ≥ Grade 3 |
| Vomiting | 8 | 4 | 1 | 0 | 2.4% | 4 | 2 | 0 | 0 | 0.0% | 1.0 |
| Appetite loss | 16 | 11 | 3 | 0 | 7.3% | 10 | 10 | 0 | 0 | 0.0% | 0.24 |
| Fatigue | 12 | 10 | 1 | 0 | 2.4% | 12 | 3 | 0 | 0 | 0.0% | 1.0 |
| Rash | 20 | 12 | 1 | 0 | 2.4% | 20 | 10 | 0 | 0 | 0.0% | 1.0 |
| Diarrhea | 14 | 6 | 4 | 0 | 9.8% | 14 | 2 | 0 | 0 | 0.0% | 0.12 |
| Stomatitis | 13 | 6 | 2 | 0 | 4.9% | 7 | 1 | 0 | 0 | 0.0% | 0.49 |
| Paronychia | 4 | 5 | 1 | 0 | 2.4% | 4 | 3 | 1 | 0 | 2.6% | 1.0 |
| Pneumonitis | 1 | 1 | 0 | 0 | 0.0% | 0 | 1 | 0 | 1 | 2.6% | 0.49 |
| AST/ALT elevation | 16 | 9 | 4 | 0 | 9.8% | 14 | 9 | 8 | 0 | 20.5% | 0.22 |
| Neutropenia | 1 | 11 | 15 | 5 | 48.8% | 1 | 5 | 13 | 5 | 46.2% | 0.83 |
| Febrile neutropenia | 0 | 0 | 1 | 0 | 2.4% | 1 | 0 | 1 | 1 | 5.1% | 0.61 |
| Anemia | 11 | 5 | 9 | 5 | 34.1% | 14 | 8 | 5 | 0 | 12.8% | 0.035 |
| Thrombocytopenia | 8 | 6 | 6 | 11 | 41.5% | 9 | 8 | 8 | 3 | 28.2% | 0.25 |

*Grade of National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

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ORIGINAL REPORT

# Randomized Phase III Trial Comparing Weekly Docetaxel Plus Cisplatin Versus Docetaxel Monotherapy Every 3 Weeks in Elderly Patients With Advanced Non–Small-Cell Lung Cancer: The Intergroup Trial JCOG0803/WJOG4307L

*Tetsuya Abe, Koji Takeda, Yuichiro Ohe, Shinzoh Kudoh, Yukito Ichinose, Hiroaki Okamoto, Nobuyuki Yamamoto, Hiroshige Yoshioka, Koichi Minato, Toshiyuki Sawa, Yasuo Iwamoto, Hideo Saka, Junki Mizusawa, Taro Shibata, Shinichiro Nakamura, Masahiko Ando, Akira Yokoyama, Kazuhiko Nakagawa, Nagahiro Saijo, and Tomohide Tamura*

See accompanying editorial on page 534 and article on page 567

A B S T R A C T

**Purpose**
This phase III trial aimed to confirm the superiority of weekly docetaxel and cisplatin over docetaxel monotherapy in elderly patients with advanced non–small-cell lung cancer (NSCLC).

**Patients and Methods**
Chemotherapy-naïve patients with stage III, stage IV, or recurrent NSCLC age ≥ 70 years with a performance status of 0 or 1 who were considered unsuitable for bolus cisplatin administration were randomly assigned to receive docetaxel 60 mg/m$^2$ on day 1, every 3 weeks, or docetaxel 20 mg/m$^2$ plus cisplatin 25 mg/m$^2$ on days 1, 8, and 15, every 4 weeks. The primary end point was overall survival (OS).

**Results**
In the first interim analysis, OS of the doublet arm was inferior to that of the monotherapy arm (hazard ratio [HR], 1.56; 95% CI, 0.98 to 2.49), and the predictive probability that the doublet arm would be statistically superior to the monotherapy arm on final analysis was 0.996%, which led to early study termination. In total, 276 patients with a median age of 76 years (range, 70 to 87 years) were enrolled. At the updated analysis, the median survival time was 14.8 months for the monotherapy arm and 13.3 months for the doublet arm (HR, 1.18; 95% CI, 0.83 to 1.69). The rates of grade ≥ 3 neutropenia and febrile neutropenia were higher in the monotherapy arm, and those of anorexia and hyponatremia were higher in the doublet arm.

**Conclusion**
This study failed to demonstrate any survival advantage of weekly docetaxel plus cisplatin over docetaxel monotherapy as first-line chemotherapy for advanced NSCLC in elderly patients.

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## INTRODUCTION

Lung cancer is the leading cause of cancer-related death in most developed countries. Non–small-cell lung cancer (NSCLC) accounts for 85% of all lung cancers, and more than 50% of patients with NSCLC already have advanced disease at diagnosis.[1] The number of elderly patients with lung cancer has also increased, and the median age at diagnosis is 70 years.[2]

The Elderly Lung Cancer Vinorelbine Italian Study, in which single-agent vinorelbine was compared with the best supportive care, first demonstrated the benefits of chemotherapy in elderly patients with advanced NSCLC.[3] In the Multicenter Italian Lung Cancer in the Elderly Study, a combination of vinorelbine plus gemcitabine did not improve survival over vinorelbine or gemcitabine alone and only increased the toxicity frequency.[4] Therefore, single-agent vinorelbine or gemcitabine was established as the standard treatment for elderly patients with NSCLC. We compared docetaxel (every 3 weeks) with vinorelbine in the West Japan Thoracic Oncology Group (the former name of the West Japan Oncology Group [WJOG]) 9904 study, which revealed significantly superior responses and better survival in the docetaxel arm.[5]

However, platinum-doublet chemotherapy has been recommended for patients with NSCLC with a performance status (PS) of 0 or 1,[6-8] and several retrospective subgroup analyses of large phase III trials have shown that the efficacy of platinum-doublet chemotherapy is similar in selected elderly patients and younger patients.[9,10] However, drug excretion or metabolic abilities generally decline because of age-related insufficiencies, especially in renal function. Therefore, modifications of anticancer drug dosages or schedules are recommended in chemotherapy for elderly patients with cancer.[11] In Japan, phase I[12] and II trials of weekly docetaxel plus cisplatin (DP) were conducted in elderly patients with NSCLC. The phase II study revealed a response rate (RR) of 52% (95% CI, 31% to 67%), a median survival time of 15.8 months, and no grade 4 toxicity.[13] On the basis of these promising results, we conducted a randomized phase III trial, the Japan Clinical Oncology Group (JCOG) 0207 trial, to compare DP with single-agent docetaxel. For the control arm, we chose weekly split docetaxel to investigate the effects of added cisplatin. In the second interim analysis, the overall survival (OS) seemed to be more favorable in the DP arm; however, an unexpected large difference was observed in the subgroup of patients age less than 75 years.[14] Therefore, considering the potential disadvantage of single-agent docetaxel therapy in this subgroup, we terminated the study and designed a new phase III trial in which the control arm received bolus infusions of docetaxel every 3 weeks, based on the West Japan Thoracic Oncology Group 9904 study.[5]

## PATIENTS AND METHODS

### Patients

Patients eligible for this study included chemotherapy-naïve patients with histologically or cytologically confirmed stage III (no indication for definitive radiotherapy), stage IV, or recurrent NSCLC who were age ≥ 70 years, with an Eastern Cooperative Oncology Group PS of 0 or 1 and adequate organ functioning, but who were unsuitable for bolus cisplatin administration. Considering that the age group of 70 to 74 years included those who were suitable and unsuitable for bolus cisplatin administration, we classified the reasons for administration unsuitability in this age group into six categories and examined patients for these conditions before enrollment. The pre-enrollment evaluation is described in the Appendix and Appendix Table A1 (online only). Prior radiotherapy, except for the primary lesion, was permitted if it had been completed at least 2 weeks before enrollment onto the study. Patients with symptomatic brain metastasis, active malignancy within the previous 5 years, superior vena cava syndrome, massive pleural effusion or ascites, critical vertebral metastasis, uncontrolled hypertension or diabetes, severe heart disease, active infection, hepatitis virus B surface antigen seropositivity, pulmonary fibrosis, polysorbate 80 hypersensitivity, or steroid dependence were excluded.

The study protocol was reviewed and approved by the JCOG Protocol Review Committee, WJOG executive board, and institutional review boards of each participating institution before study initiation. All patients provided written informed consent before enrollment.

### Study Design and Treatment Plan

Eligible patients were randomly assigned to either the docetaxel arm (docetaxel 60 mg/m$^2$ infused over 60 minutes on day 1 every 3 weeks) or the DP arm (docetaxel 20 mg/m$^2$ infused over 60 minutes plus cisplatin 25 mg/m$^2$ infused over 15 to 20 minutes on days 1, 8, and 15 every 4 weeks). Patients were randomly assigned via the minimization method to balance the arms with the institution, disease stage (III *v* IV or recurrence), and age (≥ *v* < 75 years). In the DP arm, treatment was skipped under the following conditions: total leukocyte count less than 2,000/$\mu$L, platelet count less than 50,000/$\mu$L, creatinine level ≥ 1.5 mg/dL, and presence of fever or grade ≥ 3 nonhematologic toxicity (except constipation, weight loss, cough, hoarseness, and hyponatremia) on day 8 or 15. In both arms, subsequent cycle treatment was administered when the patients met the following conditions: total leukocyte count ≥ 3,000/$\mu$L, absolute neutrophil count ≥ 1,500/$\mu$L, platelet count ≥ 100,000/$\mu$L, serum creatinine level less than 1.5 mg/dL, total bilirubin level less than 2.0 mg/dL, ALT/AST ≤ 100 IU/L, and PS 0 to 2. Administration procedures, dose reduction criteria, and methods are detailed in the Appendix. Both treatments were repeated until the detection of disease progression or appearance of unacceptable toxicity. Radiographic tumor evaluations were performed and assessed, according to RECIST (version 1.0),[15] by each investigator at least every two cycles. Laboratory examinations were performed at least once a week in both arms, and toxicity was assessed before every cycle and classified in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). Second-line treatment was administered at the investigator's discretion; however, cross-over to the other treatment arm was not permitted.

### Quality-of-Life Assessment

Quality of life (QOL) was assessed by symptom scores, using the seven items of the Lung Cancer subscale of the Functional Assessment of Cancer Therapy–Lung.[16] The patients scored themselves immediately after providing informed consent and after completing the second and third treatment cycles. The proportions of patients with improved scores between the baseline and the end of the third cycle in each arm were compared. Missing data after treatment initiation were considered as indicating no improvement. In addition, we compared least squared means of the total scores from repeated measures analysis of variance with treatment arm, time, and their interaction and the 95% CI at each time point.

### Supplementary Ad Hoc Analysis

Additional data collection and ad hoc analysis were performed. Data on the active epidermal growth factor receptor (*EGFR*) mutation status (exon 19 deletion or L858R point mutation) and poststudy treatments were collected because these were considered factors that could potentially affect survival.

### Statistical Analysis

OS was the primary trial end point. The secondary end points included RRs, progression-free survival (PFS), symptom scores, and toxicities. The study was designed to provide results with a statistical power of 80%, using a one-sided $\alpha = .05$ to detect a 33% increase in median survival from 10 to 13.3 months. A total of 364 patients was required, accrued over a 4-year period with a 1-year follow-up period. Assuming a 5% rate of ineligible patients and patients lost to follow-up, the study sample size was set at 380 patients. OS, PFS, and responses were assessed in all eligible patients on an intent-to-treat basis. OS and PFS, which are defined in the Appendix, were estimated using the Kaplan-Meier method and were compared using the stratified log-rank test, according to age. Hazard ratios (HRs) of the treatment effects were estimated using the Cox proportional hazards model. RRs were compared using Fisher's exact test.

Two interim analyses were planned, the first after 50% of the patients were enrolled and the second after enrollment was completed. In these interim analyses, the primary end point, OS, was evaluated after adjustment for multiple comparisons, according to the Lan and DeMets method.[17] The O'Brien-Fleming–type $\alpha$ spending function was used. *P* values presented for the primary analysis were one-sided, in accordance with the trial design, whereas the other analysis values were two-sided. All analyses were performed using SAS software, release 9.1 (SAS Institute, Cary, NC). This study is registered with University Hospital Medical Information Network Clinical Trials Registry (www.umin.ac.jp/ctr/; identification No.: UMIN000001424).

## RESULTS

The first interim analysis was performed in September 2010 and included data from 221 patients. Information time, defined as the

  

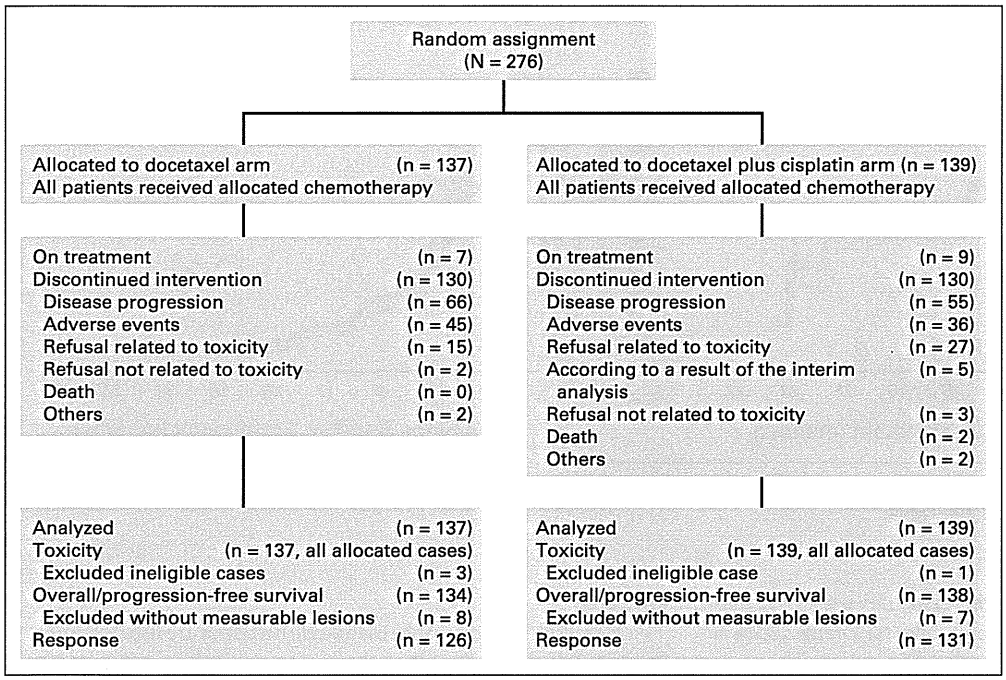


**Fig 1.** CONSORT diagram.

proportion of the interim events to the planned events, was 0.24 (73 of 304 events). Survival in the DP arm was inferior to that in the docetaxel arm (HR for DP to docetaxel arm, 1.56; 95% CI, 0.98 to 2.49; multiplicity-adjusted 99.99% CI, 0.62 to 3.88; one-sided $P = .97$ and two-sided $P = .06$ by stratified log-rank test), and the predictive probability that DP would be statistically superior to docetaxel on final analysis was 0.996% (< 1%). These results led to early study termination based on the recommendation of the Data and Safety Monitoring Committee, in accordance with the stopping guidelines prespecified in the protocol.

### *Patient Characteristics*

Between October 2008 and September 2010, 276 patients (215 patients from JCOG and 61 patients from WJOG) were enrolled from 56 institutions (36 institutions affiliated with JCOG and 20 institutions affiliated with WJOG). Of these patients, 137 and 139 patients were assigned to the docetaxel and DP arms, respectively. All patients received the study treatments; therefore, all 276 patients were included in the safety analysis set. Three patients in the docetaxel arm and one patient in the DP arm were ineligible because of uncontrolled diabetes (ie, dependence on insulin injections) or previous malignancy. Therefore, these patients were excluded from survival analyses (Fig 1). Although the proportions of female patients and patients with adenocarcinoma were slightly higher in the docetaxel arm than in the DP arm, the patients' baseline characteristics were generally well balanced between the treatment arms (Table 1).

### *Treatment Delivery*

The median number of treatment cycles was four (range, one to 18 cycles) in the docetaxel arm and three (range, one to six cycles) in the DP arm, and the proportion of patients in whom treatment continued for five or more cycles was higher in the docetaxel arm than in the DP arm (31% *v* 8%, respectively). In the docetaxel and DP arms, 37% and 4% of patients required one-step dose reductions, respectively. Furthermore, 19% of patients required two-step dose reductions in the docetaxel arm. In the DP arm, 19% of patients had one or more skipped treatments on day 8 or 15. The major reasons for

**Table 1.** Patient Demographics and Clinical Characteristics

| Demographic or Clinical Characteristic | Docetaxel (n = 137) | | Docetaxel/Cisplatin (n = 139) | |
|---|---|---|---|---|
| | No. of Patients | % | No. of Patients | % |
| Age, years | | | | |
| Median | 76 | | 76 | |
| Range | 70-87 | | 70-86 | |
| < 75 | 31 | 23 | 32 | 23 |
| ≥ 75 | 106 | 77 | 107 | 77 |
| Sex | | | | |
| Male | 95 | 69 | 101 | 73 |
| Female | 42 | 31 | 38 | 27 |
| Smoking status* | | | | |
| Never | 38 | 28 | 36 | 26 |
| Smoker | 98 | 72 | 101 | 74 |
| ECOG PS | | | | |
| 0 | 50 | 36 | 48 | 35 |
| 1 | 87 | 64 | 91 | 65 |
| Stage | | | | |
| III | 42 | 31 | 43 | 31 |
| IV or recurrence | 95 | 69 | 96 | 69 |
| Histology* | | | | |
| Adenocarcinoma | 91 | 67 | 86 | 63 |
| Squamous | 32 | 24 | 39 | 28 |
| Others | 13 | 10 | 12 | 9 |

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.
*Data for one patient in the docetaxel monotherapy arm and two patients in the docetaxel plus cisplatin arm were missing.

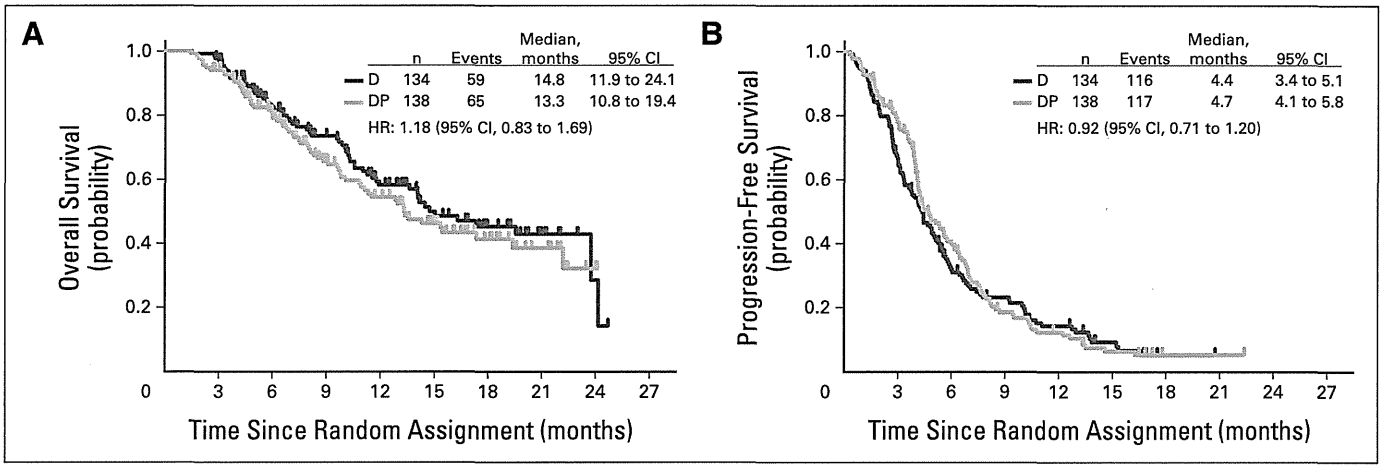


**Fig 2.** Kaplan-Meier curves for (A) overall survival and (B) progression-free survival. Tick marks indicate censored patients at the data cutoff point (November 2010). D, docetaxel; DP, docetaxel plus cisplatin; HR, hazard ratio.

treatment discontinuation in the docetaxel versus DP arms were disease progression (51% *v* 42%, respectively), adverse events (35% *v* 28%, respectively), and patient refusal to continue treatment as a result of toxicity (12% *v* 21%, respectively).

### *Efficacy*

The overall RRs were 24.6% in the docetaxel arm (95% CI, 17.4% to 33.1%) and 34.4% in the DP arm (95% CI, 26.3% to 43.2%). The difference was not statistically significant ($P = .10$).

By November 22, 2010, 124 (45.6%) of the 272 eligible patients had died (docetaxel arm, n = 59; DP arm, n = 65). The median follow-up time for all eligible patients was 9.6 months. The 1-year survival rates were 58.2% and 54.5% in the docetaxel and DP arms, respectively. The HR for OS was 1.18 (95% CI, 0.83 to 1.69; Fig 2A). The HR for PFS was 0.92 (95% CI, 0.71 to 1.20; Fig 2B).

### *Toxicity*

Hematologic and nonhematologic toxicities are listed in Table 2. Grade ≥ 3 leukopenia and neutropenia occurred more frequently in the docetaxel arm. The incidence of grade 4 neutropenia was 67.9% in the docetaxel arm but only 0.8% in the DP arm. Febrile neutropenia was observed only in the docetaxel arm at an incidence of 15.2%. Grade ≥ 3 anemia, hyponatremia, and anorexia were observed in more than 10% of patients in the DP arm. Four treatment-related deaths occurred, all in the DP arm (2.9%), including three patients who died of pneumonitis and one patient who died of unclassified sudden death.

### *QOL*

Symptom score questionnaire responses were collected from 271 (98.2%) of 276 patients at baseline, 258 patients (93.5%) after the second cycle, and 247 patients (89.5%) after the third cycle. The

**Table 2.** Toxicities

| | Docetaxel (n = 137) | | | Docetaxel/Cisplatin (n = 139) | | |
|---|---|---|---|---|---|---|
| Adverse Event | Grade 3 or 4 (%) | Grade 4 (%) | Missing (No.) | Grade 3 or 4 (%) | Grade 4 (%) | Missing (No.) |
| Hematologic* | | | | | | |
| Leukopenia | 62.7 | 8.2 | 3 | 5.4 | 0 | 10 |
| Neutropenia | 88.8 | 67.9 | 3 | 10.1 | 0.8 | 10 |
| Anemia | 3.7 | 0.7 | 3 | 16.3 | 0.8 | 10 |
| Thrombocytopenia | 0 | 0 | 3 | 0.8 | 0 | 10 |
| Nonhematologic* | | | | | | |
| Febrile neutropenia | 15.2 | 0 | 5 | 0 | 0 | 8 |
| Hyponatremia | 5.2 | 0.7 | 3 | 14.7 | 0.8 | 10 |
| Hypoalbuminemia | 1.5 | — | 6 | 4.7 | — | 10 |
| Infection | 7.6 | 0 | 5 | 8.4 | 0.8 | 8 |
| Anorexia | 1.5 | 0 | 5 | 10.7 | 0 | 8 |
| Nausea | 0.8 | 0 | 5 | 3.8 | 0 | 8 |
| Diarrhea | 3.8 | 0 | 5 | 0.8 | 0 | 9 |
| Fatigue | 3.0 | 0 | 5 | 5.3 | 0 | 8 |
| Pneumonitis | 5.3 | 0 | 5 | 2.3 | 0.8 | 8 |

NOTE. There were four treatment-related deaths (2.9%), all in the docetaxel plus cisplatin arm, including three deaths resulting from pneumonitis and one unclassified sudden death.
*Each value was calculated while excluding patients with missing data.

  

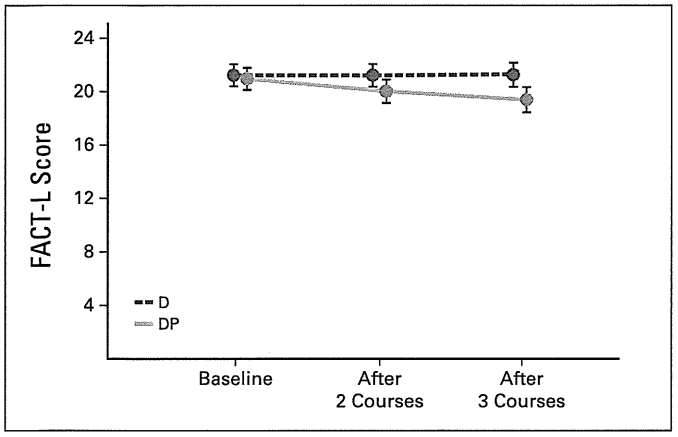


**Fig 3.** Quality-of-life assessments according to the seven-item Functional Assessment of Cancer Therapy–Lung (FACT-L). Dots and error bars indicate the least squared mean total scores and 95% CI, respectively. Higher scores indicate a better quality of life. D, docetaxel; DP, docetaxel plus cisplatin.

numbers of patients with missing data because of death or severe deterioration of the patient's general condition in the docetaxel and DP arms were one and six patients, respectively, after the second cycle and six and nine patients, respectively, after the third cycle. In the docetaxel and DP arms, 39.3% (53 of 135 patients) and 36.8% (50 of 136 patients) of patients had scores that improved from baseline to the end of the third cycle, which did not constitute a significant difference. Although the mean total score remained near its baseline value in the docetaxel arm, it declined gradually in the DP arm, changing in a statistically significant manner between baseline and cycle 3 ($P < .01$; Fig 3).

### *Supplementary Ad Hoc Analysis*

Data forms were collected from 275 patients (except one patient from the docetaxel arm). *EGFR* mutation testing was performed in 79 patients (58%) and 74 patients (53%) in the docetaxel and DP arms, respectively; the results revealed active *EGFR* mutations in 22 patients in the docetaxel arm (16% overall and 28% of those tested) and 16 patients in the DP arm (12% overall and 22% of those tested). After protocol treatment completion, further drug treatment was administered to 74 patients (54%) in the docetaxel arm and 70 patients (50%) in the DP arm. During this treatment, EGFR tyrosine kinase inhibitor was administered to 35 patients (26%) and 23 patients (17%) in the docetaxel and DP arms, respectively.

Figure 4 shows the survival HRs according to subgroup analyses of the baseline and ad hoc characteristics. No significant differences between the two treatment groups were observed in any subgroup.

## DISCUSSION

The standard treatment for fit patients with advanced NSCLC is platinum-doublet chemotherapy.[6,7] Several retrospective subgroup analyses have shown that platinum-doublet chemotherapy is similarly effective in elderly and younger patients and is well tolerated despite an increased incidence of toxicity.[9,10] These retrospective analyses, however, were performed in highly selected elderly populations. Generally, elderly patients are often unsuitable candidates for bolus cisplatin administration because of comorbid illnesses and/or organ dysfunction. Therefore, we considered it important to conduct a prospective investigation to determine whether the addition of a modified platinum agent might improve survival in elderly patients with NSCLC.

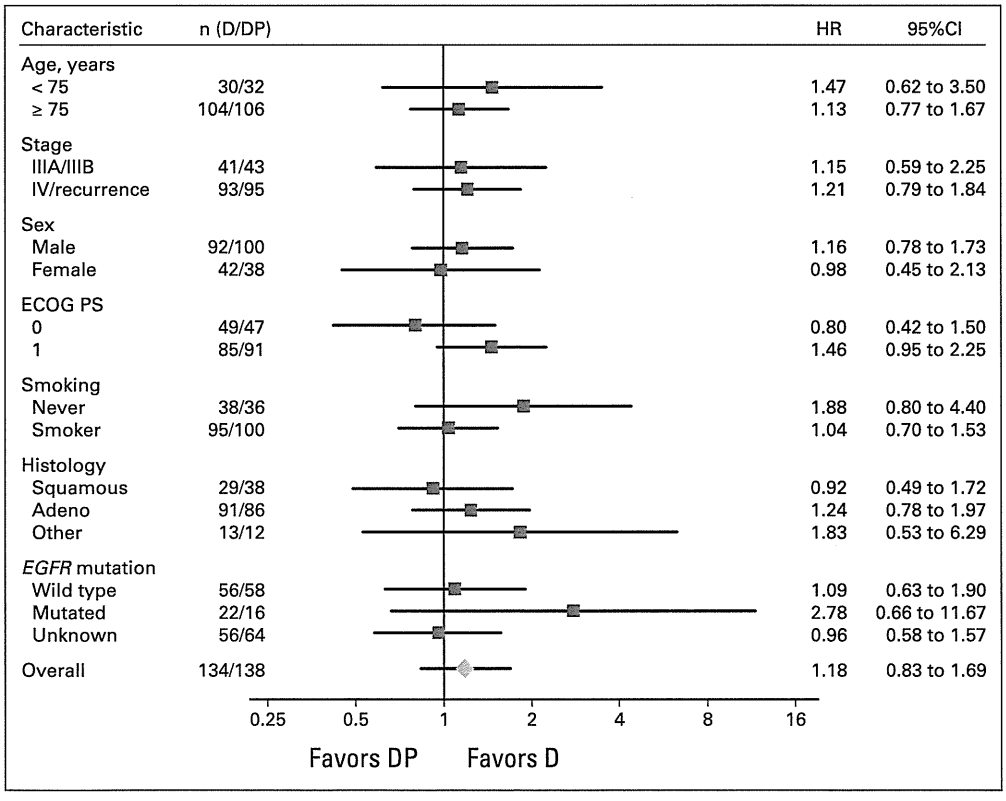


**Fig 4.** Subgroup analysis of overall survival. D, docetaxel; DP, docetaxel plus cisplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.

In the phase II and previous phase III trials, we demonstrated that weekly split docetaxel and additional cisplatin reduced myelotoxicity and increased RRs.[13,14] In this study, we analyzed the add-on effect of weekly cisplatin over docetaxel monotherapy. Although the DP arm tended to have higher RRs than the docetaxel arm, this was reflected in neither the PFS nor the OS.

Although we collected information on comorbid illnesses, we did not assess the Charlson comorbidity index. Comprehensive geriatric assessments, including basic activities of daily living (ADLs), instrumental ADLs, Mini-Mental State Examination, and Geriatric Depression Scale evaluation, were also conducted for exploratory purposes. Although the prognostic values of these assessments have not been validated for elderly patients with lung cancer, it was suggested that ADLs and Mini-Mental State Examination can be useful.[18] In future research, we should evaluate these factors prospectively.

The proportions of female patients and patients with adenocarcinoma were slightly higher in the docetaxel arm than in the DP arm. In eastern Asia, including Japan, active *EGFR* mutations are often observed in such patients and have been reported as a favorable prognostic factor in patients with NSCLC.[19,20] According to a subgroup analysis, the median survival time was 12.8 months in the 114 patients (in the docetaxel plus DP arms) without *EGFR* mutation and 24.1 months in the 38 mutation-positive patients. The proportion of patients with active *EGFR* mutations was slightly higher in the docetaxel arm than in the DP arm. However, it would have been difficult to demonstrate the superiority of the DP arm in OS, considering the slight difference in PFS, even if there were no such imbalances.

In the docetaxel arm, a higher proportion of patients required dose reductions, yet these appropriate reductions lengthened treatment. In contrast, the DP arm included fewer patients who were able to continue treatment, despite the lower proportion of dose reductions and skipped treatments. We believe that declining QOL was an important cause of treatment discontinuation in the DP arm.

The toxicity profiles also differed between the two arms. In the docetaxel arm, neutropenia was most prominent, and grade 4 neutropenia occurred in up to 68% of the patients. Consequently, febrile neutropenia was observed in 15% of the patients in the docetaxel arm, whereas no patients experienced febrile neutropenia in the DP arm. The frequency of febrile neutropenia in the docetaxel arm was similar to that seen in a previous Japanese docetaxel study for elderly patients.[5] However, because febrile neutropenia was successfully managed with appropriate supportive treatments, there were no treatment-related deaths in the docetaxel arm. However, the DP arm had higher incidences of grade $\geq 3$ anemia, hyponatremia, and anorexia. We suppose that these were the main causes of the decline in the QOL score in the DP arm. The median number of treatment cycles and the proportion of patients in whom treatment could be continued for five or more cycles in the DP arm were smaller than those in the docetaxel arm. These findings could be associated with the decline in QOL and might have affected OS in the DP arm. Three of four treatment-related deaths in the DP arm were caused by pneumonitis. It was reported that weekly docetaxel administration increases the frequency of pneumonitis.[21,22] In this study, there were few differences in the frequencies of pneumonitis between the two arms; however, more severe pneumonitis was observed in the DP arm.

Quoix et al[18] demonstrated the superiority of carboplatin plus weekly paclitaxel over conventional standard therapy, namely vinorelbine or gemcitabine monotherapy, in the Intergroupe Francophone de Cancerologie Thoracique 0501 study. The usefulness of platinum-based treatments in elderly patients was first shown in a prospective study. For elderly patients with NSCLC, carboplatin combination therapy may be preferable to a split cisplatin combination. However, the high incidence of toxicity could not be ignored, because treatment-related deaths occurred in 4.4% of patients in the doublet arm but only in 1.3% of patients in the monotherapy arm.[18] In contrast, a phase I trial of combined carboplatin plus pemetrexed (PEM), followed by maintenance PEM, showed good tolerability in elderly patients with nonsquamous NSCLC.[23] We consider that the combination of carboplatin plus PEM should be compared with docetaxel monotherapy.

In conclusion, this study failed to demonstrate any advantages of weekly DP over docetaxel monotherapy as first-line chemotherapy for elderly patients with advanced NSCLC, and docetaxel every 3 weeks remains the standard treatment for elderly patients with advanced NSCLC.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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