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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Efficacy and Safety of Two Doses of Pemetrexed Supplemented with Folic Acid and Vitamin B_{12} in Previously Treated Patients with Non-Small Cell Lung Cancer

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Abstract

Purpose: The objective of this study was to evaluate the efficacy and safety of two doses of pemetrexed supplemented with folic acid and vitamin B_{12} in pretreated Japanese patients with advanced non-small cell lung cancer (NSCLC).

Experimental Design: Patients with an Eastern Cooperative Oncology Group performance status 0 to 2, stage III or IV, and who received previously one or two chemotherapy regimens were randomized to receive 500 mg/m^2 pemetrexed (P500) or 1,000 mg/m^2 pemetrexed (P1000) on day 1 every 3 weeks. The primary endpoint was response rate.

Results: Of the 216 patients evaluable for efficacy (108 in each arm), response rates were 18.5% (90% confidence interval, 12.6-25.8%) and 14.8% (90% confidence interval, 9.5-21.6%), median survival times were 16.0 and 12.6 months, 1-year survival rates were 59.2% and 53.7%, and median progression-free survival were 3.0 and 2.5 months for the P500 and P1000, respectively. Cox multiple regression analysis indicated that pemetrexed dose was not a significant prognostic factor. Drug-related toxicity was generally tolerable for both doses; however, the safety profile of P500 showed generally milder toxicity. Main adverse drug reactions of severity grade 3 or 4 were neutrophil count decreased (20.2%) and alanine aminotransferase (glutamine pyruvic transaminase) increased (15.8%) in P500 and neutrophil count decreased (24.3%), WBC count decreased (20.7%), and lymphocyte count decreased (18.0%) in P1000. One drug-related death from interstitial lung disease occurred in the P500.

Conclusion: P500 and P1000 are similarly active with promising efficacy and acceptable safety outcomes in pretreated patients with NSCLC. These results support the use of P500 as a second- and third-line treatment of NSCLC.

Pemetrexed (LY231514; Alimta), a multitargeted antifolate, has shown antitumor activity as a single agent or in combination with other anticancer agents (1, 2). Pemetrexed at doses of 500 or 600 mg/m^2 has been evaluated in various clinical settings in a broad range of tumors including lung (non-small cell and mesothelioma), colorectal, gastric, pancreatic, head and neck, bladder, cervical, and breast cancers (3-13). In a randomized phase III trial that compared 3-week regimens of single-agent 500 mg/m^2 pemetrexed versus 75 mg/m^2 docetaxel in pretreated patients with non-small cell lung cancer (NSCLC), respective response rates (9.1% versus 8.8%) and median survival times (MST; 8.3 versus 7.9 months) did not differ between pemetrexed and docetaxel. However, fewer hematologic adverse effects, such as grade 3 or 4 neutropenia, febrile neutropenia, and neutropenic fever, were observed in patients treated with pemetrexed (3).

Myelosuppression is the predominant dose-limiting toxicity of pemetrexed as reported in phase I studies (14-16). A multivariate analysis identified the correlation between poor folate status (as indicated by elevated plasma homocysteine levels) and increased toxicity to pemetrexed, which led to the requirement that patients in all pemetrexed studies receive folic acid and vitamin B_{12} supplementation (2, 17). This has been shown to decrease toxicity to pemetrexed without compromising efficacy (18). Without supplementation, the maximum tolerated dose of pemetrexed, given every 3 weeks, has been shown to be 600 mg/m^2 in heavily pretreated patients (14); however, with supplementation, higher pemetrexed doses have been given without limiting side effects. In a Japanese phase I

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Note: The results of this study have been reported at American Society of Clinical Oncology, World Conference on Lung Cancer, and European Cancer Conference in 2007.

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study of pemetrexed that included folic acid and vitamin B_{12} supplementation, the maximum tolerated dose of pemetrexed was 1,200 mg/m^2 and recommended dose was 1,000 mg/m^2 given every 3 weeks (19). Pemetrexed pharmacokinetics in Japanese patients was not overtly different from those observed in Caucasian patients.

In view of these data, we conducted a randomized, phase II study that confirmed the efficacy and safety of a standard dose of pemetrexed (500 mg/m^2; P500) with that of a higher dose (1,000 mg/m^2; P1000), including folic acid and vitamin B_{12} supplementation, in previously treated NSCLC patients. The primary endpoint was evaluation of response rate. Secondary endpoints were assessments of response duration, progression-free survival (PFS), 1-year survival rate, MST, quality of life (QoL), and adverse events.

Materials and Methods

Patient selection. Men and women, between 20 and 75 years old, with a life expectancy of at least 12 weeks and histologically and/or cytologically confirmed advanced NSCLC were eligible for the study. In addition, all patients met the following inclusion criteria: stage III or IV disease, at least one target lesion, one or two prior chemotherapeutic regimens, an Eastern Cooperative Oncology Group performance status (PS) of 0 to 2, adequate bone marrow function (neutrophils ≥2,000/mm^3, platelets ≥100,000/mm^3, and hemoglobin ≥9.0 g/dL), hepatic function [total bilirubin within 1.5 times the upper normal limit, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) within 2.5 times the upper normal limit, and serum albumin ≥2.5 g/dL], renal function (serum creatinine ≤1.2 mg/dL and creatinine clearance ≥45 mL/min), and pulmonary function (functional oxygen saturation ≥92%).

Patients were excluded from the study for radiographic signs of interstitial pneumonitis or pulmonary fibrosis, serious or uncontrolled concomitant systemic disorders, active infections, the need for chronic administration of systemic corticosteroids, active double cancer and/or brain metastases, treatment with third-space fluid collections within 2 weeks of signing the informed consent or the need of such treatment, grade 3 or 4 toxicity, peripheral sensory neuropathy, previous pemetrexed therapy, unable or unwilling to take folic acid or vitamin B_{12} supplementation, or pregnant or breast-feeding.

This study was conducted in compliance with the guidelines of good clinical practice and the principles of the Declaration of Helsinki, and it was approved by the local institutional review boards. All patients gave written informed consent before study entry.

Study design and sample size. This open-label multicenter study had response rate as the primary objective, and 244 patients were enrolled and 226 were allocated to either 500 mg/m^2 (P500) or 1,000 mg/m^2 (P1000) randomly.

The sample size was calculated to ensure that the response rate in each group exceeded 5%. Based on the results from previous study, assuming a 13% true response rate, 5% one-sided significance level for the test with exact probability based on binomial distribution, and 90% power, at least 107 patients in each treatment arm (total of 214) were necessary. Assuming a 10% dropout rate, 240 patients were planned for the study (actual: 244 patients).

The randomization was done by an independent registration center and was dynamically balanced for PS, previous platinum chemotherapy, disease stage, gender, time from prior chemotherapy to the enrollment, and hospital. Patients were balanced with respect to the study drug in each stratum for each prognostic factor using the minimization method.

Treatment plan. Pemetrexed was administered as an i.v., 10-min infusion on day 1 of a 21-day cycle. Patients were instructed to take orally 1 g/d of a multivitamin containing 500 μg folic acid from 1 week before day 1 of course 1 until 22 days after the last administration of pemetrexed. Vitamin B_{12} (1000 μg) was injected i.m. 1 week before day 1 of course 1 and repeated every 9 weeks until 22 days after the last administration of pemetrexed. Patients were discontinued from the study for disease progression, unacceptable adverse events, inadvertent enrollment, use of excluded concomitant therapy, a cycle delay of >42 days, or if the patient requested to discontinue the study.

Administration of pemetrexed was delayed if patients met any of the following criteria: neutrophils <2,000/mm^3, hemoglobin <9.0 g/dL, platelets <100,000/mm^3, AST/ALT >2.5 times the upper normal limit, total bilirubin >1.5 times the upper normal limit, serum creatinine >1.2 mg/dL, PS 3 or 4, or grade ≥3 nonhematologic toxicity (except for anorexia, nausea, vomiting, and fatigue). The dose of pemetrexed was decreased to 400 mg/m^2 in the P500 arm and to 800 mg/m^2 in the P1000 arm, if any of the following events occurred in the previous course: grade 4 leukopenia or neutropenia, grade ≥3 febrile neutropenia, thrombocytopenia, or platelet transfusion, grade ≥3 nonhematologic toxicity (except for grade 3 anorexia, nausea, vomiting, and fatigue), or AST/ALT increased. The pemetrexed dose was similarly reduced if initiation of the next course was postponed after day 29 due to drug-related adverse events. Patients who continued to show evidence of toxicity after reducing the pemetrexed dose were discontinued from the study.

Baseline and treatment assessments. Pretreatment assessments included chest X-ray, electrocardiogram, blood chemistry, urinalysis, pregnancy test, creatinine clearance, functional oxygen saturation, vital signs, PS, body weight, and use of prior therapies. Tumor size was examined using X-ray, computer tomography, or magnetic resonance imaging done within 28 days before the planned day of the first treatment. This was repeated about every 4 weeks after the first examination.

Tumor response rate was assessed as the percentage of patients in whom complete response (CR) and partial response (PR) were confirmed based on the best overall response of the tumor response evaluation. Response was evaluated according to the Response Evaluation Criteria in Solid Tumors (20). Objective tumor responses in all responding patients were evaluated by an external review committee given no information on the treatment groups.

Duration of overall response (CR + PR) was measured from the date of the first objective assessment of CR or PR until the date of progressive disease. PFS was measured from the date of registration (for the initiation of course 1) until the date of progressive disease or death. One-year survival rate was defined as the percentage of patients who survived for 1 year from the registration date. Survival was measured from the registration date to the date of death (regardless of cause).

QoL was assessed by the QoL Questionnaire for Cancer Patients Treated with Anticancer Drugs and the Functional Assessment of Cancer Therapy for Lung Cancer (Japanese version; refs. 21–23).

Assessments of QoL were done before treatment, before the second and third courses of chemotherapy, and 3 months after the start of treatment.

Adverse events were recorded throughout the study and after the last drug administration until signs of recovery were evident. All such events were evaluated according to the Common Terminology Criteria for Adverse Events version 3.0.

Statistical analysis. Efficacy measurements were done according to the guidelines for clinical evaluation methods of anticancer drugs. Efficacy analysis was done on patients who met all selection criteria and received at least one dose of pemetrexed. Safety analysis was done on patients who received at least one dose of pemetrexed.

Statistical tests were done to establish a pemetrexed response rate of >5%; 90% confidence intervals (CI) for the objective response rate were constructed for each arm. All survival curves for time-to-event variables were created using the Kaplan-Meier method; 95% CIs were calculated for each arm. Response rate, response duration, and PFS were compared between the two arms using the χ^2 test. Cox multiple regression analysis was done on all evaluable patients from two combined arms to

identify significant prognostic factors for survival. Covariates evaluated were pemetrexed dose, gender, age, PS, disease stage, histology, interval from prior chemotherapy to registration for the first treatment course, the number of prior chemotherapeutic regimens, and use of prior platinum chemotherapy. For the QoL analysis, distributions of subscales were summarized for each arm using descriptive statistics (mean, SD, minimum, median, and maximum). As a retrospective analysis for safety, major grade 3 to 4 drug-related adverse events were compared between the two arms using the χ^2 test.

Results

Patient disposition and characteristics. From October 2004 to October 2005, a total of 244 Japanese patients with advanced NSCLC were enrolled at 28 centers. Of the 244 patients enrolled, 226 were randomly assigned (114 to the P500 arm and 112 to the P1000 arm) at least 1 week before treatment after receiving folic acid and vitamin B_{12} supplementation. A total of 225 patients (114 in the P500 arm and 111 in P1000 arm) were evaluable for safety. Of these patients, 216 (108 in each arm) were evaluable for efficacy. Gender, age, PS, histology, stage, and prior platinum chemotherapy were well balanced across the two arms (Table 1).

Efficacy evaluation. Objective tumor response rates and durations of overall response are shown in Table 2. Of the 108 patients evaluable for efficacy in the P500 arm, 20 achieved PR for an objective response rate of 18.5% (90% CI, 12.6-25.8%); the median duration of response was 4.9 months (95% CI, 3.8-8.7 months). Of the 108 patients evaluable for efficacy in the P1000 arm, 16 achieved PR for an objective response rate of 14.8% (90% CI, 9.5-21.6%); the median duration of response was 3.0 months (95% CI, 2.8-6.1 months). As seen above, the lower limits of the 90% CI in both arms were >5%, showing a statistically significant objective response rate >5% in each of the arms. The differences between arms in response rate and response duration were not statistically significant ($P = 0.5839$ and 0.1740).

By October 2006, 125 of the 216 evaluable patients had died. The MST and 1-year survival rate were 16.0 months and 59.2% in the P500 arm and 12.6 months and 53.7% in the P1000 arm ($P = 0.1463$, log-rank test for survival; Fig. 1). Median PFS was 3.0 months (95% CI, 2.0-3.5 months) in the P500 arm and 2.5 months (95% CI, 1.8-3.2 months) in the P1000 arm ($P = 0.7139$, log-rank test).

Cox multiple regression analysis indicated that pemetrexed dose was not a significant prognostic factor; however, gender (female), PS (0), disease stage (III), histologic type (non-squamous cell carcinoma), and longer intervals from prior chemotherapy were shown to be good prognostic factors (Fig. 2). Of note, patients with non-squamous cell carcinoma had a longer MST compared with those with other histologic types (16.0 versus 9.3 months; $P = 0.00264$, Cox regression analysis). Pretreatment QoL assessments in both arms were relatively high and showed neither worsening nor improvement following pemetrexed treatment (Table 3).

Safety evaluation. A total of 225 patients (114 for P500 and 111 for P1000) were evaluable for safety. Leukopenia, neutropenia, lymphopenia, anemia, elevation of AST/ALT, lactate dehydrogenase, and rash were commonly reported; however, no grade 4 leukopenia or febrile neutropenia was observed (Table 4). Other grade 4 toxicities were uncommon. Gastrointestinal toxicities such as nausea, vomiting, and anorexia were mostly mild and more frequently reported in the P1000 arm. As a retrospective analysis for safety, major grade 3 to 4 drug-related adverse events were compared

Table 1. Patient characteristics

Variable	P500	P1000
Patients who were given at least one dose of pemetrexed	114	111
Gender		
Male	72	71
Female	42	40
Age, median (range)	61.0 (37-74)	62.0 (26-74)
Eastern Cooperative Oncology Group PS		
0	45	37
1	63	68
2	6	6
Histology		
Adenocarcinoma	79	82
Squamous cell carcinoma	25	26
Others	10	3
Disease stage		
III	22	22
IV	92	88
No. prior chemotherapies		
1	44	53
2	67	57
3	3	1
Prior platinum chemotherapy		
Yes	108	104
No	6	7
Interval from prior chemotherapy to registration for the first course starts (mo)		
<3	72	66
3	42	45

Table 2. Objective tumor response and median response duration

Variable	P500 (n = 108)	P1000 (n = 108)
Objective tumor response		
CR	0	0
PR	20	16
Stable disease	40	34
Progressive disease	48	58
Response rate (90% CI), %	18.50 (12.6-25.8)	14.80 (9.5-21.6)
Median response duration (95% CI), mo	4.9 (3.8-8.7)	3.0 (2.8-6.1)

between the two arms using the χ^2 test. Grade 3 or 4 anorexia was reported more frequently in the P1000 arm (10.8% versus 2.6%; P = 0.0284). Drug-related rash was observed in 67.5% and 80.2% of the patients treated with P500 and P1000, respectively. However, all severities were grade 1 or 2. Five of the P500 patients and 3 of the P1000 patients developed interstitial lung disease related to pemetrexed treatment that resulted in the death of one patient (P500 arm). The other 7 patients recovered from their illness after discontinuing the study drug. A total 16 (14.0%) patients in the P500 arm and 26 (23.4%) patients in the P1000 arm discontinued the treatment because of drug-related adverse events.

Dose administration. The median number of treatment courses completed in both arms was 3 (range, 1-24+). Eleven percent of patients in the P500 arm and 8% in the P1000 arm completed at least 10 courses. Dose reduction occurred in 20 (17.5%) patients in the P500 arm and 27 (24.3%) patients in the P1000 arm. The most frequent cause of dose reduction was ALT elevation. Relative dose intensities were 89.6% in the P500 group and 89.8% in the P1000 group.

Discussion

This phase II, randomized study is the first report on the efficacy and safety of a higher dose of pemetrexed (1,000 mg/m^2) in pretreated Japanese patients with NSCLC. Most patients (>50%) received two courses of prior chemotherapy, and the vast majority or patients (>90%) received prior platinum-based chemotherapy. The response data indicate promising tumor reduction activity and are noteworthy in pretreated patients. The survival data are also promising and better than those reported in second- and third-line settings and comparable with those reported in first-line settings (3, 24, 25). In the phase III study (3) comparing pemetrexed with docetaxel, the response

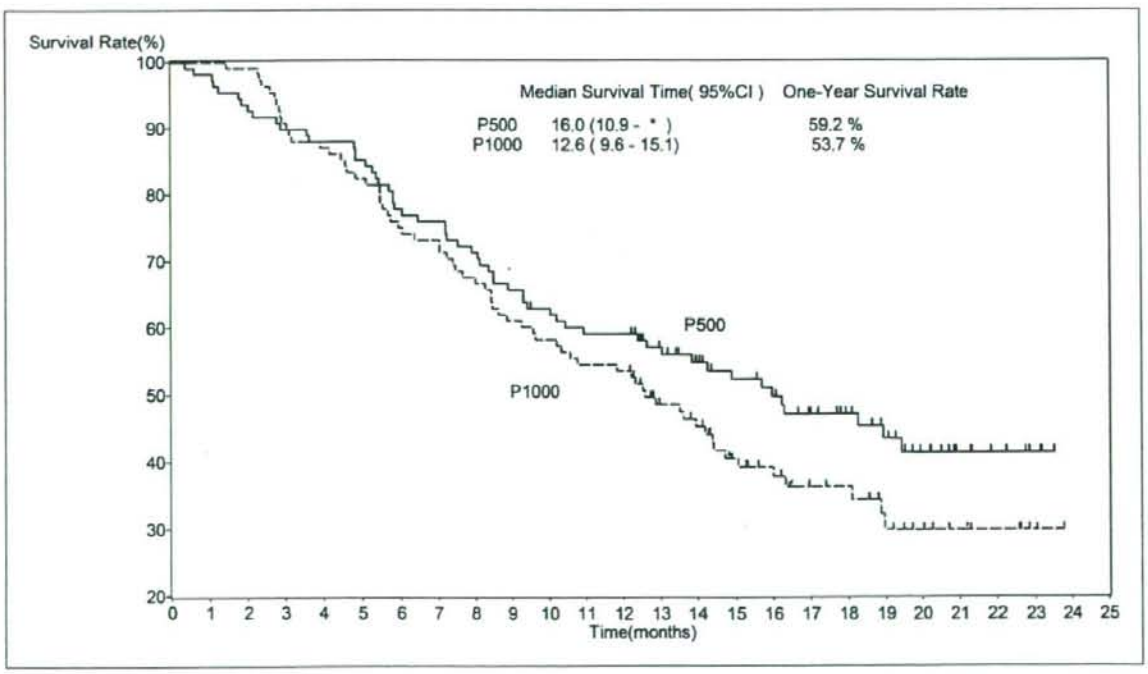

Fig. 1. Kaplan-Meier curve showing the overall survival for each arm. *Asterisk*, upper limit could not be calculated because of the censoring at the end of study period.

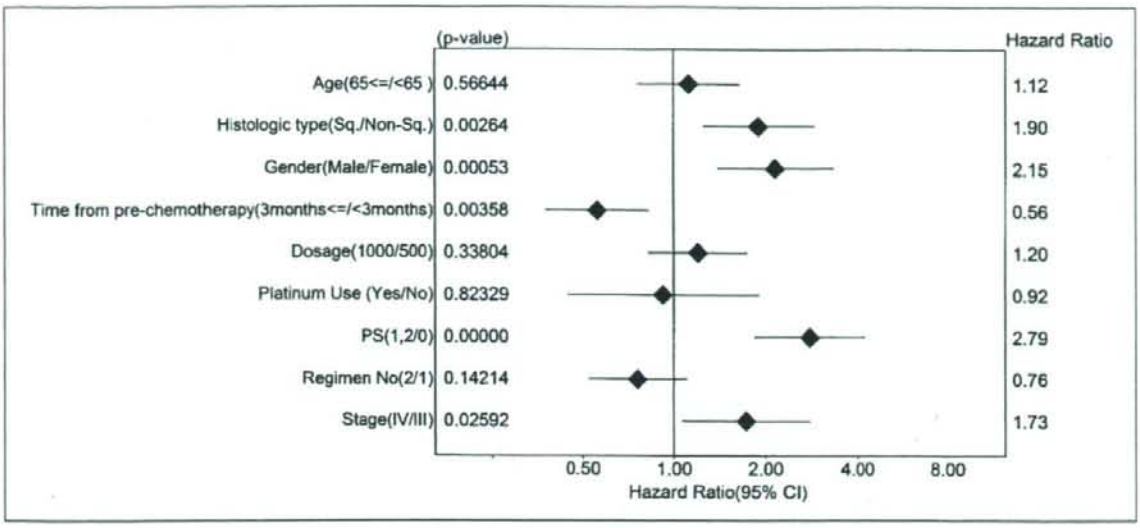

Fig. 2. Forest plot. Cox multiple regression analysis was done on all evaluable patients from two combined arms to identify significant prognostic factors for survival. Covariates evaluated were pemetrexed dose, gender, age, PS, disease stage, histology, interval from prior chemotherapy to registration for the first treatment course, the number of prior chemotherapeutic regimens, and use of prior platinum chemotherapy.

rate and median survival in the pemetrexed arm were 9.1% and 8.3 months, respectively.

Both P500 and P1000 with folic acid and vitamin B_{12} supplementation were similarly active in previously treated patients with NSCLC. All efficacy measures were similar in both arms as shown by the response rate, survival, and PFS, suggesting that doubling the standard dose of pemetrexed does not show superior efficacy. In addition, Cox multiple regression analysis showed that the difference of pemetrexed dose did not influence survival. Overall, toxicity was more frequent at the higher dose, although toxicity in both arms was mild.

Cullen et al. reported a randomized trial of 500 versus 900 mg/m^2 pemetrexed in patients with advanced NSCLC treated previously with platinum-based chemotherapy (26). The response rate, median PFS, and median survival were 7.1%, 2.6 months, and 6.7 months in patients treated with 500 mg/m^2 and 4.3%, 2.8 months, and 6.9 months in patients treated with 900 mg/m^2 pemetrexed, respectively. The higher dose did not improve survival more than the lower dose.

Dose intensification is not always accompanied by higher efficacy, such as in the case of docetaxel and cisplatin. One possible explanation for this in pemetrexed is that either the intracellular transport of pemetrexed is maximal at 500 mg/m^2 or the inhibition of target enzymes is saturated above this dose; however, there are as yet no *in vitro* data to support either mechanism. Although the mechanism still needs to be elucidated, the wide therapeutic window of pemetrexed makes it unique and safe for patients.

Of interest, our subgroup analysis identified some prognostic factors. The subgroups that were identified as good prognostic factors, gender (female), good PS, early-stage disease, and longer intervals from prior chemotherapy are well known as good prognostic factors for NSCLC. Of particular note, the MST

Table 3. Summary for Functional Assessment of Cancer Therapy for Lung Cancer Lung Cancer Subscale

	n	Mean (SD)	Min	Med	Max
P500 (*n* = 108)					
Before course 1	107	71.5 (18.81)	32.1	71.4	100
Before course 2	101	74.3 (16.68)	39.3	75	100
Before course 3	84	74.3 (18.08)	35.7	78.6	100
Registration of course 1 + 3 mo*	59	76.3 (18.1)	32.1	78.6	100
P1000 (*n* = 108)					
Before course 1	107	69.6 (18.52)	25	67.9	100
Before course 2	98	73.5 (17.21)	32.1	75	100
Before course 3	72	71.4 (18.4)	28.6	71.4	100
Registration of course 1 + 3 mo*	61	74.3 (18.62)	28.6	71.4	100

*Three months ±2 weeks after the day of registration for one course.

Table 4. Hematologic and nonhematologic toxicity evaluated by Common Terminology Criteria for Adverse Events version 3.0

	P500 (n = 114)				P1000 (n = 111)				P
	Grade (%)				Grade (%)				
	2	3	4	3/4/5	2	3	4	3/4/5	
Leukopenia	32.5	14.9	0	14.9	38.7	21.6	0	21.6	0.2582
Neutropenia	25.4	17.5	3.5	21.1	27.9	19.8	4.5	24.3	0.6695
Lymphopenia	28.9	9.6	2.6	12.3	30.6	16.2	1.8	18	0.31
Anemia	19.3	7	0.9	7.9	34.2	9	0.9	9.9	0.7667
Thrombocytopenia	0	0	0	0	8.1	0.9	0	0.9	NA
Febrile neutropenia	*	0	0	0	*	0	0	0	NA
Nausea	14	0	0	0	14.4	2.7	0	2.7	NA
Vomiting	7	0	0	0	11.7	1.8	0	1.8	NA
Anorexia	16.7	2.6	0	2.6	15.3	10.8	0	10.8	0.0284
Fatigue	3.5	0	0	0	1.8	0.9	0	0.9	NA
Diarrhea	2.6	0.9	0	0.9	1.8	1.8	0	1.8	0.9815
Constipation	1.8	0.9	0	0.9	5.4	0	0	0	NA
Rash	49.1	2.6	0	2.6	63.1	4.5	0	4.5	0.6903
Alopecia	0	*	*	*	0	*	*	*	NA
Pneumonitis	1.8	1.8	0	2.6†	0	2.7	0	2.7	1
AST	21.9	7.9	0	7.9	25.2	4.5	0	4.5	0.4375
ALT	17.5	16.7	0	16.7	32.4	7.2	0.9	8.1	0.8143

NOTE: Major grade 3 to 4 drug-related adverse events were compared between two arms using χ^2 test.
*Not indicated in Common Terminology Criteria for Adverse Events version 3.0.
†One patient died of drug-induced pneumonitis.

of patients with non-squamous cell carcinoma was significantly longer compared with that in patients with squamous cell carcinoma (16.0 versus 9.3 months; $P = 0.00264$). Pemetrexed induces its antitumor activity by inhibiting key enzymes related to the folate metabolism, such as thymidylate synthase. Studies of the tumor histology of adenocarcinoma progressive disease have reported lower-level expression of thymidylate synthase than squamous cell carcinoma (27). Good survival benefit in patients with non-squamous cell carcinoma by pemetrexed may be explained by lower levels of thymidylate synthase. Because MST was the subject of a subgroup analysis and survival was not a primary endpoint of this study, this finding should be considered exploratory requiring independent confirmation. However, if this finding of superior effectiveness in non-squamous cell carcinoma could be substantiated in future studies, it would be very useful. Indeed, histology could be a simple means of tailoring chemotherapy treatment.

In conclusion, although the recommended dose is P1000 with folic acid and vitamin B_{12} supplementation for Japanese patients, it has similar efficacy and safety with P500, the recommend dosage in rest of the world. These results support the use of P500 as a second- or third-line treatment of NSCLC.

Disclosure of Potential Conflicts of Interest

Authors have conflicts with Eli Lilly and company.

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Phase III trial of docetaxel plus gemcitabine versus docetaxel in second-line treatment for non-small-cell lung cancer: results of a Japan Clinical Oncology Group trial (JCOG0104)

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Background: This trial evaluated whether a combination of docetaxel and gemcitabine provides better survival than docetaxel alone in patients with previously treated non-small-cell lung cancer (NSCLC).

Patients and methods: Eligibility included pathologically or cytologically proven NSCLC, failure of one platinum-based regimen, performance status of zero or one, 20–75 years old, and adequate organ function. Patients received docetaxel 60 mg/m^2 (day 1) or docetaxel 60 mg/m^2 (day 8) and gemcitabine 800 mg/m^2 (days 1 and 8), both administered every 21 days until disease progression.

Results: Sixty-five patients participated in each arm. This trial was terminated early due to an unexpected high incidence of interstitial lung disease (ILD) and three treatment-related deaths due to ILD in the combination arm. Docetaxel plus gemcitabine compared with docetaxel-alone patients experienced similar grade and incidence of toxicity, except for ILD. No baseline factor was identified for predicting ILD. Median survival times were 10.3 and 10.1 months (one-sided $P = 0.36$) for docetaxel plus gemcitabine and docetaxel arms, respectively.

Conclusion: Docetaxel alone is still the standard second-line treatment for NSCLC. The incidence of ILD is higher for docetaxel combined with gemcitabine than for docetaxel alone in patients with previously treated NSCLC.

Key words: docetaxel, gemcitabine, non-small-cell lung cancer, platinum-refractory, second-line chemotherapy

original article

introduction

Lung cancer is the most common cancer worldwide, with an estimated 1.2 million new cases globally (12.3% of all cancers) and 1.1 million deaths (17.8% of all cancer deaths) in 2000 [1]. The estimated global incidence of non-small-cell lung cancer (NSCLC) in 2000 was ~1 million, which accounted for ~80% of all cases of lung cancer [1]. Treatment of advanced NSCLC is palliative; the aim is to prolong survival without leading to deterioration in quality of life [2]. The recommended first-line treatment of advanced NSCLC currently involves up to four cycles of platinum-based combination chemotherapy, with no single combination recommended over others [3]. Although this treatment improves survival rates, a substantial proportion of patients do progress and should be offered second-line treatment. With unsurpassed efficacy compared with other chemotherapeutic regimens or best supportive care [4, 5], docetaxel alone is the current standard as second-line chemotherapy for advanced NSCLC. The recommended regimen of docetaxel 75 mg/m^2 given i.v. every 3 weeks as second-line therapy has been associated with median survival times of 5.7–7.5 months [4, 5] and is also associated with better quality-of-life outcomes compared with best supportive care [2]. Docetaxel monotherapy for recurrent NSCLC after platinum-based chemotherapy has several limitations, however, including low response rates (7–11%), brief duration of disease control, and minimal survival advantage [4, 5].

Gemcitabine is also active against recurrent NSCLC after platinum-based chemotherapy [6]. Gemcitabine 1000 mg/m^2 once a week for 3 weeks every 28 days produced a 19% response rate in a phase II trial, and it shows significant activity mainly

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in patients previously responsive to chemotherapy [6]. Single-agent gemcitabine has a low toxicity profile and is well tolerated [6].

Docetaxel and gemcitabine have distinct mechanisms of action and nonoverlapping toxic effects except for neutropenia. Many studies of the combination of docetaxel and gemcitabine have been conducted in first- and second-line settings [7–16]. The following doses and schedule have been adopted in most studies: docetaxel 80–100 mg/m^2 on day 1 or 8 and gemcitabine 800–1000 mg/m^2 on days 1 and 8 or on days 1, 8, and 15. Furthermore, most studies required use of prophylactic granulocyte colony-stimulating factor (G-CSF) support.

In Japan, however, the recommended dose of docetaxel is 60 mg/m^2 every 3 weeks [17, 18]. Several studies to confirm the dose and schedule of this combination without prophylactic G-CSF support have been conducted in Japan [19–21]. Two studies recommended docetaxel 60 mg/m^2 on day 8 and gemcitabine 800 mg/m^2 on days 1 and 8, and another study recommended docetaxel 50 mg/m^2 on day 8 and gemcitabine 1000 mg/m^2 on days 1 and 8, without prophylactic G-CSF support, every 3 weeks. These studies demonstrated the consistent promising efficacy of this combination regimen. An objective response was observed in 28%–40% of patients, with a median survival time of 11.1–11.9 months and a 1-year survival rate of 41%–47%.

We conducted a multicenter, randomized, phase III trial to evaluate whether the combination regimen of docetaxel and gemcitabine provides better survival than docetaxel alone in patients with previously treated NSCLC.

patients and methods

patient selection

Eligible patients were 20–75 years of age, with histologically or cytologically confirmed stage IIIB (with malignant pleural effusion or contralateral hilar lymph node metastases) or stage IV NSCLC who had failed one platinum-based chemotherapy regimen previously. Patients who had received gemcitabine or docetaxel were excluded. Additional inclusion criteria included a Eastern Cooperative Oncology Group performance status of zero to one, and adequate organ function as indicated by white blood cell count ≥4000/μl, absolute neutrophil count ≥2000/μl, hemoglobin ≥9.5 g/dl, platelets ≥100 000/μl, aspartate aminotransferase (AST)/alanine amonotransferase (ALT) ≤2.5 times the upper limit of normal, total bilirubin ≤1.5 mg/dl, serum creatinine ≤1.2 mg/dl, and PaO_2 in arterial blood ≥70 torr. Asymptomatic brain metastases were allowed provided that they had been irradiated and were clinically and radiologically stable. Prior thoracic radiotherapy was allowed provided that treatment was completed at least 12 weeks before enrollment. Patients were excluded from the study if they had radiologically and clinically apparent interstitial pneumonitis or pulmonary fibrosis. All patients provided written informed consent, and the study protocol was approved by Japan Clinical Oncology Group (JCOG) Clinical Trial Review Committee and the institutional review board of each participating institution.

treatment plan and dose modifications

Eligible patients were centrally registered at JCOG Data Center and were randomly assigned to either docetaxel 60 mg/m^2 as a 60-min i.v. infusion on day 1 or docetaxel 60 mg/m^2 as a 60-min i.v. infusion on day 8 plus gemcitabine 800 mg/m^2 as a 30-min i.v. infusion on days 1 and 8, using a minimization method with institutions and response to prior chemotherapy (progressive disease or not) as balancing factors. Patients receiving docetaxel were administered standard dexamethasone premedication (8 mg orally at the day before, on the day, and the day after docetaxel administration) as previously reported [7] and 50 mg of diphenhidramine 30 min before docetaxel administration. Recombinant human G-CSF was not given prophylactically. Chemotherapy cycles were repeated every 3 weeks until disease progression. Docetaxel was given before gemcitabine in the docetaxel plus gemcitabine regimen.

Dose adjustments were based mainly on hematologic parameters. The doses of docetaxel and gemcitabine were reduced by 10 and 200 mg/m^2, respectively, in subsequent cycles if chemotherapy-induced febrile neutropenia, grade 4 anemia, grade 4 thrombocytopenia, grade 4 leukopenia, or grade 4 neutropenia lasting for >3 days occurred in the absence of fever. Dose reductions were maintained for all subsequent cycles. Patients requiring more than one dose reduction were off-protocol treatment.

baseline and follow-up assessments

Pretreatment evaluation included a complete medical history and physical examination, a complete blood count (CBC) test with differential and platelet count, standard biochemical profile, electrocardiogram, chest radiographs, computed tomographic scans of the chest, abdomen, and brain, magnetic resonance imaging, and a whole-body bone scan. During treatment, a CBC and biochemical tests were carried out weekly. A detailed medical history was taken and a complete physical examination with clinical assessment was carried out weekly to assess disease symptoms and treatment toxicity, and chest radiographs were done every treatment cycle. Toxicity was evaluated according to the National Cancer Institute Cancer—Common Toxicity Criteria Version 2 [22].

All patients were assessed for response by computed tomography scans after every two cycles of chemotherapy. Response Evaluation Criteria in Solid Tumors (RECIST) were used for the evaluation of response [23].

The progression-free survival (PFS) was calculated from the day of randomization until the day of the first evidence of disease progression or death. If the patient had no progression, PFS was censored at the day when no clinical progression was confirmed. Overall survival (OS) was measured from the day of randomization to death.

Disease-related symptoms were evaluated and scored at baseline and 6 weeks after the start of treatment with the seven-item Lung Cancer Subscale (LCS) of the Functional Assessment of Cancer Therapy-Lung version 4 [24], which were translated from English to Japanese. The questionnaire entries were listed as follows: 'I have been short of breath', 'I am losing weight', 'My thinking is clear', 'I have been coughing', 'I have a good appetite', 'I feel tightness in my chest', and 'Breathing is easy for me'. Patients scored using a five-point Likert scale (0–4) by themselves. The maximum attainable score of the LCS was 28, where the patient was considered to be asymptomatic.

statistical analysis

The primary endpoint was OS; secondary endpoints were PFS, the overall response rate, disease-related symptoms, and toxicity profile. Based on previous trials evaluating the docetaxel [4, 5] and docetaxel plus gemcitabine [19–21] regimens, the present study was designed to detect a 12% difference of 1-year survival rate. To attain an 80% power at a one-sided significance level of 0.05, assuming 1-year survival of docetaxel arm as 35% with 1 year of follow-up after 2 years of accrual, 284 patients (142 per each arm) were required. Analyses were to be carried out with all randomized patients. Both the OS and PFS were estimated with the Kaplan–Meier method. The comparisons of OS and PFS between arms were assessed by the stratified log-rank test with a factor used at randomization, response to prior chemotherapy. Two interim analyses were planned after half of the patients were registered and the end of registration.

For the symptom analysis, changes of LCS from initial score were compared between arms using analysis of covariance with initial score as a covariate.

All analyses were carried out with SAS software release 8.2 (SAS Institute, Cary, NC).

results

This trial was terminated early due to the unexpected high incidence of interstitial lung disease (ILD) and three treatment-related deaths due to ILD in the combination arm, which were identified by the Adverse Event Reporting system.

patient characteristics

From January 2002 to September 2003, 130 patients with NSCLC who had failed prior platinum-based chemotherapy from 32 institutions were enrolled (Appendix). These patients were randomly assigned to docetaxel alone ($n = 65$) or docetaxel plus gemcitabine ($n = 65$). One patient died as a result of rapid progressive disease before chemotherapy administration, and one patient did not meet the entry criteria in the docetaxel arm. In addition, one patient did not meet the entry criteria in the docetaxel plus gemcitabine arm. All patients were included in the analysis of survival and PFS, and 64 docetaxel and 65 docetaxel plus gemcitabine patients were assessable for toxicity. Fifty-nine patients with measurable lesions by RECIST in the docetaxel arm and 57 eligible patients in docetaxel plus gemcitabine arm were assessable for response (Figure 1). Table 1 presents baseline patient characteristics.

The median number of cycles was 3 (range 0–6) and 2 (range 1–8) in the docetaxel and docetaxel plus gemcitabine arms, respectively. The median interval between cycles was 22 days for both arms.

toxicity

This trial was terminated early due to the unexpected high incidence of ILD and three treatment-related deaths (4.6%) due to ILD in the docetaxel plus gemcitabine arm. These events were identified by the Adverse Event Reporting system. Thirteen (20.0%) patients receiving combination treatment suffered from all grades of ILD, whereas only two (3.1%) patients receiving docetaxel alone suffered from grades 1–2 ILD. Grades 2–4 ILD occurred in 16.9% of docetaxel plus gemcitabine patients, an unexpected high incidence rate. No risk factors were identified contributing to these pulmonary adverse events.

Toxicity was assessed in all patients who received at least one treatment cycle and in all cycles (Table 2). Overall, grades 3–4 neutropenia occurred in 55 docetaxel patients (85.9%) and 53 docetaxel plus gemcitabine patients (81.5%). Grades 3–4 anemia occurred in two patients (3.1%) and 12 patients (18.5%) treated with docetaxel alone and docetaxel plus

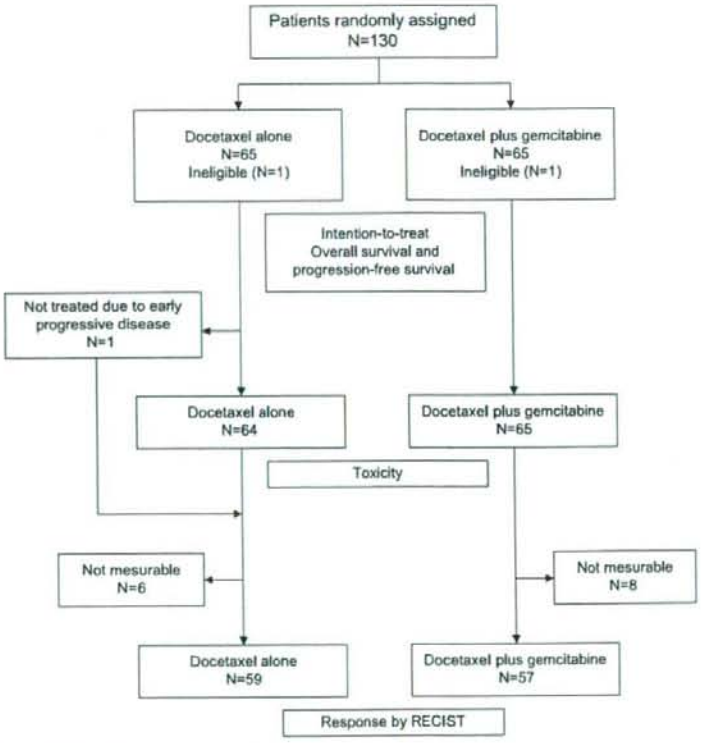

Figure 1. CONSORT diagram for the study.

Table 1. Patient characteristics

	D arm		DG arm	
	No. of patients	%	No. of patients	%
Patients enrolled	65		65	
Age, years				
Median	62		60	
Range	34–75		34–74	
Gender				
Male	48	73.8	51	78.5
Female	17	26.2	14	21.5
ECOG PS				
0	20	30.8	21	32.3
1	45	69.2	44	67.7
Histology				
Squamous	19	29.2	22	33.8
Adenocarcinoma	40	61.5	40	61.5
Large cell	4	6.2	3	4.6
Others	2	3.1	0	0
Best response of prior chemotherapy				
CR	2	3.1	0	0
PR	38	58.5	40	61.5
SD	20	30.8	19	29.2
PD	5	7.7	6	9.2

D, docetaxel; DG, docetaxel plus gemcitabine; ECOG PS, Eastern Cooperative Oncology Group performance status; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

gemcitabine, respectively. Sixteen patients treated with docetaxel (25.0%) and 11 patients with docetaxel plus gemcitabine (16.9%) developed febrile neutropenia. All required antibiotic treatment and G-CSF; however, no patient died. One patient in the docetaxel plus gemcitabine arm developed anaphylatic shock immediately after administration of docetaxel at the second cycle. Grades 2–4 ALT elevation was more frequent with docetaxel plus gemcitabine than with docetaxel (20.0% versus 4.7%). Grades 2–4 non-neutropenic infection occurred more often with docetaxel plus gemcitabine than with docetaxel (21.5% versus 15.6%). Grades 2–4 ILD was more frequent with docetaxel plus gemcitabine than with docetaxel (16.9% versus 1.6%). Other toxic effects were relatively mild (Table 2). Overall, docetaxel plus gemcitabine was more toxic than docetaxel, however, well tolerated except for ILD in docetaxel plus gemcitabine arm.

treatment efficacy

The overall response rate for docetaxel alone was 6.8% [95% confidence interval (CI) 1.9% to 16.5%] and 7.0% for docetaxel plus gemcitabine (95% CI 2.0% to 17.0%). There was no significant difference between treatment arms ($P = 0.71$; Fisher's exact test).

At the time of this analysis, 50 docetaxel patients (76.9%) and 48 docetaxel plus gemcitabine patients (73.8%) had died. The median survival time was 10.1 months for docetaxel alone and 10.3 months for docetaxel plus gemcitabine (one-sided $P = 0.36$ stratified log-rank test; Figure 2A). The respective 1-year survival rate was 43.1% (95% CI 31.0% to 55.1%) for docetaxel and 46.0% (95% CI 33.8% to 58.1%) for docetaxel plus gemcitabine.

The median PFS time was 2.1 and 2.8 months for docetaxel and docetaxel plus gemcitabine, respectively (one-sided $P = 0.028$ stratified log-rank test; Figure 2B).

Table 2. Hematological and non-hematological toxicity

	D arm ($n = 64$)					DG arm ($n = 65$)				
	NCI-CTC grade					NCI-CTC grade				
Hematological	0–1	2	3	4	3–4%	0–1	2	3	4	3–4%
Anemia	27	35	2	0	3.1	21	32	9	3	18.5
Leukopenia	9	14	29	12	64.1	11	12	32	10	64.6
Neutropenia	7	2	15	40	85.9	8	4	19	34	81.5
Thrombocytopenia	64	0	0	0	0	43	14	8	0	12.3
Non-hematological	0–1	2	3	4	2–4%	0–1	2	3	4	2–4%
Allergic reaction	64	0	0	0	0	59	5	1	0	9.2
Alopecia	45	18	–	–	28.1	49	14	–	–	21.5
ALT	61	2	1	0	4.7	52	10	3	0	20.0
Diarrhea	61	3	0	0	4.7	60	3	2	0	7.7
Edema	63	1	0	0	1.6	64	1	0	0	1.5
Fatigue	56	5	2	1	12.5	56	7	1	1	13.8
Febrile neutropenia	48	–	16	0	25.0	54	–	11	0	16.9
Infection with grades 3–4 neutropenia	59	–	5	0	7.8	56	–	9	0	13.8
Infection without neutropenia	54	8	2	0	15.6	51	4	9	1	21.5
Nausea	55	7	2	–	14.1	55	6	4	–	15.4
Neuropathy	62	2	0	0	3.1	62	2	0	1	4.6
Pneumonitis (ILD)	63	1	0	0	1.6	54	3	7	1	16.9
Stomatitis	61	3	0	0	4.7	60	5	0	0	7.7

D, docetaxel; DG, docetaxel plus gemcitabine; NCI-CTC, National Cancer Institute—Cancer Common Toxicity Criteria; ALT, alanine aminotransferase; ILD, interstitial lung disease.

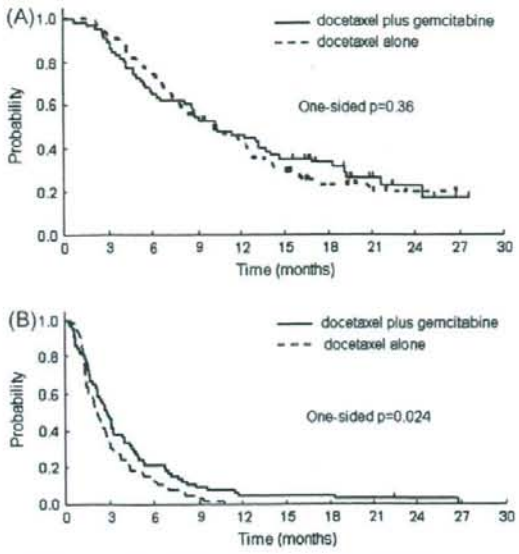

Figure 2. Overall survival (A) and progression-free survival (B) by treatment arm.

disease-related symptom assessment

Patients' compliance with disease-related symptom assessment was 100% at baseline and 95.4% at 6 weeks later. Compliance rates were not different between the arms ($P = 1.00$). LCS data were missing in four surveys due to death or severe impairment of the patient's general condition; this accounted for 1.5% of the total number of surveys scheduled. Mean LCS at baseline and 6 weeks were shown in Table 3. There were no significant differences in the LCS changes from baseline to 6 weeks between docetaxel and docetaxel plus gemcitabine arms ($P = 0.61$).

discussion

This trial was terminated early due to the unexpected high incidence of ILD and three treatment-related deaths due to ILD in the docetaxel plus gemcitabine arm. Our findings seem to indicate that the combination of docetaxel and gemcitabine may be associated with a higher incidence of pulmonary adverse events compared with docetaxel alone, especially in patients with previously treated NSCLC.

Pulmonary toxicity following chemotherapeutic agents, including ILD, has been well recognized for many years. In most cases, this toxicity is mild and self-limiting. However, the mechanism of developing drug-induced ILD is uncertain, and risk factors for developing this disorder have not been identified. In terms of combination therapy with docetaxel and gemcitabine for advanced NSCLC, there were few reports about the incidences of ILD at the time this study was planned. A phase I study of patients with transitional cell carcinoma evaluated thrice-weekly doses of docetaxel given on day 1 plus gemcitabine given on days 1 and 15 and showed that pulmonary toxicity occurred in three of five patients and was

Table 3. Disease-related symptom assessment

Lung Cancer Subscale	D arm	DG arm
Baseline		
Number	$n = 65$	$n = 65$
Mean ± SD	19.0 ± 5.48	19.7 ± 5.25
6 weeks later		
Number	$n = 62$	$n = 62$
Mean ± SD	18.1 ± 5.56	18.9 ± 5.05
Difference		
Mean ± SD	−1.11 ± 3.81	−0.99 ± 4.49

D, docetaxel; DG, docetaxel plus gemcitabine; SD, standard deviation.

the cause of death in one [25]. Recently, some reports have been published about the high incidence of ILD due to the combination regimen of docetaxel and gemcitabine in patients with NSCLC [13, 26, 27], including the present study (Table 4). In Japanese population, ILD is a very complex issue in treatment of patients with lung cancer. Epidermal growth factor tyrosine kinase inhibitor gefitinib is developing ILD significantly in Japanese patients with NSCLC [28]. It is uncertain why ILD is developing more in Japanese patients with NSCLC than the Western patients. Ethnic difference may be one of the explanations for this occurrence. The combination of gemcitabine and docetaxel is associated with a high incidence of severe pulmonary toxicity. The regimen should not be used outside a clinical trial.

The median survival times of 10.1 and 10.3 months and estimated 1-year survival rates of 43.1% and 46.0% with docetaxel alone and docetaxel plus gemcitabine, respectively, suggest that adding gemcitabine to docetaxel did not provide any increased efficacy in patients with previously treated NSCLC. Interestingly, the combination regimen of docetaxel plus gemcitabine significantly improved the median PFS time ($P = 0.028$). Possible reasons for failing to detect a significant difference between survival curves may include an insufficient occurrence of documented events as a result of the study population comprising patients with relatively good prognosis, in addition to a high proportion of patients subsequently receiving third-line therapy. During this study, gefitinib treatment was commonly used for patients with recurrent NSCLC in Japan [29]. Asian ethnicity is a well-known predictive factor for a response for gefitinib [30].

Two randomized phase II trials compared docetaxel alone with docetaxel plus irinotecan in second-line chemotherapy for NSCLC [31, 32]. No significant treatment differences in survival were observed in either trial; however, the trials were phase II study and were not powered or designed to compare survival. This study was not powered to compare survival when it was terminated early due to the unexpected high incidence of ILD in the docetaxel plus gemcitabine arm. However, based on previous studies, as well as the present results, combination chemotherapy with docetaxel and another chemotherapeutic agent has not improved survival in patients with previously treated NSCLC.

In conclusion, docetaxel alone is still the standard second-line treatment for advanced NSCLC. The combination of docetaxel and gemcitabine was too toxic to obtain any survival

Table 4. Reports of interstitial lung disease due to docetaxel plus gemcitabine regimen

Author	Year	Study type	Treatment schedule	n	Grades 3–4 ILD (%)	TRD (%)
Rebattu et al. [13]	2001	Phase I/II	Docetaxel (60, 75, 85, 100 mg/m^2) day 8; gemcitabine (1000 mg/m^2), days 1 and 8, every 3 weeks	49	3 (6.1)	0
Kouroussis et al. [25]	2004	Phase I	Docetaxel (30, 35, 40 mg/m^2), days 1, 8 and 15; gemcitabine (700, 800, 900, 1000 mg/m^2), days 1, 8 and 15, every 4 weeks	26	6 (23)	2 (7.7)
Matsui et al. [21]	2005	Phase I/II	Docetaxel (50, 60 mg/m^2) day 1 or 8; gemcitabine (800, 1000 mg/m^2), days 1 and 8, every 3 weeks	59	3 (5.1)	0
Pujor et al. [27]	2005	Phase III	Docetaxel (85 mg/m^2) day 8; gemcitabine (1000 mg/m^2), days 1 and 8, every 3 weeks	155	8 (5.2)	1 (0.6)
			Cisplatin (100 mg/m^2) day 1; vinorelbine (30 mg/m^2), days 1, 8, 15 and 22, every 4 weeks	156	1 (0.6)	0
Takeda (present study)	2008	Phase III	Docetaxel (60 mg/m^2) day 8; gemcitabine (800 mg/m^2), days 1 and 8, every 3 weeks	65	8 (12.3)	3 (4.6)
			Docetaxel (60 mg/m^2) day 1, every 3 weeks	64	0 (0)	0

ILD, interstitial lung disease; TRD, treatment-related death.

benefit in patients with recurrent advanced NSCLC. The development of less toxic and more effective chemotherapeutic agents, including molecular targeted drugs, is warranted for the second-line treatment of NSCLC.

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appendix

The following institutions participated in the study: Hokkaido Cancer Center (Sapporo), Ibaragi Prefectural Central Hospital (Kasama), Tochigi Cancer Center (Utsunomiya), Nishigunma National Hospital (Shibukawa), Gunma Prefectural Cancer Center Hospital (Ohta), Saitama Cancer Center Hospital (Ina), National Cancer Center Hospital East (Kashiwa), National Cancer Center Hospital (Tokyo), International Medical Center of Japan (Tokyo), Cancer Institute Hospital (Tokyo), Toranomon Hospital (Tokyo), Kanagawa Cancer Center Hospital (Yokohama), Yokohama Municipal Hospital (Yokohama), Niigata Cancer Center Niigata Hospital (Niigata), Gifu Municipal Hospital (Gifu), Aichi Cancer Center Hospital (Nagoya), Nagoya National Hospital (Nagoya), Prefectural Aichi Hospital (Okazaki), Osaka City University Medical School (Osaka), Kinki University School of Medicine (Osaka-Sayama), Osaka Medical Center for Cancer and Cardiovascular Disease (Osaka), Osaka Prefectural Medical Center for Respiratory and Allergic disease (Habikino), Kinki-Chuo Chest Medical Center (Sakai), Toneyama National Hospital (Toyonaka), Osaka Prefectural General Hospital (Osaka), Osaka City General Hospital (Osaka), Kobe City General Hospital (Kobe), Hyogo Collage of Medicine (Nishinomiya), Hyogo Cancer Center (Akashi), Shikoku Cancer Center Hospital (Matsuyama), Kyusyu University Hospital (Fukuoka), and Kumamoto Regional Medical Center (Kumamoto).

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A Randomized, Double-Blind, Phase IIa Dose-Finding Study of Vandetanib (ZD6474) in Japanese Patients With Non-Small Cell Lung Cancer

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Introduction: Vandetanib (ZACTIMA™) is a once-daily, oral anticancer drug that selectively inhibits vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) signaling. Vandetanib was evaluated as a monotherapy in a randomized, double-blind, dose-finding study in Japan.

Patients and Methods: Eligible patients with locally advanced or metastatic (stage IIIB/IV) or recurrent non-small cell lung cancer, previously treated with chemotherapy, were randomized to receive once-daily oral vandetanib 100, 200, or 300 mg (1:1:1). The primary objective was to determine the objective response rate for each vandetanib dose.

Results: Fifty-three patients received vandetanib (100 mg, $n = 17$; 200 mg, $n = 18$; 300 mg, $n = 18$). The objective response rate in each dose arm was 17.6% (3 of 17; 100 mg), 5.6% (1 of 18; 200 mg), and 16.7% (3 of 18; 300 mg). Common adverse events included rash, diarrhea, hypertension, and asymptomatic QTc prolongation. The adverse event profile was generally consistent with that reported previously for agents that inhibit the VEGFR or EGFR signaling pathways. Among the three responders evaluated for *EGFR* mutation, two had no mutation, and in one case, the *EGFR* mutation status could not be determined by direct DNA sequencing and amplification refractory mutation system assay of *EGFR* exons 19–21. Baseline plasma VEGF levels appeared to be lower in patients who experienced clinical benefit after vandetanib treatment.

Conclusion: In Japanese patients with advanced non-small cell lung cancer, vandetanib monotherapy (100–300 mg/d) demonstrated antitumor activity with an acceptable safety and tolerability profile.

Key Words: Non-small cell lung cancer, Vandetanib, EGFR, VEGFR.

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Non-small cell lung cancer (NSCLC) accounts for approximately 75% of lung cancers and is the leading cause of cancer-related death worldwide.[1] Despite the introduction of more effective chemotherapeutic agents, new approaches are required to further improve patient outcome and survival. A major focus of new anticancer research is the targeting of cell-signaling pathways that contribute to tumor growth and progression.

Vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) are key drivers of tumor angiogenesis and cell proliferation, respectively, and both pathways have been validated as clinically relevant targets in NSCLC. The addition of bevacizumab, a humanized anti-VEGF-A monoclonal antibody, to paclitaxel and carboplatin has demonstrated clinical benefit in patients with NSCLC,[2] and the EGFR inhibitors gefitinib and erlotinib have demonstrated clinical activity as single agents in NSCLC.[3,4] Furthermore, EGFR is known to regulate the production of VEGF and other proangiogenic factors[5] and resistance to EGFR inhibition has been associated with increased expression of VEGF in a human tumor xenograft model of NSCLC.[6] Therefore, targeting the VEGFR and EGFR pathways may be more effective than inhibiting either pathway alone. This hypothesis is supported by the promising results from early clinical evaluation of erlotinib and bevacizumab in combination in patients with recurrent NSCLC.[7]

Vandetanib (ZACTIMA™) is a once-daily, orally available anticancer drug that inhibits VEGFR- and EGFR-dependent signaling,[8] as well as the RET (REarranged during

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Transfection) receptor tyrosine kinase, which is an important growth driver in certain types of thyroid cancer.[9] Early clinical evaluation of vandetanib has demonstrated a promising efficacy and safety profile in a broad population of patients with advanced cancer. Phase I studies in advanced solid tumors conducted in the USA/Australia[10] and Japan[11] showed that once-daily doses of vandetanib (up to and including 300 mg) were generally well tolerated. In the Japanese study, objective tumor responses were observed in 4 of 9 patients with refractory NSCLC. Subsequent phase II studies in advanced NSCLC demonstrated antitumor activity both as a monotherapy and in combination with certain chemotherapy.[12–14] The positive outcome of these phase II trials led to the ongoing phase III evaluation of vandetanib in previously treated advanced NSCLC.

The primary objective of this randomized phase IIa study was to assess the objective response rate (ORR) to vandetanib (100, 200, or 300 mg/d) in Japanese patients with refractory NSCLC. The three doses investigated were selected based on the outcome of the Japanese phase I trial.[11]

PATIENTS AND METHODS

Patients

Patients with histologic or cytologic confirmation of locally advanced/metastatic (stage IIIB/IV) or recurrent NSCLC after failure of 1 or 2 platinum-based chemotherapy regimens were recruited from eight centers in Japan. The main eligibility criteria were age ≥20 years, a WHO performance status of 0 to 2, an estimated life expectancy ≥12 weeks, and completion of prior chemotherapy and/or radiotherapy at least 4 weeks before study entry (8 weeks for chest radiation and 6 weeks for mitomycin C). Patients with squamous cell histology were also eligible, and brain metastases were permitted if patients were asymptomatic and did not require corticosteroid treatment. Key exclusion criteria were a mixed small-cell and non-small cell histology, evidence of severe or uncontrolled systemic diseases, poorly controlled hypertension, a QTc interval ≥460 milliseconds by electrocardiogram during the screening period, and prior treatment with EGFR or VEGFR signaling inhibitors. All patients provided written informed consent. The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki, applicable guidelines on good clinical practice, local Institutional Review Board approval, and the AstraZeneca policy on Bioethics.

Study Design and Treatments

This was a randomized, double-blind, parallel-group, phase IIa dose-finding multicenter study to assess the efficacy and safety of vandetanib. A total of 53 patients were randomized (1:1:1) to receive once-daily oral vandetanib (100, 200, or 300 mg/d; Figure 1). Patients were stratified by histology (adenocarcinoma versus others), gender (male versus female), and smoking history (smoker versus nonsmoker). Treatment continued until a withdrawal or dose-interruption criterion was met. These criteria included progressive disease (PD), unacceptable toxicity, protocol noncompliance, or voluntary discontinuation by the patient.

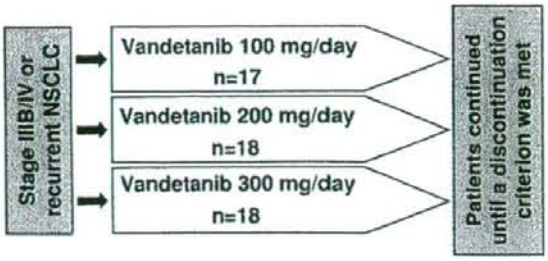

FIGURE 1. Study design.

Efficacy

The primary objective of the study was to determine ORR with vandetanib monotherapy, using the Response Evaluation Criteria in Solid Tumors (RECIST); assessments were performed at baseline and every 4 weeks for the first 24 weeks of treatment, and then every 8 weeks until withdrawal. A confirmed complete response or partial response (PR) was considered to be an objective tumor response. Investigator assessment of best overall tumor response was used for the primary analysis and these assessments were subsequently submitted to AstraZeneca for review by the response evaluation committee. Secondary efficacy endpoints included time to progression (TTP), duration of response (the time interval between the date of first documented objective tumor response until the date of PD or death), and disease control rate (DCR) for each dose of vandetanib. Time to progression was calculated from the date of randomization until the date of PD or death (in the absence of progression) and estimated using the Kaplan–Meier method. DCR was defined as confirmed complete response, PR, or stable disease (SD) ≥8 weeks.

Safety and Tolerability

Safety was assessed by monitoring for adverse events (AEs) and collecting laboratory data. All AEs were collected for up to 30 days after the last dose of vandetanib and were graded according to Common Terminology Criteria for Adverse Events (CTCAE, version 3). Unless otherwise clinically indicated, 12-lead electrocardiograms were performed twice at screening, weekly for the first 8 weeks of treatment, and then once every 4 weeks thereafter. Vandetanib treatment was interrupted following: a single QTc measurement ≥550 milliseconds; 2 consecutive QTc measurements ≥500 milliseconds but <550 milliseconds; an increase of ≥100 milliseconds from baseline; or an increase of ≥60 milliseconds from baseline QTc to a QTc value ≥460 milliseconds. Upon resolution of QTc prolongation, vandetanib treatment was recommenced at a reduced dose.

Pharmacokinetics

To investigate the pharmacokinetic (PK) profile of vandetanib, blood samples were collected on the same days as scheduled electrocardiogram measurements. Plasma concentrations of vandetanib were determined using reversed-phase liquid chromatography–mass spectrometry. The col-

lected data were related to a nonlinear mixed effects model to estimate population PK using NONMEM V (v 1.1).

Tumor Biomarkers

An exploratory objective of this study was to investigate how variations in copy number or mutational status of the *EGFR* gene affect tumor response in advanced NSCLC patients receiving vandetanib treatment. Tumor biopsy samples were obtained from consenting patients, formalin-fixed, and embedded in paraffin. Gene copy number was investigated by fluorescence in situ hybridization using the LSI EGFR SpectrumOrange/CEP 7 SpectrumGreen probe (Vysis, Abbott Laboratories, IL) according to a previously published method.[15] Tumor samples had a high *EGFR* gene copy number if there was high gene polysomy (≥4 *EGFR* gene copies in ≥40% of tumor cells) or gene amplification (presence of tight *EGFR* gene clusters, an *EGFR* gene to chromosome 7 ratio of ≥2, or ≥15 copies of the *EGFR* gene per tumor cell in ≥10% of analyzed cells).

EGFR mutations were analyzed by DNA sequencing of exons 19–21, and additionally by using the amplification refractory mutation system (ARMS) assay to detect the exon 21 L858R point mutation and the most common exon 19 deletion (del G2235–A2249).[16]

Plasma Biomarkers

Plasma samples were collected from patients at baseline, day 29, and day 57, and stored at −70°C. The concentrations of the following angiogenic markers were determined by colorimetric Sandwich ELISA (R&D Systems, Minneapolis, USA): VEGF (Cat. #DVE00), the soluble angiopoietin receptor Tie-2 (Cat. #DTE200), and VEGFR-2 (Cat. #DVR200).

RESULTS

Patient Characteristics

Fifty-three patients were recruited from eight centers in Japan between December 27, 2004, and September 30, 2005. All were randomized on this study and received study drug. Patient characteristics and baseline demographics were generally similar in the three arms, and the patient populations were considered to be appropriate for the dose-finding objectives of this study (Table 1). At the time of data cut-off (23 January 2006), 11 patients were ongoing; PD was the most common reason for discontinuation (n = 35). Other reasons for discontinuation were AEs (n = 6) and withdrawal of consent (n = 1).

Efficacy

The overall ORR was 13.2% (95% CI: 5.5–25.3%) (7 of 53 patients), and all 7 responders were PRs (Table 2). According to vandetanib dose received, the ORRs were 17.6% (95% CI: 3.8–43.4%) (3 of 17 patients; 100 mg), 5.6% (95% CI: 0.1–27.3%) (1 of 18 patients; 200 mg), and 16.7% (95% CI:3.6–41.4%) (3 of 18 patients; 300 mg). In all cases, the response evaluation committee assessment of tumor responses was similar to the investigator assessments. The characteristics of those patients who achieved a PR are described in Table 3. Secondary efficacy assessments are presented in Table 2 and Figure 2.

Safety

Overall, the most common AEs were rash, diarrhea, hypertension, and QTc prolongation (Table 4). In general, no major differences were observed in the incidences of

TABLE 1. Patient Demographic and Baseline Characteristics (Full Analysis Set)

	Vandetanib 100 mg/d (n = 17)	Vandetanib 200 mg/d (n = 18)	Vandetanib 300 mg/d (n = 18)	Total (n = 53)
Median age, yr (range)	58 (30–78)	61 (43–77)	61 (44–77)	60 (30–78)
Male (%)	11 (64.7)	12 (66.7)	11 (61.1)	34 (64.2)
Female (%)	6 (35.3)	6 (33.3)	7 (38.9)	19 (35.8)
Smoking history[a]				
No (%)	5 (29.4)	8 (44.4)	7 (38.9)	20 (37.7)
Yes (%)	12 (70.6)	10 (55.6)	11 (61.1)	33 (62.3)
WHO performance status 0/1/2	5/12/0	7/11/0	6/12/0	18/35/0
Previous chemotherapy				
One regimen (%)	13 (76.5)	9 (50.0)	14 (77.8)	36 (67.9)
Two regimens (%)	4 (23.5)	9 (50.0)	4 (22.2)	17 (32.1)
Staging (%)				
IIIB	2 (11.8)	3 (16.7)	1 (5.6)	6 (11.3)
IV	14 (82.4)	12 (66.7)	15 (83.3)	41 (77.4)
Recurrent	1 (5.9)	3 (16.7)	2 (11.1)	6 (11.3)
Histology (%)				
Squamous	5 (29.4)	6 (33.3)	4 (22.2)	15 (28.3)
Adenocarcinoma	11 (64.7)	12 (66.7)	12 (66.7)	35 (66.0)
Other	1 (5.9)	0	2 (11.1)	3 (5.7)
Brain metastasis at study entry (%)	4 (23.5)	3 (16.7)	5 (27.8)	12 (23.6)

[a] No, patients who have smoked <100 cigarettes in their lifetime; Yes, patients who have smoked >100 cigarettes in their lifetime.

TABLE 2. Efficacy Summary

	Vandetanib 100 mg/d (n = 17)	Vandetanib 200 mg/d (n = 18)	Vandetanib 300 mg/d (n = 18)
Primary efficacy assessment			
Best response (RECIST)			
Partial response, n (%)	3 (17.6)	1 (5.6)	3 (16.7)
Stable disease ≥8 wk, n (%)	5 (29.4)	6 (33.3)	8 (44.4)
Disease progression, n (%)	9 (52.9)	10 (55.6)	7 (38.9)
Not evaluable, n (%)	0	1 (5.6)	0
Secondary efficacy assessments			
Disease control ≥8 wk, n (%)	8 (47.1)	7 (38.9)	11 (61.1)
Duration of response (wk)			
Median (range)[a,b]	na	na	15.9 (7.3–20.1)
Time to progression (wk)			
Median (range)[a]	8.3 (4.0–40.7)	12.3 (0–40.3)	12.3 (1.4–32.7)
No. of events	12	13	13

na, not applicable; RECIST, Response Evaluation Criteria in Solid Tumors.
[a] Median estimated using the Kaplan–Meier method.
[b] This parameter could not be estimated in the 100 and 200 mg/d arms owing to the lack of progressions by the date of data cut-off.

TABLE 3. Characteristics of Patients Who Were Partial Responders

Treatment (initial dose)	Gender	Age (yr)	Smoking History[a]	Histology	Previous Chemotherapy Regimens	Time to PR (d)	Duration of Response (d)
100 mg	Male	65	Yes	Adenocarcinoma	1	28	204[b]
100 mg	Female	72	No	Adenocarcinoma	1	78	141[b]
100 mg	Male	52	No	Adenocarcinoma	1	143	141[b]
200 mg	Female	69	No	Adenocarcinoma	1	26	140[b]
300 mg[c]	Male	69	Yes	Adenocarcinoma	2	31	51
300 mg	Female	68	No	Adenocarcinoma	1	28	81[b]
300 mg	Female	55	No	Adenocarcinoma	1	82	141

[a] No, patients who have smoked <100 cigarettes in their lifetime; Yes, patients who have smoked >100 cigarettes in their lifetime.
[b] Censored on the day of last tumor evaluation due to absence of disease progression (response ongoing at data cut-off).
[c] Patient started study treatment with 300 mg and the treatment was stopped 29 d after the start due to QTc prolongation. The patient re-started at a reduced dose level (200 mg) 35 d after the start.

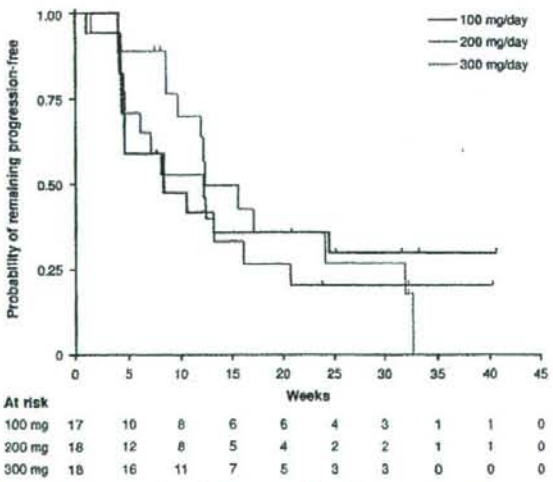

FIGURE 2. Kaplan–Meier curve for time to progression.

the common AEs across the three vandetanib arms, although the incidences of diarrhea, constipation, and abnormal hepatic function were numerically higher in the vandetanib 300 mg arm compared with the 100 or 200 mg arms. A dose-dependent increase in the incidence of CTC grade 3 and 4 events was observed; the incidence of these events in the 100, 200, and 300 mg dose arms were 29.4% (5 of 17 patients), 38.9% (7 of 18 patients), and 66.7% (12 of 18 patients), respectively. Of the 24 CTC grade 3 or 4 AEs considered by the investigator to be vandetanib-related, hypertension (100 mg, n = 4; 200 mg, n = 3; 300 mg, n = 3), and asymptomatic QTc prolongation (200 mg, n = 1; 300 mg, n = 1) were reported in more than one patient. Across the three dose levels, the AEs in this study were generally manageable with symptomatic treatment, dose interruption, or reduction.

Six patients discontinued vandetanib because of an AE considered by the investigator to be vandetanib-related: cryptogenic organizing pneumonia (COP), hepatic steatosis, and photosensitivity reaction (each n = 1, 200 mg arm); QTc prolon-

TABLE 4. Number of Patients With Most Commonly Reported Adverse Events (Occurring in ≥10% Across all Treatment Groups), Regardless of Causality

MedDRA Preferred Term[a]	Vandetanib 100 mg/d (n = 17)	Vandetanib 200 mg/d (n = 18)	Vandetanib 300 mg/d (n = 18)	Total (n = 53)
Rash (%)	10 (59)	9 (50)	9 (50)	28 (53)
CTC grade 3/4	0/0	1/0	0/0	1/0
Diarrhea (%)	8 (47.1)	8 (44)	11 (61)	27 (51)
CTC grade 3/4	0/0	1/0	1/0	2/0
Hypertension (%)	8 (47)	10 (56)	7 (39)	25 (47)
CTC grade 3/4	4/0	3/0	3/0	10/0
ECG QTc prolonged (%)	4 (24)	9 (50)	8 (44)	21 (40)
CTC grade 3/4	0/0	1/0	1/0	2/0
Photosensitivity reaction (%)	2 (12)	5 (28)	5 (28)	12 (23)
CTC grade 3/4	0/0	0/0	0/0	0/0
Nasopharyngitis (%)	3 (18)	4 (22)	4 (22)	11 (21)
CTC grade 3/4	0/0	0/0	0/0	0/0
Dry skin (%)	2 (12)	4 (22)	5 (28)	11 (21)
CTC grade 3/4	0/0	0/0	0/0	0/0
Nausea (%)	3 (18)	3 (17)	4 (22)	10 (19)
CTC grade 3/4	0/0	0/0	0/0	0/0
Constipation (%)	2 (12)	1 (6)	6 (33)	9 (17)
CTC grade 3/4	0/0	0/0	0/0	0/0
Fatigue (%)	4 (24)	1 (6)	2 (11)	7 (13)
CTC grade 3/4	0/0	0/0	0/0	0/0
ECG QT prolonged (%)	1 (6)	2 (11)	4 (22)	7 (13)
CTC grade 3/4	0/0	0/0	0/0	0/0
Hepatic function abnormal (%)	1 (6)	1 (6)	4 (22)	6 (11)
CTC grade 3/4	0/0	0/0	1/0	1/0
Hematuria (%)	2 (12)	2 (12)	2 (12)	6 (11)
CTC grade 3/4	0/0	0/0	0/0	0/0

[a] MedDRA version 8.1.

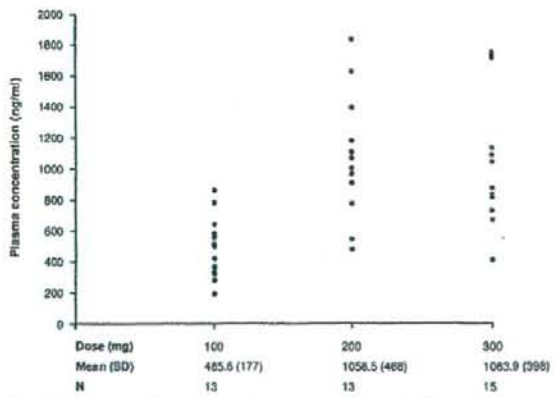

FIGURE 3. Observed maximum vandetanib plasma concentration at day 28. Patients who received dose reduction within the first 28 days were excluded.

gation, alanine aminotransferase increased, and erythema multiforme (each n = 1, 300 mg arm). Only COP was classed as a serious AE. Six patients had vandetanib dose reductions due to AEs (100 mg, n = 1; 200 mg, n = 1; 300 mg, n = 4).

Seven patients experienced eight respiratory-related events (COP, dyspnoea, interstitial lung disease [ILD], hypoxia, pneumonitis [all n = 1], and pneumonia [n = 3]). The incidence of these events in the three dose levels was 5.9% (1 of 17 patients; 100 mg), 11.1% (2 of 18 patients; 200 mg) and 22.2% (4 of 18 patients; 300 mg), respectively. Four of these events were considered to be related to vandetanib (COP, ILD, pneumonia [n = 2]). The ILD event was reported in a 64-year-old male patient in the 300 mg arm and resulted in patient death. This event was reported 8 days after vandetanib 300 mg was discontinued because of disease progression. No postmortem examination was performed and the investigator and a third-party physician considered the cause of death to be ILD.

All QTc prolongation was asymptomatic and manageable with dose interruption and/or reduction. The incidence of QTc prolongation was lower in the vandetanib 100 mg (24%) arm compared with the 200 mg (50%) and 300 mg (44%) arms. The mean change in QTc interval from baseline to week 3 (when maximum prolongation was observed) in the 100, 200, and 300 mg arms was +14 milliseconds (range, −25 to 29 milliseconds), +16.5 milliseconds (range, −36 to 49 milliseconds), and +27.6 milliseconds (range, 4 to 51 milliseconds), respectively. Protocol-defined QTc prolongation determined at the treatment site resulted in dose reduc-