Advanced lung cancer (non-small cell lung cancer)

First-line chemotherapy

The efficacy of lung cancer chemotherapy with cytotoxic anticancer agents has reached a plateau,[2–4] and under the present circumstances it is difficult to expect any cytotoxic novel anticancer agents to become available although some hope exists in assessment of the efficacy of pemetrexed against adenocarcinoma,[5] the significance of TS1,[6], etc. The statement of "the results of treatment with 2-drug combinations consisting of cisplatin (CDDP) or carboplatin (CBDCA) and a new drug are the same no matter which of them is used" is a basic assumption everywhere in the world, but a close examination of the data reveals the following. (1) In the Eastern Cooperative Oncology Group (ECOG) study CDDP + Gemcitabine (GEM) prolonged progression free survival (PFS) significantly more than the other three regimens,[1] and (2) in the Four Arm Clinical Trial (FACS) trial, which was conducted in Japan, CDDP + GEM yielded approximately the same overall survival (OS) as CDDP + Irinotecan (CPT-11) did, and the results of treatment tended to be better than with CDDP + NBV or CBDCA + paclitaxel(PTL).[4] (3) In the South Western Oncology Group (SWOG) trial the survival curves for CDDP + NBV and CBDCA + PTL were exactly the same.[3] (4) In the Tax326 study, CDDP + docetaxel (DTX) yielded treatment results that were statistically significantly superior to those obtained with CDDP + NBV.[7] (5) In a study conducted in Japan comparing CDDP + DTX with CDDP + Vindesin (VDS), the CDDP + DTX combination statistically significantly prolonged survival time in comparison with CDDP + VDS.[8] When all of this evidence is considered together, if the desire is to obtain more favorable results of treatment by clinical trials among first-line chemotherapies for advanced lung cancer, then one of three combinations, CDDP + GEM, CDDP + CPT-11, or CDDP + DTX, is chosen. However, in actual medical practice, treatment arms are selected out of consideration for such conditions as toxicity profile and ease of use on an outpatient basis, and choices of treatment for use in combination with radiation therapy and surgery are made with compliance in mind. The only regimen for which evidence is available as postoperative adjuvant therapy is CDDP + NBV[9,10] with the exception of Uracil-Futoraful (UFT) against stage II adenocarcinoma in Japanese study.[11] The debate in regard to CBDCA or CDDP has continued for many years, and a consensus has been reached that while regimens that contain CDDP are slightly superior to regimens containing CBDCA in efficacy, toxicity is more frequent and severe.[12,13] Thus, when treatment is cure-oriented, CDDP is chosen, and when the objective is palliation, CBDCA is chosen. In terms of duration of treatment and number of cycles, four courses at 3- to 4-week intervals are sufficient, and no efficacy of intensification therapy or maintenance therapy has been observed. Moreover, while improvement in response rate is achieved when an additional drug is added to the 2-drug combination, toxicity also becomes severer, and no improvement in final survival is obtained.[1]

Expectations of molecularly targeted therapy

When Epidermoid Growth Factor Receptor Thyrosine kinase Inhibitors (EGFR-TKIs) became available, a great progress was expected in the treatment of non-small cell lung cancer.[14,15] However, lung cancer investigators were surprised to find that according to the results of the Iressa NSCLC trial Assessing Combination Treatment (INTACT) 1 and 2 studies[16,17] and the TALENT and TRIBUTE studies[18,19] EGFR-TKIs provided no efficacy in addition to standard chemotherapy. Because the response rate to EGFR-TKIs in Western populations was a mere 10% or less,[14,15,20] some did not consider these results to be surprising, however, examination of the results of subsequent clinical trials in which the subjects were Japanese in which EGFR-TKI shows 25–30% of response rate indicated that it might not necessarily be so simple.[21] It certainly is true that the significance of combined use with chemotherapy as first-line therapy for unselected patients was denied, and it seems that in the future assessment as first-line therapy will be limited to patients who have been selected according to biomarkers or clinical characteristics.[22–25] Patient entry in the Iressa pan Asian trial (IPASS) trial has already been completed, and in the West Japan Oncology Group (WJOG), a comparative study has been conducted on patients with postoperative recurrence who had mutations. In these trials the control group is receiving standard chemotherapy. The survivals of patients with EGFR mutation treated with EGFR-TKI was significantly better compared with that without EGFR mutation. The crucial question remains, however, whether EGFR mutation is not only a prognostic factor but also a predictive factor for response to EGFR-TKIs resulting in the survival prolongation. It will also be an interesting research task that may show how effective it is in relation to anticancer agents against lung cancer that has EGFR mutations.

The ECOG4599 study (855 cases)[26] and Avastin in lung (AVAIL) trial (1050 cases)[27] are large comparative studies of bevacizumab. The ECOG4599 study assessed CBDCA + PTL ± bevacizumab (15 mg/kg), and the Avail trial assessed CDDP + gemcitabine ± bevacizumab (7 mg/kg or 15 mg/kg). In the ECOG4599 study both progression free survival (PFS) and OS were significantly better in the CBDCA + PTL + bevacizumab group, and the response rate was twice as high.[26] In the Avail trial, on the other hand, the response rate did not differ much when bevacizumab was added to CDDP + gemcitabine, and although PFS was better in both the 7.5 mg/kg group and 15 mg/kg group when bevacizumab was added, no data on difference in OS was available.[27] The results of ECOG4599 seemed to show that bevacizumab intensified the effect of anticancer drug, but that could not necessarily be concluded from the results of the AVAIL study. No consensus has been reached in Japan regarding whether to make combined treatment with two anticancer drugs + bevacizumab the standard treatment for advanced non-small cell lung cancer (NSCLC) based on these results.

Second-line treatment of advanced non-small cell lung cancer

DTX is the standard second-line therapy for advanced non-small cell cancer.[28] In Western countries, pemetrexed has

been reported to have similar efficacy and mild adverse effects.[29] Four comparative studies have been conducted to rank EGFR-TKIs as second-line therapy. The Iressa survival evaluation in lung cancer (ISEL) study and BR21 study compared gefitinib and erlotinib, respectively, with placebo, and while the *P* value in the ISEL study was close to being significant, it was a negative study,[30] whereas the BR21 study was a positive study.[31] Post-stratification in the ISEL study revealed a significant difference in the Asian subjects,[32] but there was no difference at all in the Western subjects. In the BR-21 study, on the other hand, survival time in the erlotinib group was superior in both the Asian subjects and the Western subjects.[31] In both studies survival time in the EGFR-TKI groups was statistically significantly longer in never smokers. The hazard ratio for males was slightly better than for females.[30,31] The results of a phase II trial of gefitinib and erlotinib in patients with EGFR mutations showed high response rates of 75–80% in both of them.[22–25] On the other hand, from the results of BR-21 study, it may be possible that erlotinib is capable of exhibiting efficacy linked to a survival benefit even against in patients with EGFR-TK that does not have mutations. However, this tentative conclusion needs to be verified by a clinical trial in which biomarkers are used. Two clinical trials comparing gefitinib and DTX were conducted in second-line and third-line patients. The V15-32 trial was a comparative study of approximately 500 patients that was conducted in Japan.[21] The response rate in the gefitinib group was approximately twice as high as in the DTX group, but it was impossible to demonstrate non-inferiority of gefitinib compared with DTX, and the survival rate at an early stage such as less than one year, the confidence interval for therapeutic effects indicated that DTX was better than gefitinib. Three reasons can possibly be postulated for these findings. The first is that gefitinib is more toxic, and the gefitinib group died sooner. The second is that tumor progressed as a result of gefitinib administration, and the gefitinib group died sooner. Both of these hypotheses seem to be false from the data of the clinical trial. The third possibility is that survival time in the DTX group was better, because DTX had higher antitumor activity than gefitinib against the tumors as a whole, and this hypothesis is most possible. Although half of patients of DTX group have been crossed over to gefitinib after completion of protocol study, it is unlikely that the gefitinib after DTX failure influenced the survival of DTX group during twelve months after the start of therapy. It is even more interesting that among the cases that it was possible to analyze for EGFR mutations, median survival time (MST) was better in the cases that had an EGFR mutation than in the cases that did not, and this finding was observed both in the DTX group as well as in the gefitinib group (unpublished data). These data appear to be very interesting biologically and pharmacologically in terms of whether EGFR mutations is only one of prognostic factors, or whether they are also predictors of the efficacy of taxanes, such as DTX.

The endpoint of the INTEREST trial,[33] whose results were presented at the World conference for lung cancer (WCLC) 2007 conducted in Seoul, was overall survival time. A total of 1466 patients were enrolled during the period from March 2004 to February 2006, and the non-inferiority of the gefitinib group compared the docetaxel group was demonstrated with a hazard ratio of 1.020 (96% CI: 0.905–1.150). Superiority of the gefitinib group was not observed in the Fluorescence in situ hybridization (FISH)–positive cases. The point that should be focused in this study is that all of the predictors of efficacy identified in the gefitinib versus placebo studies, including adenocarcinoma, women, Asian person, and non-smoker, disappear in the comparison with the DTX group.[33] As commented by Shepherd, the results suggest that these clinical characteristics, EGFR-FISH positivity, and mutation positivity may be efficacy predictors for DTX as well as gefitinib. Thus, both the V15-32 and the INTEREST trial can be concluded to have unexpectedly yielded the similar results. It is not clear why the biomarkers have not only to be prognostic factors but also to be efficacy predictors with both docetaxel and gefitinib. It will be very interesting to see the results of the IPASS trial (comparative study of first-line gefitinib versus CDDP + PTL in Asian, non-smoker and adenocarcinoma), whose patient enrollment has now been completed. In any event, if taxanes are assumed to be more effective in women, adenocarcinoma, and non-smokers, investigation of the reasons for these findings may be linked to identification of new targets for cancer drug therapy. Both the BR21 study and the Interest trial were studies that were conducted without any patient selection including biomarker selection and in which Western persons, who have a low response rate and EGFR mutation rate, accounted for a large number of the subjects, and their significance needs to be interpreted with care.

Chemotherapy of non-small cell cancer in the elderly

The mean age of lung cancer patients is 60–65 years old, and it has been rising with the aging of the population. The elderly generally have low tolerance for anticancer drugs, and it appears difficult to administer the usual doses of anticancer agents to them regularly. Since no differences in survival time were found between young and elderly patients who participated in an identical protocol in Western countries,[34] especially in the United States, there did not appear to be any need to use a special protocol to evaluate elderly persons. However, subjects 65 years of age and older accounted for 39% of the lung cancer patients enrolled in the clinical trial conducted by SWOG from 1993 to 1996, and that percentage was much lower than the 66% of lung cancer patients in the US accounted for by those 65 years of age and older in the same period.[35] Thus, there is a strong likelihood that some sort of patient selection was involved, and thus judging on the basis of the clinical trial data alone might lead to a misunderstanding. Adequate treatment of the elderly with an effective anticancer agent while avoiding severe toxicity would seem to result in successful treatment.[36,37] Not enough results have been available in regard to the need for platinum mainly with CDDP. In the JCOG study weekly DTX and weekly DTX + CDDP were compared to assess the significance of platinum combination therapy.[38] In the second interim analysis comparison between the 70- and 74-year-old group and the 75 years old and over group showed that the results of treatment in the weekly DTX + CDDP were better in the 70- to 74-year-old group, and since some interaction was found between age and

treatment group, there was an advisory from the Independent data monitoring committee (IDMC) to discontinue the trial, and it was stopped in the early phase. This study aimed at a landmark study that was able to show that if cisplatin administration is modified, favorable results of treatment can be obtained even in elderly lung cancer patients, and it is unfortunate that because of being discontinued in the early phase, only a small number of cases could be analyzed. It was a post-study stratification analysis and no conclusion could be drawn. In the second interim analysis of all cases, the survival of the weekly DTX + CDDP group was favorable, and questions remain as to why the IDMC advised stopping the trial based on the additional analysis, despite the fact that the early-phase discontinuation criteria were not met. The JCOG and WJOG are currently conducting a comparative study of weekly DTX + CDDP versus DTX alone (administration every 3 weeks), and it is hoped that landmark results will be obtained by this study.

Localized lung cancer

Adjuvant chemotherapy

The field of adjuvant chemotherapy in non-small cell lung cancer has changed totally over the last 5 years. Until ASCO2003, there was no evidence except for a meta-analysis of MRC, that chemotherapy may have a role. However, beginning with the presentation of International Adjuvant Lung Cancer Trial (IALT) study by LeChavalier,[40] there have been five randomized controlled studies that have been reported to show improved survival. According to the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis of 4584 patients who received cisplatin-based adjuvant chemotherapy, efficacy was observed only in Stage II and Stage IIIA non-small cell cancer.[39] CDDP + VNB was used as adjuvant chemotherapy in both the BR-10 and Adjuvant Navelbine International Trialist Association (ANITA) trials,[9,10] which yielded positive data, but the Cancer and Leukemia Group B (CALGB) study (Stage IB), in which CBDCA + PTL[41] was used, and Italian study in which mitomycin (MMC) + Ifosfamamide (Ifo) + CDDP was used[42] yielded negative data. By contrast, the results from Japan showed that UFT is effective in Stage IB adenocarcinoma patients,[11] and it was found to also be capable of improving the cure rate in stage IA if the tumor diameter was 2 cm or more. Despite the fact that we have five studies actually showing that adjuvant chemotherapy plays a role, there has clearly been conflicting data with regard to which subsets deserve benefit. There is some evidence that adjuvant chemotherapy is effective in stage II and IIIA, there is no evidence that adjuvant chemotherapy is effective in stage IA and 1B disease except for Japanese trial. Sufficient results have not been obtained as to whether these adjuvant chemotherapies are effective in patients with performance status (PS)2 or more or in patients who are 75 years old or over. Among the platinum doublets, CDDP + GEM, CDDP + DTX, CDDP + CPT-11, etc. have shown a potent antitumor effect against advanced cancer, and it seems they should be used for cure-oriented therapy, however, no results of adjuvant chemotherapy have been obtained. Western investigators have also claimed that CDDP, and not CBDCA, should be used for adjuvant chemotherapy, but that seems unrealistic, and maintaining compliance can be cited as a problem with adjuvant chemotherapy. Four courses of postoperative combination chemotherapy seem to be standard, but in reality compliance is about 50–60%.[9,10] Regimens that are expected to be capable of maintaining adequate compliance even postoperatively, such as pemetrexed + CDDP,[5] S1 + CDDP,[43] etc., have recently been developed and have attracted interest. It seems that in the future comparative studies with patient groups that have been selected according to disease stage and histological type will be necessary. Recently Olaussen reported that patients with completely resected non-small cell lung cancer and ERCC1 negative tumors appear to benefit from adjuvant cisplatin-based chemotherapy, whereas patients with ERCC1-positive tumors do not.[44] Clinical trials selected by pharmacogenomics will be essential in future adjuvant clinical trials of lung cancer. Comparative studies of molecularly targeted therapy in patients selected according to their molecular biological characteristics are also in the process of being implemented. The Randomized Double-Blind Trial in Adjuvant NSCLC with Tarceva (RADIANT study) is an ongoing, phase III clinical trial of adjuvant erlotinib in resected NSCLC with EGFR overexpression by immunohistochemistry (IHC) or EGFR gene amplification by Fluorescence in situ hybridization (FISH). On the other hand, it will also be interesting to see how much drugs, such as bevacizumab, that act on the tumor environment contribute to improving the results of treatment. However, such type of drugs display dangerous toxicity profile to be safely introduced in the contact of a patients who just received radical surgery and potentially cured.

Preoperative chemotherapy

Evaluations of preoperative chemotherapy have varied. Roth and Rossel obtained promising data,[45,46] but some studies, such as the Japanese Clinical Oncology Group (JCOG) study, have yielded completely negative data.[47] All of them have been comparative studies on small numbers of subjects. Promising results were subsequently obtained in fairly large numbers of subjects, as can be seen in the report by Depiere et al.[48] and, recently, in the report by Pisters et al.[49] By contrast, according to a multicenter cooperative study conducted by Medical Research Council (MRC), Vereniging voor Artsen Longziekten en Tuberculose (NVALT), and European Organization for Research and Treatment of Cancer (EORTC) ($n = 519$), preoperative cisplatin chemotherapy was feasible and safe, and although with a 45% response rate and 20% down staging the results were favorable, it did not produce any improvement in PFS or OS.[50] It seemed that the most potent cisplatin-based 2-drug combination therapy should be used as preoperative chemotherapy. There is no clear consensus regarding the number of times to perform preoperative chemotherapy. The greatest difficulty lies in the imprecision of preoperative staging, and it is not suitable for a meta-analysis of various studies like postoperative chemotherapy. It is difficult to compare the results of treatment with postoperative chemotherapy, but the current consensus seems to be that little progress is seen even when chemotherapy is performed preoperatively. We hope that, the same as in breast cancer, the results of chemotherapy will improve, and that the time will come when its significance will be assessed again.

Locally advanced cancer

The gold standard for the treatment of locally advanced cancer is radiochemotherapy, and the median survival time is approximately 20 months.[51–53] A consensus in relation to surgical treatment following radiochemotherapy has been achieved by Albain and the EORTC studies. According to the results of the Albain's study,[54] adding surgical treatment after radiochemotherapy resulted in an improvement in curative treatment rate in the lobectomy patients, but the opposite was observed in the patients who underwent pneumonectomy, and their survival time was shortened although these results have been obtained by post hoc analysis. The EORTC study[50] also showed no added effect of surgical treatment overall, but in the pneumonectomy group the addition of surgical treatment instead brought about a reduction in the results of treatment. These results need to be borne in mind if further study is planned.

An effect of treatment with second-line anticancer drugs has been demonstrated as a result of the introduction of numerous effective anticancer agents. Results showing that intensification therapy with docetaxel contributed to prolonging life even when used as adjuvant chemotherapy for locally advanced cancer have been published by SWOG and have attracted attention, but that study was a phase II study.[55] Docetaxel was assessed for an additive effect by a phase III study in the Hoosier Oncology Group (HOG) Lun 01-24/US oncology (USO) 02-033 trial, but the data were all negative,[56] and no additive effect of docetaxel was detected. Thus, at present there does not appear to be any change in the gold standard for locally advanced cancer. No favorable results of molecularly targeted drug therapy have been obtained either, and it is particularly noteworthy that results obtained for the use of gefitinib after radiochemotherapy have shown that the outcome was poor (SWOG0023).[57] It appears that it will become possible to use a variety of molecularly targeted drugs in the future, but not many patients with locally advanced cancer are available to serve as subjects of clinical trials, and after a thorough discussion, it seems necessary to conduct studies that will lead to clear conclusions.

Conflict of interest statement

I have no potential conflict of interest to disclose except for stock option of Takeda pharmaceutical company.

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ORIGINAL REPORT

Phase III Study, V-15-32, of Gefitinib Versus Docetaxel in Previously Treated Japanese Patients With Non–Small-Cell Lung Cancer

Riichiroh Maruyama, Yutaka Nishiwaki, Tomohide Tamura, Nobuyuki Yamamoto, Masahiro Tsuboi, Kazuhiko Nakagawa, Tetsu Shinkai, Shunichi Negoro, Fumio Imamura, Kenji Eguchi, Koji Takeda, Akira Inoue, Keisuke Tomii, Masao Harada, Noriyuki Masuda, Haiyi Jiang, Yohji Itoh, Yukito Ichinose, Nagahiro Saijo, and Masahiro Fukuoka

From the National Kyushu Cancer Center, Fukuoka; National Cancer Center Hospital East, Chiba; National Cancer Center Hospital; Tokyo Medical University Hospital, Tokyo; Shizuoka Cancer Center, Shizuoka; Kinki University School of Medicine; Osaka Medical Center for Cancer and Cardiovascular Diseases; Osaka City General Hospital; AstraZeneca KK, Osaka; Shikoku Cancer Center, Ehime; Hyogo Medical Center for Adults; Kobe City General Hospital, Hyogo; Tokai University Hospital, Kanagawa; Tohoku University Hospital, Miyagi; Hokkaido Cancer Center, Hokkaido; and Kitasato University School of Medicine, Kanagawa, Japan.

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Corresponding author: Yukito Ichinose, MD, Department of Thoracic Oncology, National Kyushu Cancer Center, 3-1-1 Notame Minami-ku, Fukuoka, 811-1395, Japan; e-mail: yichinos@nk-cc.go.jp.

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ABSTRACT

Purpose
This phase III study (V-15-32) compared gefitinib (250 mg/d) with docetaxel (60 mg/m^2) in patients (N = 489) with advanced/metastatic non–small-cell lung cancer (NSCLC) who had failed one or two chemotherapy regimens.

Methods
The primary objective was to compare overall survival to demonstrate noninferiority for gefitinib relative to docetaxel. An unadjusted Cox regression model was used for the primary analysis.

Results
Noninferiority in overall survival was not achieved (hazard ratio [HR], 1.12; 95.24% CI, 0.89 to 1.40) according to the predefined criterion (upper CI limit for HR ≤ 1.25); however, no significant difference in overall survival (P = .330) was apparent between treatments. Poststudy, 36% of gefitinib-treated patients received subsequent docetaxel, and 53% of docetaxel-treated patients received subsequent gefitinib. Gefitinib significantly improved objective response rate and quality of life versus docetaxel; progression-free survival, disease control rates, and symptom improvement were similar for the two treatments. Grades 3 to 4 adverse events occurred in 40.6% (gefitinib) and 81.6% (docetaxel) of patients. Incidence of interstitial lung disease was 5.7% (gefitinib) and 2.9% (docetaxel). Four deaths occurred due to adverse events in the gefitinib arm (three deaths as a result of interstitial lung disease, judged to be treatment related; one as a result of pneumonia, not treatment related), and none occurred in the docetaxel arm.

Conclusion
Noninferiority in overall survival between gefitinib and docetaxel was not demonstrated according to predefined criteria; however, there was no statistically significant difference in overall survival. Secondary end points showed similar or superior efficacy for gefitinib compared with docetaxel. Gefitinib remains an effective treatment option for previously treated Japanese patients with NSCLC.

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INTRODUCTION

In Japan, patients with advanced non–small-cell lung cancer (NSCLC) who fail first-line platinum-based therapy often receive second-line docetaxel.[1,2] However, docetaxel has been associated with significant levels of toxicity, especially grades 3 to 4 neutropenia (40% to 67% and 63% to 73% for docetaxel 75 mg/m^2 and 60 mg/m^2, respectively).[1-4] In North America and in European countries, docetaxel,[3,4] pemetrexed,[2] and erlotinib[5] are approved second-line treatments for NSCLC.[3,6]

In phase II trials (IDEAL 1 and 2), the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor gefitinib (Iressa; AstraZeneca, London, United Kingdom) 250 mg/d showed response rates of 12% to 18% and median survival of 7.0 to 7.6 months in patients who had pretreated advanced NSCLC.[7,8] A subset of Japanese patients in IDEAL 1 demonstrated a higher response rate (27.5%) and longer median survival (13.8 months) compared with the overall population.[9] A phase III study (Iressa Survival Evaluation in Lung Cancer) in patients who had previously treated refractory NSCLC

showed that gefitinib was associated with a nonsignificant trend toward improved overall survival versus placebo.[10] Preplanned subgroup analyses demonstrated a statistically significant increase in survival for gefitinib compared with placebo in patients of Asian origin (hazard ratio [HR], 0.66; 95% CI, 0.48 to 0.91; $P = .010$; median survival, 9.5 *v* 5.5 months) and in never-smokers (HR, 0.67; 95% CI, 0.49 to 0.92; $P = .012$; median survival, 8.9 *v* 6.1 months).[10,11]

Reported here is the first phase III study to compare the effects of targeted therapy (gefitinib) with chemotherapy (docetaxel) on overall survival in Japanese patients with advanced/metastatic (stages IIIB to IV) or recurrent NSCLC who failed one or two chemotherapy regimens.

METHODS

Study Design

This multicenter, randomized, open-label, postmarketing clinical study (V-15-32) compared gefitinib with docetaxel in Japanese patients who had pretreated, locally advanced/metastatic (stages IIIB to IV) or recurrent NSCLC. Patients were randomly assigned by using stratification factors of sex (female *v* male), performance status (PS; 0 to 1 *v* 2), histology (adenocarcinoma *v* others), and study site.

The primary end point was overall survival, and the study aimed to show noninferiority of gefitinib versus docetaxel. Secondary end points were progression-free survival (PFS), time to treatment failure, objective response rate (ORR), disease control rate (DCR), quality of life (QoL), disease-related symptoms, safety, and tolerability.

A late protocol amendment included exploratory end points, such as EGFR gene copy number, protein expression, and mutation status of tumor tissue.

Patients

Patients age 20 years or older were eligible if they had the following: histologically or cytologically confirmed NSCLC (stages IIIB to IV) not amenable to curative surgery or radiotherapy, or postoperative recurrent NSCLC; failure of prior treatment with one or two chemotherapy regimens ($\geq$ 1 platinum-based regimen); life expectancy of 3 months or greater; WHO PS 0 to 2; and measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST). To improve recruitment, the protocol was amended approximately 6 months after study initiation to allow patients without measurable lesions to participate. This was not expected to greatly impact the primary end point.

Treatment

Gefitinib 250 mg/d was administered orally; docetaxel was administered every 3 weeks as a 1-hour intravenous infusion of 60 mg/m^2 (ie, the approved dose in Japan). Patients received treatment until disease progression, intolerable toxicity, or discontinuation for another reason. Poststudy treatment was at physician and patient discretion; a switch to other study treatment was prohibited unless requested by the patient.

Assessments

Overall survival was assessed from date of random assignment to date of death as a result of any cause, or data were censored at the last date the patient was known to be alive. Tumor response by RECIST was performed at baseline, every 4 weeks for the first 24 weeks, and every 8 weeks thereafter. Complete response (CR) or partial response (PR) was confirmed on the basis of two consecutive examinations that were at least 28 days apart. Investigator assessment of best overall tumor response was used for the primary analysis; sensitivity analyses were performed with independent response evaluation committee assessment. PFS was defined as the time from random assignment to the earliest occurrence of disease progression or death from any cause; patients who had not progressed or died at data cutoff were censored at last tumor assessment. QoL was assessed with the FACT-L questionnaire at baseline and every 4 weeks during study treatment until week 12. The FACT-L total score and trial outcome index (TOI; sum of FACT-L physical well-being + functional well-being + additional concerns subscales) were calculated. Disease-related symptoms were assessed weekly with the FACT-L lung cancer subscale (LCS). Improvement was defined as an increase from baseline of at least six points for FACT-L or TOI, or an increase of at least two points for LCS, on two visits that were at least 28 days apart. Adverse events (AEs) were monitored and graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC; version 2.0). Routine laboratory assessments were performed. EGFR gene copy number was determined by fluorescent in situ hybridization (FISH).[12] EGFR mutations were assessed by direct sequencing of exon 18 to 21 of chromosome 7. EGFR protein expression was measured by immunohistochemistry with the DAKO EGFR pharmaDxTM kit (DAKO, Glostrup, Denmark).[10]

Statistical Analysis

The primary overall survival analysis was conducted in the intent-to-treat (ITT) population by estimating the HR and two-sided 95.24% CI for gefitinib versus docetaxel, derived from a Cox regression model without covariates (significance level adjusted because of interim analysis). Noninferiority was to be concluded if the upper CI limit was $\leq$ 1.25. Superiority was concluded if the upper CI limit was less than 1. A total of 296 death events were required for 90% power to demonstrate noninferiority, with the assumption that gefitinib had better overall survival than docetaxel (median survival, 14 *v* 12 months[4]), and the study plan was to recruit 484 patients.

Robustness of the primary conclusion was assessed by supportive analyses in the per-protocol population and by using a Cox regression model with covariate adjustment for sex (male *v* female), PS (0 or 1 *v* 2), tumor type (adenocarcinoma *v* other), smoking history (ever *v* never), number of prior chemotherapy regimens (1 *v* 2), age at random assignment ($<$ 65 years *v* $\geq$ 65 years), time from diagnosis to random assignment ($<$ 6 *v* 6 to 12 *v* $>$ 12 months), and best response to prior chemotherapy (CR/PR *v* stable disease [SD] *v* progressive disease not assessable/unknown).

Preplanned subgroup analyses were performed on the basis of these covariates. Subgroups were first assessed for evidence of randomized treatment effect by subgroup interactions, to ensure that outcomes between subgroups were likely to be different; then, the subgroups for which evidence existed were examined further.

For PFS, the HR and its 95% CI for gefitinib versus docetaxel were calculated for the population that was assessable for response (defined as patients with $\geq$ 1 measurable lesion at baseline by RECIST) by using a Cox regression model without covariates. Supportive analyses were performed in the ITT population by using a model adjusted for covariates. Overall survival and PFS were summarized with Kaplan-Meier methods.

The ORR (proportion of CR + PR) and the DCR (proportion of CR + PR + SD $\geq$ 12 weeks) were estimated in the assessable-for-response population and were compared between treatments by generating an odds ratio and a 95% CI from a logistic regression model that included covariates.

The exploratory analysis of biomarker subgroups was performed with similar methods to the overall and clinical subgroup analyses when possible.

RESULTS

Patients

From September 2003 to January 2006, 490 patients were randomly assigned from 50 institutes. In the ITT population, 245 patients were randomly assigned to gefitinib, and 244 patients were randomly assigned to docetaxel; one patient was excluded because of a Good Clinical Practice violation (Fig 1). Treatment groups were generally well balanced for baseline demographics (Table 1), except for some small imbalances in smoking history (7% fewer never-smokers and 10% more ex-smokers in the gefitinib arm). The overall population was representative of an advanced, pretreated NSCLC population in a clinical trial setting in Japan. The median (range) duration of treatment for gefitinib was 58.5 (4 to 742) days and, for docetaxel, was 3 (1 to 12) cycles.

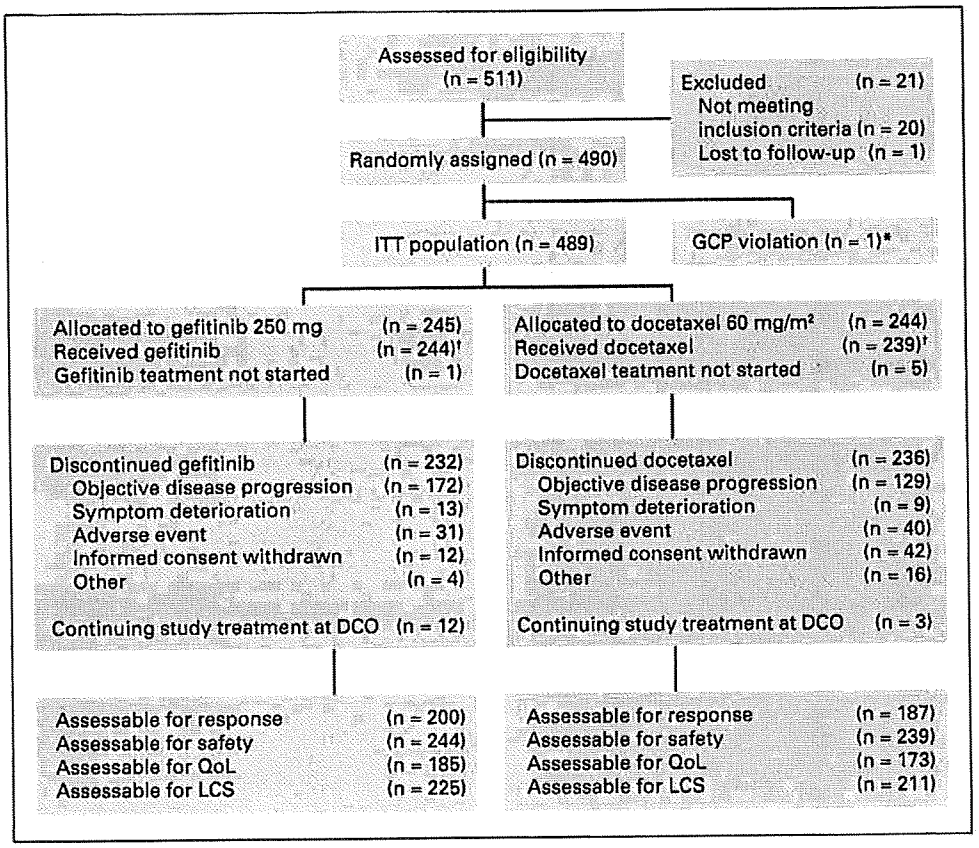

Fig 1. Study flow. (*) Allocated to the docetaxel group. (†) The safety analysis, conducted according to treatment received, was performed on this population. ITT, intent to treat; GCP, Good Clinical Practice; DCO, data cutoff date for overall survival (October 31, 2006); QoL, quality of life; LCS, Lung Cancer Subscale.

Poststudy, 36% of gefitinib-treated patients received subsequent docetaxel, and 40% received no other therapy except for gefitinib; 53% of docetaxel-treated patients received subsequent gefitinib, and 26% received no other therapy except for docetaxel.

Survival

At data cutoff for overall survival (October 31, 2006), overall mortality was 62.6%, and median follow-up was 21 months. Noninferiority in overall survival was not achieved (HR, 1.12; 95.24% CI, 0.89 to 1.40) according to the predefined criterion (upper CI limit for HR $\leq$ 1.25). However, no statistically significant difference in overall survival was apparent (P = .330; Fig 2A).

A supportive Cox analysis, which took into account imbalances in known prognostic factors, showed an HR of 1.01 (95% CI, 0.80 to 1.27; P = .914), which suggested that a demography imbalance that favored docetaxel may have had some impact on the primary, unadjusted, overall survival result.

The median survival and the 1-year survival rates were 11.5 months and 47.8%, respectively, for gefitinib and were 14.0 months and 53.7%, respectively, for docetaxel.

PFS

There was no significant difference between treatments in PFS in the unadjusted analysis (HR, 0.90; 95% CI, 0.72 to 1.12; P = .335); median PFS was 2.0 months with both treatments (Fig 2B). Similar PFS results were obtained from supportive Cox regression analysis adjusted for covariates (HR, 0.81; 95% CI, 0.65 to 1.02; P = .077).

Tumor Response

For ORR, gefitinib was statistically superior to docetaxel (22.5% *v* 12.8%; odds ratio, 2.14; 95% CI, 1.21 to 3.78; P = .009; Table 2). Gefitinib was similar to docetaxel in terms of DCR (34.0% *v* 33.2%; odds ratio, 1.08; 95% CI, 0.69 to 1.68; P = .735). The primary ORR results that were based on investigator judgment were generally consistent with those obtained from independent response evaluation committee assessment.

Symptom Improvement and QoL

Gefitinib showed statistically significant benefits compared with docetaxel in QoL improvement rates (FACT-L: 23.4% *v* 13.9%; P = .023; TOI: 20.5% *v* 8.7%; P = .002; Table 2), but there were no significant differences between treatments in LCS improvement rates (22.7% *v* 20.4%; P = .562).

Subgroup Analyses

Survival outcomes were generally consistent across subgroups, with the exception of best response to prior chemotherapy (treatment by subgroup interaction test P = .017). For patients with best response to prior chemotherapy of progressive disease, overall survival was numerically longer on gefitinib than on docetaxel, whereas patients with a best response of SD had significantly longer survival on docetaxel than on gefitinib (HR, 1.58; 95% CI, 1.09 to 2.27; P = .015; Fig 3A). However, the result was not supported by the PFS (Fig 3B) or ORR results in this subgroup, which favored gefitinib.

Table 1. Baseline Patient Characteristics in Intent-to-Treat Population

Characteristic	Patients per Arm: Gefitinib (n = 245) No.	%	Docetaxel (n = 244) No.	%
Age, years				
≤ 64	138	56.3	135	55.3
≥ 65	107	43.7	109	44.7
Sex				
Male	151	61.6	151	61.9
Female	94	38.4	93	38.1
WHO performance status				
0	85	34.7	93	38.1
1	149	60.8	141	57.8
2	11	4.5	10	4.1
Smoking status				
Ever	174	71.0	157	64.3
Never	71	29.0	87	35.7
Histology				
Adenocarcinoma	192	78.4	188	77.0
Squamous cell carcinoma	37	15.1	41	16.8
Other	16	6.5	15	6.2
Time from diagnosis to random assignment, months				
< 6	70	28.6	60	24.6
6-12	99	40.4	96	39.3
> 12	76	31.0	87	35.7
Disease stage at diagnosis				
IIIB	47	19.2	50	20.5
IV	159	64.9	150	61.5
Recurrent	39	15.9	44	18.0
Number of prior chemotherapy regimens				
1	212	86.5	201	82.4
2	33	13.5	42	17.2
Best response to previous chemotherapy				
CR/PR	113	46.1	106	43.4
SD	91	37.1	101	41.4
PD/NA/unknown	41	16.7	37	15.2
Target lesions at baseline				
Yes	201	82.0	187	76.6
No	44	18.0	57	23.4

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NA, not assessable.

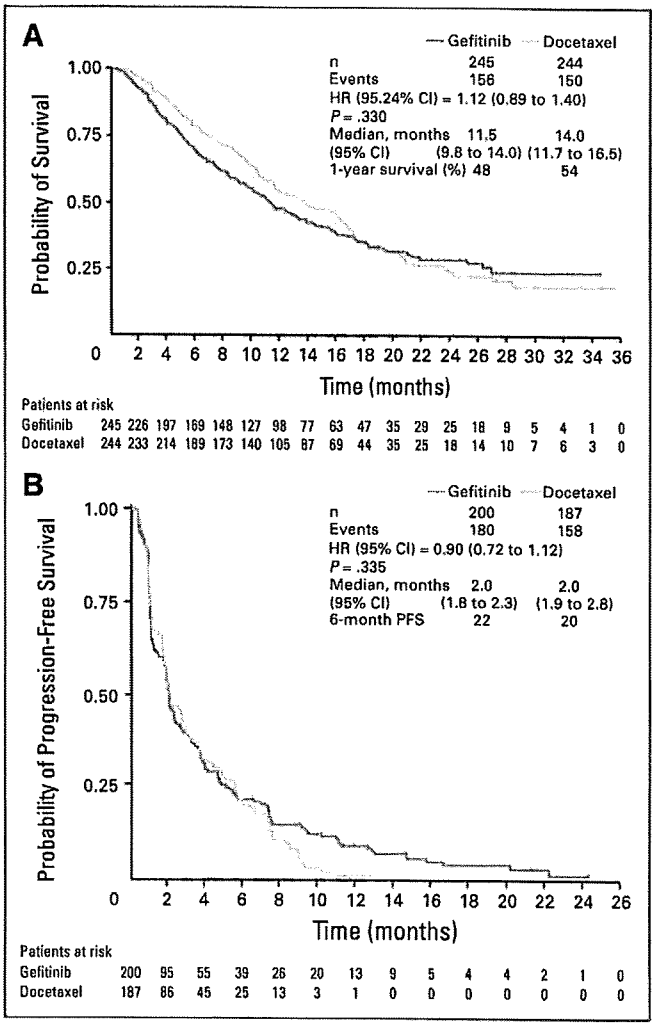

Fig 2. (A) Overall survival in the intent-to-treat population; (B) Progression-free survival (PFS) in the assessable-for-response population. HR, hazard ratio.

Safety

Gefitinib was associated with fewer dose interruptions or delays than docetaxel (26% *v* 52%, respectively). There were no clinically relevant differences in the frequencies of serious AEs or discontinuations of study treatment as a result of AEs between treatment groups (Table 3). Fewer NCI-CTC grades 3 to 4 AEs occurred with gefitinib compared with docetaxel (40.6% *v* 81.6%). There were four deaths as a result of AEs in the gefitinib arm (three as a result of interstitial lung disease that was considered by the investigator to be treatment related; one as a result of pneumonia that was not considered treatment-related), and none in the docetaxel arm.

The most common AEs with gefitinib were rash/acne (76.2%) and diarrhea (51.6%), and the most common AEs with docetaxel were neutropenia (79.5%) and alopecia (59.4%; Table 4). There was a higher incidence of grades 3 to 4 neutropenia with docetaxel (73.6%) compared with gefitinib (8.2%). Interstitial lung disease events occurred in 5.7% (n = 14) and 2.9% (n = 7) of patients who received gefitinib and docetaxel, respectively (Table 3).

Biomarkers

Of the 74 EGFR biomarker samples provided, 53 to 60 were assessable (depending on biomarker). Because of the late protocol amendment, these samples were from long-term survivors who were recruited early or from patients who were recruited later in the study. Compared with the overall study population, this subgroup was over-representative of some stratification factors on both treatment arms: good PS, females, never-smokers, greater than 12 months from diagnosis to random assignment, and best response to prior chemotherapy of CR/PR. There were insufficient events to allow meaningful evaluation of overall survival in relation to biomarker status, and the PFS and ORR data should be interpreted with caution.

Thirty-one (54.4%) of 57 patients had EGFR mutation–positive tumors, and 42 (70.0%) of 60 had EGFR FISH–positive tumors. There

Table 2. Response Rates and Improvement Rates

Rate	Treatment Arm				Analysis		
	Gefitinib		Docetaxel				
	Total No. of Assessable Patients	%	Total No. of Assessable Patients	%	OR	95% CI	*P*
Response*	200		187				
Overall		22.5		12.8	2.14	1.21 to 3.78	.009
Disease control		34.0		33.2	1.08	0.69 to 1.68	.735
Improvement							
FACT-L	185	23.4	173	13.9	1.89	1.09 to 3.28	.023
TOI	185	20.5	173	8.7	2.72	1.44 to 5.16	.002
LCS	225	22.7	211	20.4	1.15	0.72 to 1.81	.562

Abbreviations: OR, odds ratio; FACT-L, Functional Assessment of Cancer Therapy—Lung (Japanese version 4-A, which includes two additional Japan-specific questions in the subscale on social/family well-being); TOI, trial outcome index; LCS, lung cancer subscale.
*Overall response rate consists of complete response plus partial response rates. Disease control rate consists of the complete response plus partial response rates plus those with stable disease for at least 12 weeks.

was a high degree of overlap between EGFR mutation and clinical characteristics (eg, high frequency in females, in those with adenocarcinoma, and in never-smokers). EGFR mutation–positive patients appeared to have better PFS than EGFR mutation–negative patients on both treatments (gefitinib-positive *v* gefitinib-negative HR, 0.33; 95% CI, 0.11 to 0.97; 17 events; docetaxel HR, 0.15; 95% CI, 0.04 to 0.57; 15 events). In addition, EGFR FISH–positive patients appeared to have better PFS than EGFR FISH–negative patients on both treatments (gefitinib-positive *v* gefitinib-negative HR, 0.75; 95% CI, 0.28 to 1.98; 18 events; docetaxel HR, 0.45; 95% CI, 0.14 to 1.41; 16 events). There were no clear PFS differences between gefitinib and docetaxel in any biomarker subgroups, although the number of events was small and the CIs for the HRs were wide. PFS could not be assessed for EGFR protein expression because of the small number of events in the expression-negative group. For EGFR mutation–positive patients, the ORR was 67% (six of 9 patients) with gefitinib administration and 46% (five of 11 patients) with docetaxel administration. For EGFR FISH–positive patients, the ORR was 46% (five of 11) with gefitinib administration and 33% (six of 18) with docetaxel administration. For EGFR expression–positive patients, the ORR was 36% (five of 14) with gefitinib administration and 31% (four of 13) with docetaxel administration. There were no responses among EGFR mutation–negative, or EGFR FISH–negative, patients, and there was one response (13%) of eight EGFR expression–negative patients who received docetaxel.

DISCUSSION

V-15-32 is the first phase III study to compare gefitinib versus docetaxel in previously treated Japanese patients who have advanced NSCLC. Both gefitinib and docetaxel demonstrated efficacy and tolerability, and findings were consistent with previous experience for both agents in Japan.

Although noninferiority in overall survival for gefitinib versus docetaxel was not proven, there was no statistically significant difference between the two treatments. The original statistical assumption was that gefitinib would have 20% longer survival than docetaxel; hence, the relatively small sample size for a noninferiority study. However, since the study was initiated, data from postmarketing experience in Japan (the SIGN study[13]) and substantial switching to the alternative study treatment on progression in V-15-32 indicated that it would be more likely that gefitinib and docetaxel had similar overall survival. With the assumption of equal survival, the chance (power) of showing noninferiority with this study size is reduced to 48%. The median survival with gefitinib 250 mg/d in our study was consistent with previous experience in Japan (11.5 *v* 13.8 months for Japanese subset of IDEAL 1).[9] Docetaxel demonstrated a longer median survival in V-15-32 (14.0 months) compared with previous Japanese studies (7.8 to 9.4 months).[1,4,14]

In line with increasingly available therapy for NSCLC since the trial was designed and with standard practice in Japan, a large proportion of patients received additional anticancer therapy after discontinuation of the randomly assigned study treatment. Crossover was greater than initially expected, and differences in the number and types of patients who received these poststudy treatments complicated interpretation of survival results. A greater proportion of patients who received docetaxel received poststudy therapy compared with those who received gefitinib. Imbalances in the use of gefitinib after chemotherapy have been reported recently in a phase III study of Japanese patients with lung cancer who were treated with docetaxel and have been cited as a possible explanation for the prolonged median survival seen with docetaxel.[15] INTEREST (Iressa NSCLC Trial Evaluating Response and Survival against Taxotere), a worldwide phase III trial that is comparing gefitinib with docetaxel in pretreated patients who have advanced NSCLC recently demonstrated that gefitinib had statistically noninferior survival to docetaxel.[16] In contrast to V-15-32, INTEREST was larger (1,466 patients) and had subsequent therapies that were well-balanced between treatment arms.

Secondary end points, largely unaffected in this study by subsequent therapy, provided further evidence of the clinical efficacy of both gefitinib and docetaxel in Japanese patients. PFS was similar with gefitinib and docetaxel, and ORR was statistically significantly improved with gefitinib. The ORR in V-15-32 with gefitinib (22.5% *v* 12.8% with docetaxel) was consistent with a subset analysis from IDEAL 1 in Japanese patients (27.5%).[3,8,9]

A number of patient subgroups (including females, patients with adenocarcinoma, and never-smokers) have been reported

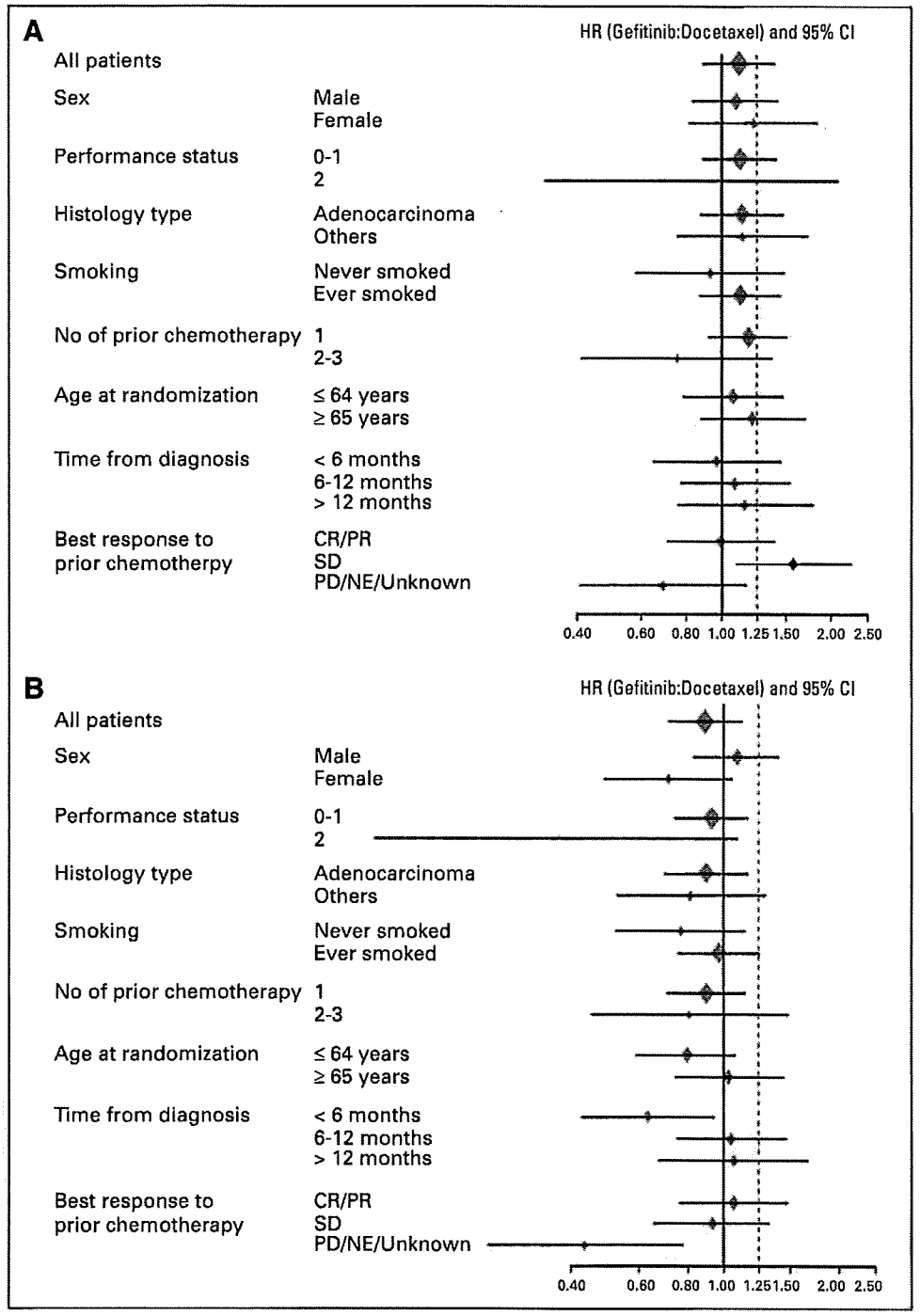

Fig 3. Forest plots of (A) overall survival and (B) progression-free survival that compare treatment groups within clinically relevant subgroups. HR, hazard ratio; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not assessable.

previously to experience improved clinical benefit with gefitinib.[2,4,7,8,10] Subgroup analyses in this study should be interpreted with caution, as the primary objective was not met, some subgroups were small, and there were imbalances in poststudy treatments. In between-treatment comparisons, no statistically significant overall survival benefit was found for gefitinib compared with docetaxel in any subgroup. However, when post hoc, within-treatment comparisons were performed, females, never-smokers, and patients with adenocarcinoma (and also patients with poor PS and > 12 months since diagnosis) had significantly longer survival than their opposite subgroups on both gefitinib and docetaxel ($P < .001$ for females *v* males, adenocarcinoma *v* others, and never-smokers *v* ever-smokers on both treatments). It appears that the subgroups typically associated with a gefitinib benefit were seen but that they also did well on docetaxel. However, the rate of subsequent gefitinib prescription in the docetaxel arm was high in

Table 3. Summary of Adverse Event Data in the Assessable-for-Safety Population

Category*	Patients			
	Gefitinib (n = 244)		Docetaxel (n = 239)	
	No.	%	No.	%
Adverse events	242	99.2	236	98.7
Treatment-related adverse events	233	95.5	233	97.5
Treatment discontinuation because of an adverse event	33	13.5	42	17.6
NCI-CTC adverse event grades 3 to 4	99	40.6	195	81.6
Serious adverse events	42	17.2	34	14.2
Death as a result of a serious adverse event	4	1.6	0	0
ILD events	14	5.7	7	2.9

Abbreviations: NCI-CTC, National Cancer Institute Common Toxicity Criteria; ILD, interstitial lung disease.
*Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories.

these subgroups (eg, approximately two-thirds of docetaxel never-smokers and females had gefitinib as their first poststudy treatment); for PFS and ORR, which are largely unaffected by subsequent treatment, the benefit in these subgroups remained for gefitinib but not for docetaxel, which suggested that poststudy treatments are confounding the interpretation of overall survival in the subgroups.

AEs in our study were consistent with those previously observed, and the most commonly reported AEs were rash/acne and diarrhea for gefitinib and neutropenia for docetaxel. Docetaxel demonstrated a

Table 4. Most Common Adverse Events

Adverse Event	Occurrence by Treatment Arm							
	Gefitinib (n = 244)				Docetaxel (n = 239)			
	Total		Grades 3 to 4		Total		Grades 3 to 4	
	No.	%	No.	%	No.	%	No.	%
Rash/acne*	186	76.2	1	0.4	73	30.5	1	0.4
Diarrhea	126	51.6	5	2.0	67	28.0	2	0.8
Dry skin	90	36.9	0	0.0	13	5.4	0	0.0
Constipation	69	28.3	14	5.7	74	31.0	6	2.5
Anorexia	68	27.9	10	4.1	119	49.8	17	7.1
Nausea	61	25.0	5	2.0	92	38.5	9	3.8
Abnormal hepatic function†	59	24.2	27	11.1	13	5.4	2	0.8
Stomatitis	55	22.5	0	0.0	42	17.6	0	0.0
Nasopharyngitis	50	20.5	0	0.0	32	13.4	0	0.0
Pruritus	42	17.2	0	0.0	15	6.3	0	0.0
Vomiting	41	16.8	4	1.6	41	17.2	3	1.3
Fatigue	36	14.8	1	0.4	107	44.8	6	2.5
Paronychia	33	13.5	1	0.4	2	0.8	0	0.0
Insomnia	32	13.1	0	0.0	20	8.4	0	0.0
Neutropenia‡	24	9.8	20	8.2	190	79.5	176	73.6
Pyrexia	24	9.8	1	0.4	51	21.3	1	0.4
Alopecia	19	7.8	0	0.0	142	59.4	0	0.0
Leukopenia	18	7.4	15	6.1	136	56.9	94	39.3
Headache	12	4.9	1	0.4	25	10.5	0	0.0
Edema§	11	4.5	0	0.0	30	12.6	2	0.8
Myalgia	8	3.3	0	0.0	25	10.5	0	0.0
Dysgeusia	7	2.9	0	0.0	37	15.5	0	0.0
Febrile neutropenia	4	1.6	2	0.8	17	7.1	17	7.1

NOTE. The most common adverse events were considered those that occurred in ≥ 10% of the study population or occurred with > 5% difference between treatments.
*Includes MedDRA high-level terms of rashes, eruptions and exanthems; and of acnes and preferred terms of rash pustular, dermatitis, dermatitis exfoliative, and dermatitis exfoliative generalized.
†Includes MedDRA preferred terms of hepatic function abnormal, alanine aminotransferase increased, aspartate aminotransferase increased and liver disorder.
‡With the exception of one treatment-related adverse event, all other instances of neutropenia reported with gefitinib were in patients who had switched to docetaxel 60 mg/m^2 or other chemotherapy and were reported within the 30-day reporting period. In these other instances, no causal relationship was assigned by the investigator.
§Includes MedDRA preferred terms of edema, edema peripheral, face edema, eyelid edema, and macular edema.

typically high incidence of neutropenia (79.5%) and febrile neutropenia (7.1%) compared with gefitinib (9.8% and 1.6%, respectively). These neutropenia levels that accompanied docetaxel treatment are consistent with previously reported studies in Japanese patients (95.4%[1] and 81.5%[4]). The incidence of interstitial lung disease reported in this study with gefitinib (5.7%) is consistent with that reported in the Japanese postmarketing study (5.8%).[17]

Although the patient numbers were too small for firm conclusions, the biomarker data from this study suggest that EGFR mutation–positive or EGFR FISH–positive patients have a greater response to both gefitinib and docetaxel compared with EGFR mutation– or FISH–negative patients. The gefitinib data are consistent with several previous reports.[18] The docetaxel data provide potential new information about EGFR biomarkers and chemotherapy; this has not been consistently seen before, because there are only a few small studies in the literature, and they have conflicting results.[19] Hence, it is difficult to say conclusively that EGFR mutation or EGFR FISH–positivity predict for docetaxel as well as gefitinib benefit.

Although the study did not prove noninferior survival for gefitinib compared with docetaxel in this patient population, the clinical efficacy and tolerability of gefitinib 250 mg/d in Japanese patients who had NSCLC, reported here, is consistent with the clinical experience reported to date, and gefitinib remains an effective treatment option for previously treated Japanese patients who have locally advanced/metastatic NSCLC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: Yutaka Nishiwaki, Shunichi Negoro, Nagahiro Saijo, Masahiro Fukuoka

Administrative support: Haiyi Jiang, Yohji Itoh

Provision of study materials or patients: Riichiroh Maruyama, Yutaka Nishiwaki, Tomohide Tamura, Nobuyuki Yamamoto, Masahiro Tsuboi, Kazuhiko Nakagawa, Tetsu Shinkai, Shunichi Negoro, Fumio Imamura, Kenji Eguchi, Koji Takeda, Akira Inoue, Keisuke Tomii, Masao Harada, Noriyuki Masuda, Yukito Ichinose

Collection and assembly of data: Riichiroh Maruyama, Yutaka Nishiwaki, Tomohide Tamura, Nobuyuki Yamamoto, Masahiro Tsuboi, Kazuhiko Nakagawa, Tetsu Shinkai, Shunichi Negoro, Fumio Imamura, Kenji Eguchi, Koji Takeda, Akira Inoue, Keisuke Tomii, Masao Harada, Noriyuki Masuda, Yukito Ichinose

Data analysis and interpretation: Yutaka Nishiwaki, Shunichi Negoro, Haiyi Jiang, Yohji Itoh, Nagahiro Saijo, Masahiro Fukuoka

Manuscript writing: Riichiroh Maruyama, Haiyi Jiang, Yohji Itoh

Final approval of manuscript: Yukito Ichinose, Nagahiro Saijo, Masahiro Fukuoka

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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®).

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Clinical Studies

A randomised phase II trial of preoperative chemotherapy of cisplatin–docetaxel or docetaxel alone for clinical stage IB/II non-small-cell lung cancer: results of a Japan Clinical Oncology Group trial (JCOG 0204)

H Kunitoh*[,1], H Kato[2], M Tsuboi[2], H Asamura[3], H Tada[4], K Nagai[5], T Mitsudomi[6], T Koike[7], K Nakagawa[8], Y Ichinose[9], M Okada[10], T Shibata[11] and N Saijo[12], JCOG Lung Cancer Surgical Study Group, Tokyo, Japan

[1]Department of Medical Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan; [2]Department of Thoracic Surgery, Tokyo Medical University, 6-7-1 Nishishinnjuku, Shinjuku-ku, Tokyo 160-0023, Japan; [3]Division of Thoracic Surgery, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan; [4]Department of General Thoracic Surgery, Osaka City General Hospital, 2-13-22 Miyakojima-Hondori, Miyakojima-ku, Osaka 534-0021, Japan; [5]Department of Thoracic Surgery, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwashi, Chiba 277-8577, Japan; [6]Department of Thoracic Surgery, Aichi Cancer Center, 1-1 Kanokoden, Chikusa-ku, Nagoya City, Aichi 464-8681, Japan; [7]Department of Thoracic Surgery, Niigata Cancer Center, 2-15-3, Kawagishi-cho, Niigata-shi, Niigata 951-8566, Japan; [8]Thoracic Oncology Center, Cancer Institute Hospital, 3-10-6 Ariake, Koto-ku, Tokyo 135-8550, Japan; [9]Department of Thoracic Oncology, National Kyushu Cancer Center, 3-1-1 Notame, Minami-ku, Fukuoka City, Fukuoka 811-1395, Japan; [10]Department of Surgical Oncology, Hiroshima University Research Institute for Radiation Biology and Medicine, 1-2-3 Kasumi, Minami-ku, Hiroshima City, Hiroshima 734-8553, Japan; [11]JCOG Data Center, Center for Cancer Control and Information Services, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan; [12]National Cancer Center Hospital East, 6-5-1 Kashiwanohara, Kashiwashi, Chiba 277-8577, Japan

Preoperative chemotherapy is a promising strategy in patients with early-stage resectable non-small-cell lung cancer (NSCLC); optimal chemotherapy remains unclear. Clinical (c-) stage IB/II NSCLC patients were randomised to receive either two cycles of docetaxel (D)–cisplatin (P) combination chemotherapy (D 60 mg m^{-2} and P 80 mg m^{-2} on day 1) every 3–4 weeks or three cycles of D monotherapy (70 mg m^{-2}) every 3weeks. Thoracotomy was performed 4–5 weeks (DP) or 3–4 weeks (D) after chemotherapy. The primary end point was 1-year disease-free survival (DFS). From October 2002 to November 2003, 80 patients were randomised. Chemotherapy toxicities were mainly haematologic and well tolerated. There were two early postoperative deaths with DP (one intraoperative bleeding and one empyema). Pathologic complete response was observed in two DP patients. Docetaxel–cisplatin was superior to D in terms of response rate (45 *vs* 15%) and complete resection rate (95 *vs* 87%). Both DFS and overall survival were better in DP. Disease-free survival at 1, 2 and 4 years were 78, 65 and 57% with DP, and were 62, 44 and 36% with D, respectively. Preoperative DP was associated with encouraging resection rate and DFS data, and phase III trials for c-stage IB/II NSCLC are warranted.

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Surgery is the standard of care for clinical (c-) stage IB/II non-small-cell lung cancer (NSCLC), but the treatment outcome remains poor, with 5-year survival rates of 50% or less (Mountain, 1997; Goya *et al*, 2005). The majority of post-surgical relapse occurs as distant metastases (Pisters and Le Chevalier, 2005); therefore, effective systemic therapy is necessary. Recently, a series of postoperative adjuvant chemotherapy trials reported modest but significant improvement in survival, mainly in patients with pathological stage II or IIIA NSCLC (Arriagada *et al*, 2004; Scagliotti, 2005; Winton *et al*, 2005; Douillard *et al*, 2006). Compliance to the chemotherapy remains a problem (Arriagada *et al*, 2004; Scagliotti, 2005; Winton *et al*, 2005; Douillard *et al*, 2006).

On the other hand, previous small phase III trials had reported that preoperative chemotherapy was better than surgery alone in stage III NSCLC (Rosell *et al*, 1994; Roth *et al*, 1994). Recent trials of preoperative platinum-based chemotherapy have reported promising results in c-stage IB/II NSCLC (Pisters *et al*, 2000; Depierre *et al*, 2002; Rosell *et al*, 2002). One advantage of the preoperative chemotherapy is better tolerability and compliance.

No data are available, however, as to the optimal preoperative therapy strategy for early-stage NSCLC. Although platinum-based 'standard' combination chemotherapy regimens have widely been used and reported to be generally safe, results of randomised trials

*Correspondence: Dr H Kunitoh; E-mail: hkkunito@ncc.go.jp
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reported nonsignificant but modest excess of post-surgical morbidity and mortality (Depierre *et al*, 2002; Pisters *et al*, 2007). Monotherapy with an active agent is associated with lower response rate, but less toxicity (Delbaldo *et al*, 2004); it might well be favourable for preoperative therapy in early stage, when surgery must not be compromised by adjuvant therapy.

Docetaxel (D) is a semisynthetic taxoid derived from the European yew *Taxus baccata*. It is active against NSCLC either in monotherapy (D)(Fossella *et al*, 1994; Francis *et al*, 1994; Kunitoh *et al*, 1996) or in combination with cisplatin (DP) (Zalcberg *et al*, 1998; Fossella *et al*, 2003). In advanced NSCLC, DP was reported to be better than P-vinca combination (Fossella *et al*, 2003; Kubota *et al*, 2004), one of the 'standard' adjuvant therapies. The DP combination was also reported to be active and promising as preoperative chemotherapy in c-stage III NSCLC (Betticher *et al*, 2006).

Docetaxel monotherapy, on the other hand, was reported to be not inferior to DP, with better tolerability in advanced NSCLC (Georgoulias *et al*, 2004). For stage III NSCLC, Mattson *et al* (2003) reported the results of D as preoperative chemotherapy; it was active, and did not compromise surgery.

On the basis of this rationale, we undertook a randomised phase II trial of DP *vs* D in resectable, c-stage IB/II NSCLC. The objectives of the study were to evaluate the safety and efficacy of the preoperative chemotherapy and to select promising one for future phase III trials. The primary end point was the disease-free survival (DFS) rate at 1 year.

PATIENTS AND METHODS

Patient eligibility criteria

Patients with untreated, histologically or cytologically documented NSCLC with clinical stage IB (c-T2N0M0), IIA (c-T1N1M0) or IIB (c-T2N1M0 or T3N0M0) were eligible for study entry. Each patient was required to meet the following criteria: 20–74 years of age, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; measurable disease; and adequate organ function (leukocyte count $\geqslant 4000/\mu l$ and $\leqslant 12\,000/\mu l$, neutrophil count $\geqslant 2000/\mu l$, platelet count $\geqslant 10^5/\mu l$, haemoglobin $\geqslant 10.0\,g\,dl^{-1}$, serum creatinine $\leqslant$ the upper limit of the institutional normal range (ULN), creatinine clearance calculated by the Cockcroft–Gault formula $\geqslant 60\,ml\,min^{-1}$, serum bilirubin $\leqslant$ ULN, serum ALT and AST $\leqslant 2 \times$ ULN and $PaO_2 \geqslant 70\,mm\,Hg$). Women who were pregnant or lactating were excluded from the study. Other exclusion criteria included patients with active infection, unstable angina or a history of myocardial infarction within 6 months, interstitial pneumonia or active lung fibrosis, uncontrolled diabetes or hypertension, systemic use of corticosteroid or active concomitant malignancy. Patients with tumour invading the first rib or more superior chest wall (Pancoast type) were also excluded. All mediastinal nodes measuring 1.0 cm or more in size on computed tomographic (CT) scans were required to be biopsied to be histologically benign before patient entry.

Patient eligibility was confirmed by the Japan Clinical Oncology Group Data Centre before registration. The study protocol was approved by the institutional review boards at each participating centre, and all patients provided written informed consent.

Treatment plan

This was an open-label, randomised trial. Patients were randomly assigned to one of two treatment arms. Dosages of the chemotherapy were based on the regulatory notes and clinical data in Japan (Kubota *et al*, 2004). In the DP combination arm, patients received D at $60\,mg\,m^{-2}$ as a 1-h intravenous infusion followed by P at $80\,mg\,m^{-2}$ as a 2-h infusion on day 1. Two cycles of the chemotherapy were repeated at an interval of 4 weeks. The interval was permitted to be shortened to 3 weeks, if the patient was judged to have adequately recovered enough from the first cycle. Surgery (lobectomy or pneumonectomy with systematic lymph node dissection) was performed 4–5 weeks after completion or early termination of the chemotherapy. Patients in the D monotherapy arm received D at $70\,mg\,m^{-2}$ as a 1-h intravenous infusion on day 1. Three cycles of the chemotherapy were repeated at 3 weeks intervals. Surgery in the D arm was performed 3–4 weeks after completion or early termination of chemotherapy. The preoperative periods were thus set at 8–10 weeks in each arm, which was designed to be easier to accept for the patients and the surgeons.

In each arm, when chemotherapy was judged to be ineffective with $\geqslant 10\%$ unidirectional tumour growth, or when the patient experienced unacceptable toxicity (such as, grade 3 neurotoxicity, grade 2 pulmonary toxicity, grade 3 cardiac toxicity or other grade 4 non-haematological toxicities), chemotherapy was discontinued and the patient was taken up for surgery as clinically indicated. With minor toxicities, such as uncomplicated grade 4 haematologic or grade 3 non-critical, non-haematological toxicities, dosages of subsequent chemotherapy courses were reduced (P by $20\,mg\,m^{-2}$ and D by $10\,mg\,m^{-2}$).

No protocol therapy was predetermined for those with unresectable tumours, either during chemotherapy or at operation, and those with microscopically or macroscopically incompletely resected tumours. Those who underwent curative resection were observed until recurrence without additional therapy.

Chemotherapy was supported with routine premedication for hypersensitivity and antiemetics. For the DP arm, ample hydration was ensured. Recombinant human granulocyte colony-stimulating factor was administered when grade 4 neutropaenia or neutropaenic fever occurred.

Patient evaluation and follow-up

Before study enrolment, a complete medical history and physical examination, blood cell count determinations, biochemistry testing, chest X-ray, ECG, CT scan of the chest and CT scan or ultrasound of upper abdomen were conducted for each patient. Whole-brain CT or magnetic resonance imaging (MRI) or isotope bone scanning was performed if clinically indicated. Positron emission tomography (PET) was not widely available in Japan at the time of the protocol activation and was not routinely used for staging. Blood cell counts, differential WBC counts and biochemistry testing were performed weekly during each course of chemotherapy.

Toxicity of the chemotherapy was evaluated with the National Cancer Institute Common Toxicity Criteria Tumour (NCI-CTC; version 2.0). Tumour responses were assessed radiographically according to the RECIST guideline (Therasse *et al*, 2000). Response confirmation at 4 weeks or longer intervals was not necessitated. Response was assessed by the attending physicians in each participating institution, and no central confirmation was performed. Chest X-ray was taken at each course, and when suggested for even minor tumour growth ($\geqslant 10\%$), confirmatory chest CT was performed to decide on the continuation of chemotherapy.

After curative resection, the patients were followed up with periodic reevaluation. This included chest CT every 6 months for the first 2 years and annually thereafter, until 5 years or tumour recurrence.

Statistical considerations

This trial was designed as a randomised phase II selection design. Therefore, formal statistical hypothesis testing of the differences between the arms, including the calculation of *P*-values, was not to be performed. The aim was to select the 'preferable' preoperative chemotherapy arm for a future definitive phase III trial, with the DFS rate at 1 year as primary end point. The DFS was calculated

from the date of enrolment by the Kaplan–Meier method, as was the overall survival (OS).The 'events' for the determination of the DFS included tumour relapse after curative surgery, death from any cause and non-curative operation. Those with non-curative operation include patients without surgery and those with incomplete resection, either microscopically or macroscopically. Non-curative operation was to be counted as an event on the date of registration, not on that of surgery. The sample size was determined to provide sufficient probability to choose the 'preferable' arm (Simon *et al*, 1985). Assuming DFS rates at 1 year of 70 and 80%, 40 patients per arm were required to correctly select the arm that is not inferior with the probability of 84.9%. The 'minimal' DFS rate of 70% was assumed with the prior report from North America, in which the 1- and 2-year survival rates were reported to be 85 and 56%, respectively (Pisters *et al*, 2000). The assumption was rough and might well be inaccurate, for no DFS data were available from the literature. The randomisation was carried out by the JCOG data centre using a minimisation method with c-stage (IB *vs* II) and institutions as balancing factors.

The secondary end points included the objective tumour response to chemotherapy, complete resection rate, intra- and post-surgical morbidity/mortality and the OS rate. Tumour responses in both arms were compared using Fisher's exact test.

During the accrual period, an interim analysis was planned after 40 patients were randomised and followed up for at least 4 months. All analyses were performed with the SAS software version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

From October 2002 to October 2003, 80 patients from 18 institutions were enroled and randomised. After 40 patients were randomised, an interim analysis was carried out. Following the JCOG Data and Safety Monitoring Committee's review, the study was continued. One patient in the D arm was found to be ineligible because of the wrong histology (sarcoma). All 80 patients were analysed for characteristics and chemotherapy toxicity, and the 79 eligible patients were analysed for the clinical and pathological response to chemotherapy, surgical results, DFS and OS.

Table 1 lists the characteristics of the patients, which were well balanced between the arms.

Chemotherapy delivery and toxicity

Table 2 summarises the chemotherapy delivery, and Table 3 summarises toxicity in the subject group. Only 60% in the D arm completed the planned chemotherapy courses, mainly arising from the clinical ineffectiveness of the therapy. On the other hand, compliance was very good in the DP arm, and the toxicity was not greater. Hyponatraemia, probably due to hydration with P administration, was an unexpected toxicity in the DP arm, but it was clinically silent and transient in all the cases. All patients recovered without any particular management, with no clinically relevant sequelae. Other toxicities were mainly haematologic, and both chemotherapy arms were generally well tolerated by the patients.

Clinical response and pathological results

Table 4 shows the clinical responses to the chemotherapy. The overall response rates, 45% in the DP arm and 15% in the D arm, were compatible with earlier reports for each of the chemotherapy regimen in patients with NSCLC.

Thoracotomy was performed in 39 of the 40 patients in the DP arm, and in 37 of the 39 patients in the D arm. The tumour was surgically resected in 39 (98%) patients in the DP arm, including pneumonectomy in 3 cases, bi-lobectomy in 2 cases and lobectomy in 34 cases. Tumour resection was performed in 35 (90%) patients of the D arm, including pneumonectomy in 1 case, bi-lobectomy in 4 cases and lobectomy in 30 cases. Five patients, including four in the DP arm and one in the D arm, suffered from massive ($\geqslant$1 l) intraoperative bleeding: due to severe adhesion in three cases (two in DP and one in D arm), to incomplete suture of the autostapler resulting in injury of pulmonary artery in one case (DP arm) and accidental injury to the aorta in one case (DP arm). None was judged to be related to preoperative therapy. The postoperative complications included one patient with empyema and another with pulmonary oedema, both in the DP arm. There were two surgical deaths, both in the DP arm; one died on postoperative day 59 because of empyema, and another on postoperative day 2 because of massive intraoperative bleeding resulting from surgical injury to the aorta.

Pathological complete resection (R0), without residual tumour found either macroscopically or microscopically, was achieved in 38 (95%) cases in the DP arm, and 34 (87%) cases in the D arm.

Table 1 Patient characteristics

Arm	Cisplatin–docetaxel	Docetaxel alone
N	40	40
Clinical stage		
IB	22	23
II	18	17
Clinical T stage		
T1	5	5
T2	31	29
T3	4	6
Clinical N stage		
N0	26	28
N1	14	12
ECOG performance status		
PS0	35	31
PS1	5	9
Histology		
Adenocarcinoma	30	24
Squamous cell carcinoma	10	11
Others	0	5
Body weight loss within 6 months		
None	24	22
$\leqslant$5 kg	13	14
>5 kg	1	2
Missing	2	2
Smoking		
Median smoking	40 pack-years	40 pack-years
Never-smoker	6	8

Table 2 Delivery of chemotherapy

Arm	Cisplatin–docetaxel	Docetaxel alone
N	40	40
Completed	38 (95%)	24 (60%)
Not completed	2	16
Ineffective[a]	1	11
Adverse event	1	3
Patient refusal	0	1
Found ineligible	0	1

[a]Ineffectiveness was judged upon $\geqslant$10% unidirectional increase in tumour size, and did not necessarily mean progressive disease by RECIST.

Table 3 Toxicity of chemotherapy

Arm	Cisplatin–docetaxel	Docetaxel alone
N	40	40
Grade	2/3/4 (% grade 3+4)	2/3/4 (% grade 3+4)
Haematological		
Leukopaenia	18/14/1 (38)	12/15/2 (43)
Neutropaenia	5/16/17 (83)	5/10/21 (78)
Anaemia	4/0/0 (0)	7/0/0 (0)
Thrombocytopenia	1/0/0 (0)	0/0/0 (0)
Nonhaematological		
Total bilirubin	4/0/0 (0)	0/0/0 (0)
Serum AST	0/0/0 (0)	3/1/0 (3)
Serum ALT	5/0/0 (0	5/1/0 (3)
Serum creatinine	3/0/0 (0)	0/0/0 (0)
Hypoxia	0/0/0 (0)	3/0/0 (0)
Hypercalcaemia	0/0/0 (0)	0/1/0 (3)
Hyponatraemia	–/6/0 (15)	–/1/0 (3)
Hypersensitivity	0/0/0 (0)	0/1/0 (3)
Fatigue	3/1/0 (3)	0/0/0 (0)
Constipation	4/1/0 (3)	5/0/0 (0)
Diarrhea	3/3/0 (8)	2/0/0 (0)
Nausea	9/7/– (18)	0/0/– (0)
Vomiting	5/1/0 (3)	0/0/0 (0)
Febrile neutropaenia	–/1/0 (3)	–/0/0 (0)
Infection with neutropaenia	–/2/0 (5)	–/3/0 (8)
Infection without neutropaenia	1/0/0 (0)	4/2/0 (5)
Neuropathy	0/0/0 (0)	1/0/0 (0)
Any grade 3/4 toxicity	35 (88%)	32 (80%)
Any grade 3/4		
Non-haematological toxicity	15 (38%)	9 (23%)

Table 4 Clinical response to chemotherapy based on RECIST

Arm	Cisplatin–docetaxel	Docetaxel alone
N	40	39
Completed chemotherapy	38 (95%)	24 (62%)
CR	1	0
PR	17	6
CR+PR	18	6
SD	18	23
PD	4	10
NE	0	0
ORR	45%	15%
(95% confidence interval)	(29–62%)	(6–31%)

CR = complete response; NE = not evaluable; ORR = overall response rate; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumor; SD = stable disease.

On pathological examination, 23% of the 75 patients who underwent surgery were found to have N2 or N3 status. Pathologic CR was achieved in two patients, both in the DP arm. Clinical N-stage was poorly correlated to pathological nodal status (Table 5).

DFS and OS

The DFS and OS were updated in November 2007. The DFS rates at 1, 2 and 4 years were 78, 65 and 57% in the DP arm, and were 62, 44 and 36% in the D arm, respectively (Figure 1). Table 6 summarises the outcome at 1 year, the primary end point of the study. The DFS rate at 1 year was 78% (31 out of 40) in the DP arm, which was consistent with the study assumption that it would be 80% in the 'better' arm, whereas it was a disappointing 62% (24 out of 39) in the D arm. The 16% difference was more than presumed in the protocol.

Table 5 Pathological results

Arm	Cisplatin–docetaxel			Docetaxel alone		
c-N stage	N0	N1	Total	N0	N1	Total
Number of cases	26	14	40	27	12	39
p-N0	17	6	23	18	4	22
p-N1	3	5	8	3	1	4
p-N2	5	2	7	5	4	9
p-N3	1	0	1	0	0	0
Not assessable	0	1	1	1	3	4

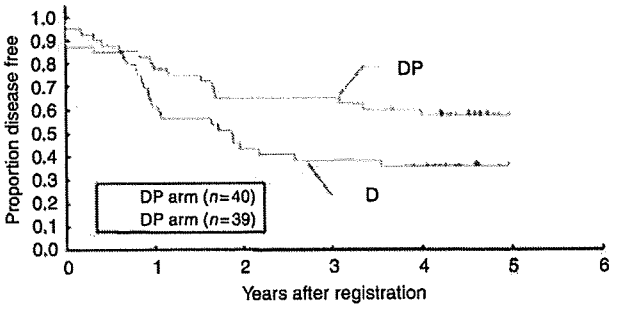

Figure 1 Disease-free survival.

Table 6 Outcome at 1 year

Arm	Cisplatin–docetaxel	Docetaxel alone	Total
Number of cases	40	39	79
Alive, disease-free	31	24	55
Alive with disease	4	11	15
Dead, due to cancer	3	2	5
Dead, treatment-related	2	0	2
Dead, other causes	0	2	2

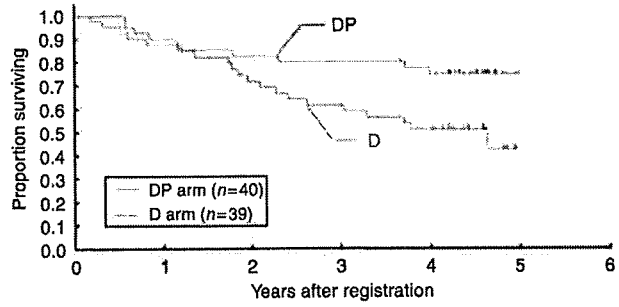

Figure 2 Overall survival.

The OS rates at 1, 2 and 4 years were 88, 83 and 75% in the DP arm, and were 87, 72 and 57% in the D arm, respectively (Figure 2). Both the DFS and the OS rates were better in the DP arm. The OS was better in the DP arm in both adenocarcinoma and non-adenocarcinoma histological subtypes.

DISCUSSION

As compared with post-surgical adjuvant therapy, preoperative chemotherapy has several practical as well as theoretical advan-

tages (Pisters *et al*, 2000; Pisters, 2003). The practical advantages include better patient tolerance and clinical visualisation of chemotherapy effect.

There are very few reports as to the optimal preoperative therapy strategy. The majority of trials have used 'standard' platinum-based doublets (Pisters, 2003). Although they are the 'standard' for advanced, stage IV NSCLC, a trade-off between the cytotoxic effect and toxicity of the chemotherapy, not only toxicity itself but also its influence on surgery and post-surgical morbidity and mortality (Depierre *et al*, 2002; Pisters *et al*, 2007), must be considered for preoperative therapy.

In this randomised phase II study, we evaluated DP combination chemotherapy and D monotherapy as preoperative treatment for early stage NSCLC. Although the DFS assumptions of the protocol, 70 *vs* 80% at 1 year, were rough and arbitrary due to lack of historical data, subsequent S9900 trial (Pisters *et al*, 2007) showed DFS rate of 68% in the surgery alone group and 69% in those with preoperative carboplatin–paclitaxel therapy, consistent with our assumption.

Our results showed that single-agent D was inadequate in this setting; an unexpectedly high progression rate led to an early chemotherapy termination rate of as high as 40%. The reason for the high PD rate is unknown. In addition, we tried to minimise the disadvantage of continuation of ineffective chemotherapy by defining the ineffectiveness as $\geqslant$10% tumour size increase instead of $\geqslant$20% in the RECIST guideline (Therasse *et al*, 2000). This subtle decision rule might require centralised confirmation. The DFS rate in the D arm was disappointing and was, in fact, very similar to that in the surgery-alone arm in the S9900 study in the United States (Pisters *et al*, 2007).

On the other hand, both the DFS and OS rates of the DP arm were promising. Disease-free survival at 1 year of 78% was fully consistent with the estimation in the study protocol. Although our data do not refute other platinum-based chemotherapy as candidates of preoperative treatment, it would be justified to conclude that DP was active and promising, regardless of disappointing data of D monotherapy. One might argue that DFS at 1 year was too premature as an end point. Because the DFS and OS curves of the DP arm seem to have reached to plateau at 2 years, DFS at 2 years might be a more appropriate end point.

The number of chemotherapy courses of the DP combination was two, whereas many previous studies used three courses. In the North American trials with carboplatin and paclitaxel, three preoperative courses appeared to have no advantage when compared with two courses (Pisters *et al*, 2000; Pisters, 2003). Although patients with 'two preoperative courses' were to have two additional courses after the operation, compliance to the post-surgical courses was very poor anyway (Pisters *et al*, 2000). But, as the majority of the patients appeared fit enough after two courses of DP and a major operation, we could consider the addition of a couple of postoperative chemotherapy cycles at least for responders.

One of the major disadvantages of preoperative therapy is the inaccuracy of the clinical staging, as reported by Depierre *et al* (2002). In our trial, 23% of the 74 patients who underwent thoracotomy were found to have p-N2/N3 disease. In Japan, mediastinoscopy for patients with mediastinal nodes measuring 1 cm or less in size on CT is not performed as a routine clinical practise, and nor was it in our study. Although the introduction of PET may improve the accuracy of the clinical staging, it would still be unlikely to be comparable to surgical staging (Lardinois *et al*, 2003; Cerfolio *et al*, 2004; Shim *et al*, 2005). This would inevitably lead to heterogeneity of the patient population, necessitating a sophisticated study design and large sample size for any future trial on preoperative therapy.

We conclude that the DP combination regimen is active and well tolerated as preoperative chemotherapy, with highly promising survival data. Future clinical trials are warranted based on our results.

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Conflict of interest

Hideo Kunitoh, Masahiro Tsuboi, Yukito Ichinose and Nagahiro Saijo have received honoraria from Sanofi-Aventis.

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Appendix

The following institutions and investigators participated in the trial:

Tohoku University Hospital (Takashi Kondo and Akira Sakurada), Tochigi Cancer Center (Haruhisa Matsuguma), Saitama Cancer Center (Hirohiko Akiyama), National Cancer Center Hospital East (Kanji Nagai, Junji Yoshida and Nagahiro Saijo), National Cancer Center Hospital (Hisao Asamura, Kenji Suzuki and Hideo Kunitoh), Kyorin University School of Medicine (Tomoyuki Goya and Yoshihiko Koshiishi), Tokyo Medical University (Harubumi Kato and Masahiro Tsuboi), Cancer Institute Hospital (Ken Nakagawa and Yukitoshi Satoh), Yokohama Munipical Citizen's Hospital (Koshiro Watanabe and Jun-ichi Nitadori), Niigata Cancer Center Hospital (Teruaki Koike and Yasushi Yamato), Aichi Cancer Center Hospital (Tetsuya Mitsudomi and Shoichi Mori), Osaka Prefectural Hospital Organization Osaka Medical Center for Cancer and Cardiovascular Diseases (Ken Kodama and Masahiko Higashiyama), Osaka Prefectural Hospital Organization Osaka Prefectural Medical Center for Respiratory and Allergic Disease (Mitsunori Ota), Osaka City General Hospital (Hirohito Tada and Ryoji Yamamoto), Hyogo Cancer Center (Morihito Okada, Masahiro Yoshimura and Koichiro Iwanaga), National Hospital Organization Shikoku Cancer Center (Motohiro Yamashita), National Kyushu Cancer Center (Yukito Ichinose and Koji Yamazaki), Nagasaki University School of Medicine (Takeshi Nagayasu and Tsutomu Tagawa).