systemic chemotherapy. Currently, both cisplatin plus etoposide (PE) and cisplatin plus irinotecan (IP) are considered as standard chemotherapeutic regimens for SCLC.[3,4] Despite the high initial sensitivity to chemotherapy, the majority of patients develop disease recurrence. The prognosis of patients with recurrent SCLC is usually abysmal, and the overall survival time after recurrence is reportedly 2 to 4 months.[5]

In general, second-line chemotherapy is considered for cases with recurrent SCLC, and a few studies have reported on the efficacy of some second-line treatments.[6,7] For example, a prospective randomized trial comparing oral topotecan with best supportive care (BSC) revealed the benefits of treatment with oral topotecan in terms of the survival and quality of life.[7]

Although some studies have shown the importance of both response and the duration of the response to initial chemotherapy in predicting the efficacy of second-line chemotherapy,[8-10] the number of studies conducted to identify the prognostic factors in recurrent SCLC patients is quite limited. In this retrospective study, we investigated the prognostic factors in recurrent SCLC patients administered second-line chemotherapy to determine the factors that need to be used for stratifying the patients in future clinical trials.

MATERIALS AND METHODS

Patient Flow

Between July 1992 and December 2003, 515 patients were diagnosed to have SCLC at the National Cancer Center Hospital East, and 474 of these patients received initial chemotherapy with or without thoracic radiotherapy. Of 474 patients, radiographic response was observed in 409 patients, with 98 demonstrating complete response and 311 demonstrating partial response. An evaluation in April 2007 revealed that among these responders, 322 had developed disease recurrence, 75 had maintained responses, and 12 patients could not be evaluated for disease recurrence. Thus, 387 patients (including the 322 with disease recurrence and the 65 nonresponders) were considered potential candidates for second-line chemotherapy. Of these, 232 received second-line chemotherapy, whereas the remaining 155 did not. There were no distinct eligibility criteria for second-line chemotherapy, and the decision to administer chemotherapy was based on the patient's general condition and willingness to undergo second-line therapy. The patient flow is shown in Figure 1. Among patients who received second-line chemotherapy, those who deemed to have stable disease or not to be evaluable to first-line chemotherapy were treated right after completion of front-line therapy. All patients' data were obtained from our database.

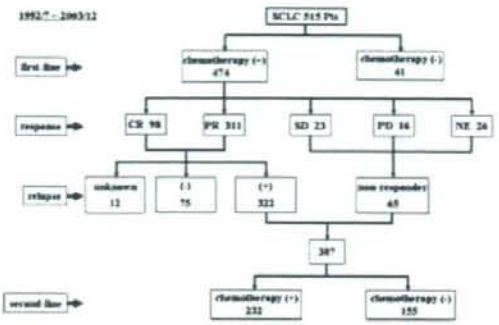

FIGURE 1. Patient flow is depicted. CR indicates complete response; NE, not evaluable; PD, progressive disease; PR, partial response; Pts, patients; SCLC, small-cell lung cancer; SD, stable disease; +, positive; −, negative.

Analyzed Clinical Factors

The correlations between clinical factors evaluated at the time of disease recurrence, such as the age (<70/≥70), sex (women/men), Eastern Cooperative Oncology Group performance status (PS) (0-1 or 2-4), disease extent (limited disease [LD]/extensive disease), sensitivity to first-line chemotherapy (sensitive/refractory), and response to second-line chemotherapy or survival after disease recurrence were retrospectively investigated in the 232 patients. In this study, patients who responded to initial chemotherapy and developed disease recurrence more than 3 months after the completion of chemotherapy were defined as sensitive recurrence cases, whereas patients who did not respond to initial chemotherapy or developed disease recurrence within 3 months were defined as refractory recurrence cases.

Tumor Evaluation and Statistical Analysis

Tumor response was re-evaluated by 2 physicians (Y.H.K. and K.G.) using the Response Evaluation Criteria in Solid Tumors (RECIST).[11] The survival time was measured from the date of disease recurrence. The survival curve was estimated by the Kaplan-Meier method, and compared by the log-rank test. Comparison between each clinical factor and response was performed by the chi-square test. Multivariate analysis was conducted according to the Cox proportional hazard model. $P < .05$ was considered to denote statistical significance. All statistical analyses were performed using StatView statistical

TABLE 1
Characteristics of All Patients at the Time of Disease Recurrence (N = 387)

Characteristics	Second-line Chemotherapy (+) (n=232)	(−) (n=155)	P
Age at recurrence, y			<.0001
Median	65	68	
Range	30-80	28-87	
Gender			.9867
Women	38 (16%)	25 (16%)	
Men	194 (84%)	130 (84%)	
PS at recurrence			<.0001
0-1	162 (70%)	43 (28%)	
2-4	70 (30%)	112 (72%)	
Disease extent at recurrence			.0476
LD	65 (28%)	30 (19%)	
ED	167 (72%)	125 (81%)	
Response to first-line chemotherapy			<.0001
CR/PR	216 (93%)	108 (70%)	
SD/PD	16 (7%)	47 (30%)	
Sensitivity to first-line chemotherapy			.1661
Sensitive	146 (63%)	63 (41%)	
Refractory	86 (37%)	92 (59%)	

+ indicates positive; −, negative; PS, performance status; LD, limited disease; ED, extensive disease; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

software (version 5.0; Abacus Concepts, Berkley, Calif).

RESULTS

Patient Characteristics

The characteristics of the 387 patients who were believed to be potential candidates for second-line chemotherapy (of whom only 232 eventually received second-line chemotherapy, designated as the chemotherapy group) are listed in Table 1. The patients in the chemotherapy group were significantly younger ($P < .0001$), had better PS ($P < .0001$), and had a higher frequency of LD ($P = .0476$) than the nonchemotherapy group. Whereas the response to first-line chemotherapy was significantly different ($P < .0001$), the sensitivity to first-line chemotherapy was not significantly different ($P = .1661$) between the 2 groups, and approximately 33% of the patients who received second-line chemotherapy were refractory recurrence cases. As first-line chemotherapy, 156 patients (67%) had received platinum plus etoposide combination chemotherapy, and 24 (10%) had received the IP regimen. The second-line chemotherapy regimens administered to the 232 patients are listed in Table 2. At our hospital, the vast majority of the patients had received some kind of platinum-based combination chemotherapy, such as cisplatin, vincristine, doxorubicin, and etoposide; cisplatin, etoposide, and irinotecan (PEI); IP; PE; or carboplatin plus etoposide. The distribution of these regimens was similar in the sensitive and refractory recurrence patients.

TABLE 2
Second-line Chemotherapy Regimens Administered to 232 Patients

Regimen	No. of Patients	No. Sensitive (%)	No. Refractory (%)
CODE	80	50 (34)	30 (35)
PEI	44	17 (12)	27 (31)
IP	34	28 (19)	6 (7)
PE	19	13 (9)	6 (7)
CE	14	12 (8)	2 (2)
TOP	14	9 (6)	5 (6)
CPT-11	13	9 (6)	4 (5)
AMR	6	5 (4)	1 (1)
Others	8	3 (2)	5 (6)
Total	232	146 (100)	86 (100)

CODE indicates cisplatin, vincristine, doxorubicin, and etoposide; PEI, cisplatin, etoposide, and irinotecan; IP, cisplatin and irinotecan; PE, cisplatin and etoposide; CE, carboplatin and etoposide; TOP, topotecan; CPT-11, irinotecan; AMR, amrubicin.

TABLE 3
Univariate Analysis for Response and Survival

Characteristics	No. of Patients	Response Rate, %	P	MST, Months	P
Age at recurrence, y					
<70	167	56	.5058	9.0	.6347
≥70	65	62		8.8	
Gender					
Women	38	68	.1826	10.0	.5672
Men	194	55		8.7	
PS at recurrence					
0-1	162	63	.0126	11.0	<.0001
2-4	70	44		4.9	
Disease extent at recurrence					
LD	65	62	.5085	12.6	.0043
ED	167	56		7.3	
Sensitivity to first-line chemotherapy					
Sensitive	146	60	.4413	10.6	.0016
Refractory	86	53		6.8	

MST indicates median survival time; PS, performance status; LD, limited disease; ED, extensive disease.

Predictive and Prognostic Factors

According to the results of the univariate analyses, response was significantly associated with the PS alone, whereas survival was significantly associated with the PS, disease extent, and sensitivity to first-line chemotherapy (Table 3). Survival curves drawn according to the PS and sensitivity to first-line chemotherapy are shown in Figure 2 and 3, respectively. Multivariate analysis identified PS ($P < .0001$) and

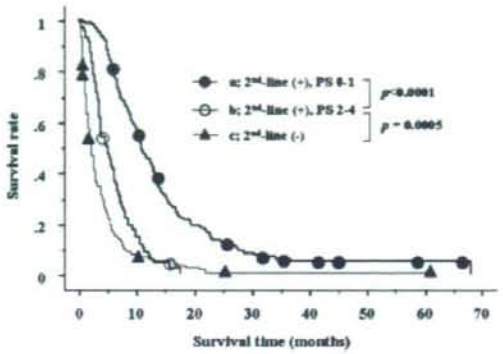

FIGURE 2. Survival curves according to the performance status (PS) at the time of disease recurrence. + indicates positive; −, negative.

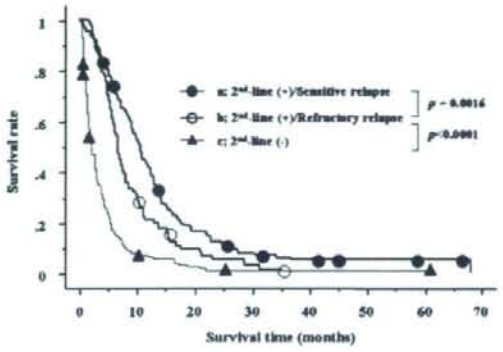

FIGURE 3. Survival curves according to sensitivity to first-line chemotherapy. + indicates positive; −, negative.

sensitivity to first-line chemotherapy ($P = .0024$) as the independent prognostic factors for survival (Table 4). The survival of patients with a PS of 2 to 4 ($P = .005$) (Fig. 2) and refractory disease recurrences ($P < .0001$) (Fig. 3) was significantly better than that of those who did not receive second-line chemotherapy.

In addition, we performed further analysis, in which all patients who received second-line chemotherapy were divided into 4 groups according to the combination of the 2 identified independent prognostic factors for survival: Group A (PS of 0-1/sensitive recurrence), Group B (PS of 0-1/refractory recurrence), Group C (PS of 2-4/sensitive recurrence), and Group D (PS of 2-4/refractory recurrence). The survival curves for each group are shown in Figure 4. The survival of patients with a PS of 0 to 1 was significantly better than that of the patients with a PS of 2 to 4 among both cases with sensitive

TABLE 4
Multivariate Analysis for Survival

Variables	Odds Ratio	95% CI	P
PS at recurrence, 0-1	3.171	2.307-4.357	<.0001
Disease extent at recurrence, LD	1.308	0.956-1.790	.093
Sensitivity to first-line chemotherapy, sensitive	1.544	1.166-2.043	.0024

95% CI indicates 95% confidence interval; PS, performance status; LD, limited disease.

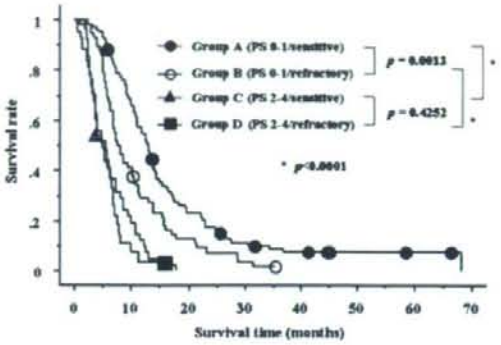

FIGURE 4. Survival curves according to the 2 independent prognostic factors. PS indicates performance status.

(Group A vs Group C; $P < .0001$) and those with refractory recurrence (Group B vs Group D; $P = .0001$). Whereas the survival of the sensitive recurrence cases was significantly better than that of the refractory recurrence cases among the patients with a PS of 0 to 1 (Group A vs Group B; $P = .0013$), no survival difference was observed between the sensitive and refractory recurrence cases among the patients with a PS of 2 to 4 patients (Group C vs Group D; $P = .4252$).

Among the 232 patients who received second-line chemotherapy, 29 received the same regimen as first-line chemotherapy, and the rest received a regimen different from first-line chemotherapy. However, these differences did not appear to have an impact on either response ($P = .7519$) or survival ($P = .5873$).

DISCUSSION

Some studies have shown the importance of both response and the duration of the response to initial chemotherapy in predicting the survival of recurrent SCLC patients receiving second-line chemotherapy,[8-10] and currently it is widely accepted that recurrent SCLC patients should be classified into 2 groups: cases with sensitive recurrence and those with refrac-

tory recurrence.[12] In contrast, Sundstrom et al, who recently analyzed 19 clinical factors at both the time of initial diagnosis and the time of recurrence, have suggested that the PS at the time of disease recurrence, and not the sensitivity status to first-line chemotherapy, was the only significant prognostic indicator for survival after second-line chemotherapy.[13] In this study, we investigated the relation between clinical factors evaluated at the time of disease recurrence and survival after recurrence, and identified both PS and sensitivity to first-line chemotherapy as being significant prognostic factors for survival.

Some may argue that the survival time of the patients with a PS $\geq$3 in this study was too short, which might have strongly influenced the inferior survival of the patients with a PS of 2 to 4 as compared with that of the patients with a PS of 0 to 1. Although our study included 18 cases with a PS $\geq$3 among the patients administered second-line chemotherapy, the results of the analyses were found to be the same even after exclusion of these patients with a PS $\geq$3 (data not shown). This finding suggests that the prognosis of the patients with a PS of 2 is clearly different from that of the patients with a PS of 0 to 1 patients. The diversity of our second-line regimens may be criticized as well, because the differences in the regimens could have affected the patients' outcomes. However, to our knowledge, there are no comparative studies suggesting the superiority of any particular regimen for second-line chemotherapy. At our hospital, as shown in Table 2, mainly platinum-based combination chemotherapy is used even for second-line chemotherapy, and various agents are combined with platinum agents.

The results of the current study indicate that the prognosis of patients with impaired PS is inevitably poor. In such patients, no survival difference was found between the cases with sensitive and those with refractory recurrence. Does this mean that patients with a PS $\geq$2 should not receive second-line chemotherapy? A phase 3 trial comparing oral topotecan with BSC demonstrated a significant survival advantage of oral topotecan, and such survival benefit was also found to be preserved for patients with a PS of 2 who accounted for approximately 30% of the enrolled patients.[7] Conversely, with regard to the patients with a PS $\geq$3, there is no evidence as yet to suggest the clinical benefit of administering second-line chemotherapy. In our study, however, response rates of 64% in patients with a PS of 3 (n = 14) and 25% in patients with a PS of 4 (n = 4) were observed. These results suggest that second-line chemotherapy might be beneficial for adequately selected patients with a PS of $\geq$2, although the survival benefit is limited as compared with that for the patients with a PS of 0 to 1. Further studies are required for precise selection of criteria for second-line chemotherapy.

In this study, the survival of patients who received second-line chemotherapy with a PS of 2 to 4 or refractory recurrences was still significantly better than that of those who did not receive second-line chemotherapy. However it was not surprising, because the patient selection for second-line chemotherapy was performed pragmatically, and patients who were thought to be unfit for chemotherapy were not administered second-line chemotherapy. The finding that the nonchemotherapy group had more patients with a PS of 2 to 4 and refractory recurrence, the 2 independent prognostic factors identified in this study, suggests that our patient selection was reasonable.

The prognosis of recurrent SCLC patients is generally poor, and to our knowledge no standard treatment has been established for these patients. In addition to the randomized trial comparing oral topotecan with BSC mentioned above, 2 phase 3 trials for recurrent SCLC have been reported to date.[14,15] A trial comparing intravenous topotecan with the combination of cyclophosphamide, doxorubicin, and vincristine demonstrated comparable response rates and survival; however, intravenous topotecan yielded greater symptomatic improvement for 4 of the 8 symptoms evaluated.[14] In the other trial, comparing oral topotecan with intravenous topotecan, no survival difference was observed.[15] Currently, topotecan is the only drug approved by the US Food and Drug Administration for recurrent SCLC. Recently, however, promising results of phase 2 studies have been reported for drugs other than topotecan for recurrent SCLC. In particular, amrubicin[16,17] and PEI[18,19] have been shown to yield excellent response rates and survival in not only sensitive but also refractory recurrent cases. In Japan, a phase 3 randomized trial comparing topotecan with PEI is now ongoing.

In conclusion, we identified PS and sensitivity to initial chemotherapy as being significant prognostic factors for survival in patients with recurrent SCLC treated with second-line chemotherapy. PS was also found to be predictive in terms of response. In future clinical trials of second-line chemotherapy, both PS and sensitivity to initial chemotherapy should be incorporated as stratification factors. The survival benefit of second-line chemotherapy is limited in patients with impaired PS, even among sensitive recurrence cases. Therefore, careful consideration of the potential risks and benefits is required in the treatment of these patients.

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ANTI TUMOUR TREATMENT

Advances in the treatment of non-small cell lung cancer

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KEYWORDS
Lung cancer;
Molecular target drugs;
Chemotherapy;
Clinical trials

Summary While there have been advances in the treatment of lung cancer, they have been marginal in comparison with recent advances in the chemotherapy and molecularly targeted treatment of breast cancer, colorectal cancer and genitourinary cancer. Lung cancer is an extremely difficult disease to treat, and to obtain positive results and to develop new standard treatment. The results of clinical trial on gefitinib and erlotinib suggest that the evaluation of molecular target drugs seems to be quite difficult in unselected patient population and may be different from cytotoxic drugs. We need to find out specific molecular biomarkers for each drug. With global studies in view, it will be essential to obtain even more significant results by sophisticated clinical trials in selected patient populations and contribute to improving the treatment outcome of lung cancer patients.

It is a well-known fact that lung cancer ranks first as a cause of cancer deaths in developed countries. The number of new cases of lung cancer and the number of deaths from lung cancer are very similar, and the cure rate is regarded to be about 15% even in advanced countries, and 7–8% in developing countries. Despite numerous comparative studies and positive data, very few patients experience any benefit from them. The importance of primary prevention (anti-smoking measures) is recently becoming widely recognized, but an even greater effort is needed. In terms of secondary prevention (lung cancer screening), there are no definitive data in clinical trials, such as quality control, and the conduct of screening examinations has not been reflected in reduced mortality. Under these circumstances the incidence of lung cancer is still rapidly increasing in many countries. A wide variety of clinical trials of treatments have been conducted for lung cancer, which is diagnosed in more than 70,000 new patients annually in Japan. In addition, the results of many of the studies obtained recently have been contrary to expectations, and it seems necessary to reassess the relationship between the pharmacology such as pharmacokinetics, pharmacodynamics and pharmacogenomics and clinical efficacy of each drug in regard to drug therapy.[1]

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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

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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 pharmaDx™ 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.

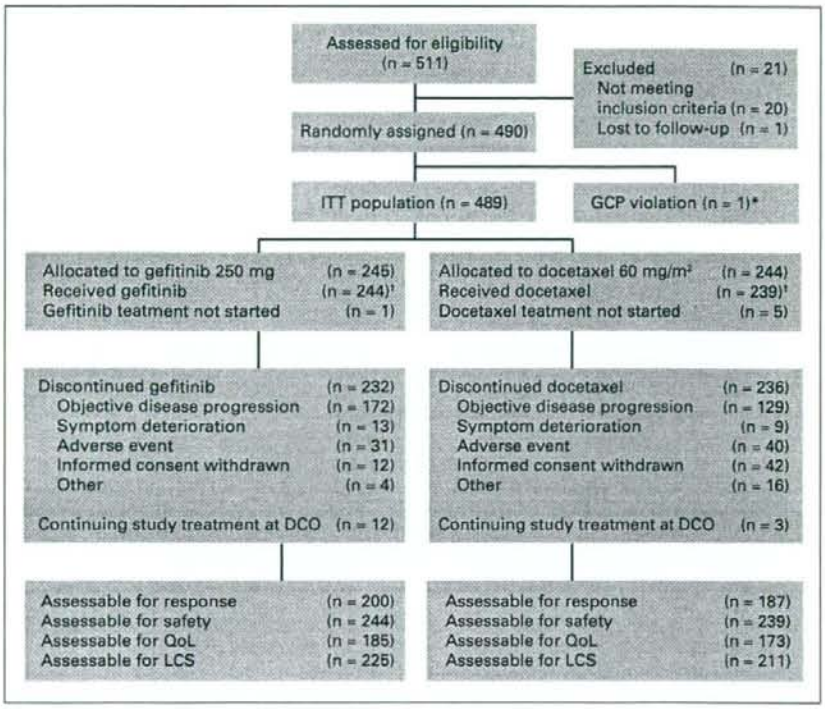

Fig 1. Study flow. (*) Allocated to the docetaxel group. (†) The safety analysis, conducted according to treatment received, was performed on this population. ITT, intent to treat; GCP, Good Clinical Practice; DCO, data cutoff date for overall survival (October 31, 2006); QoL, quality of life; LCS, Lung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

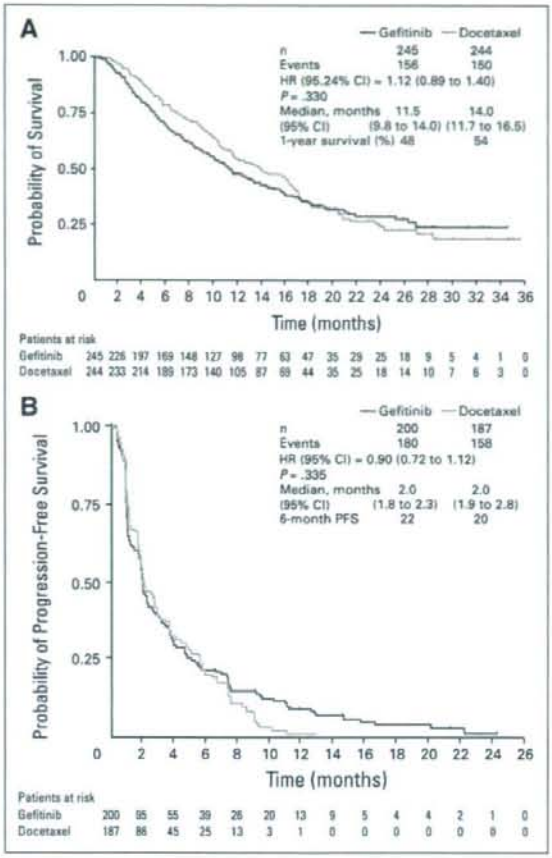

Fig 2. (A) Overall survival in the intent-to-treat population; (B) Progression-free survival (PFS) in the assessable-for-response population. HR, hazard ratio.

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: Gefitinib — Total No. of Assessable Patients	Gefitinib — %	Treatment Arm: Docetaxel — Total No. of Assessable Patients	Docetaxel — %	Analysis — OR	Analysis — 95% CI	Analysis — 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

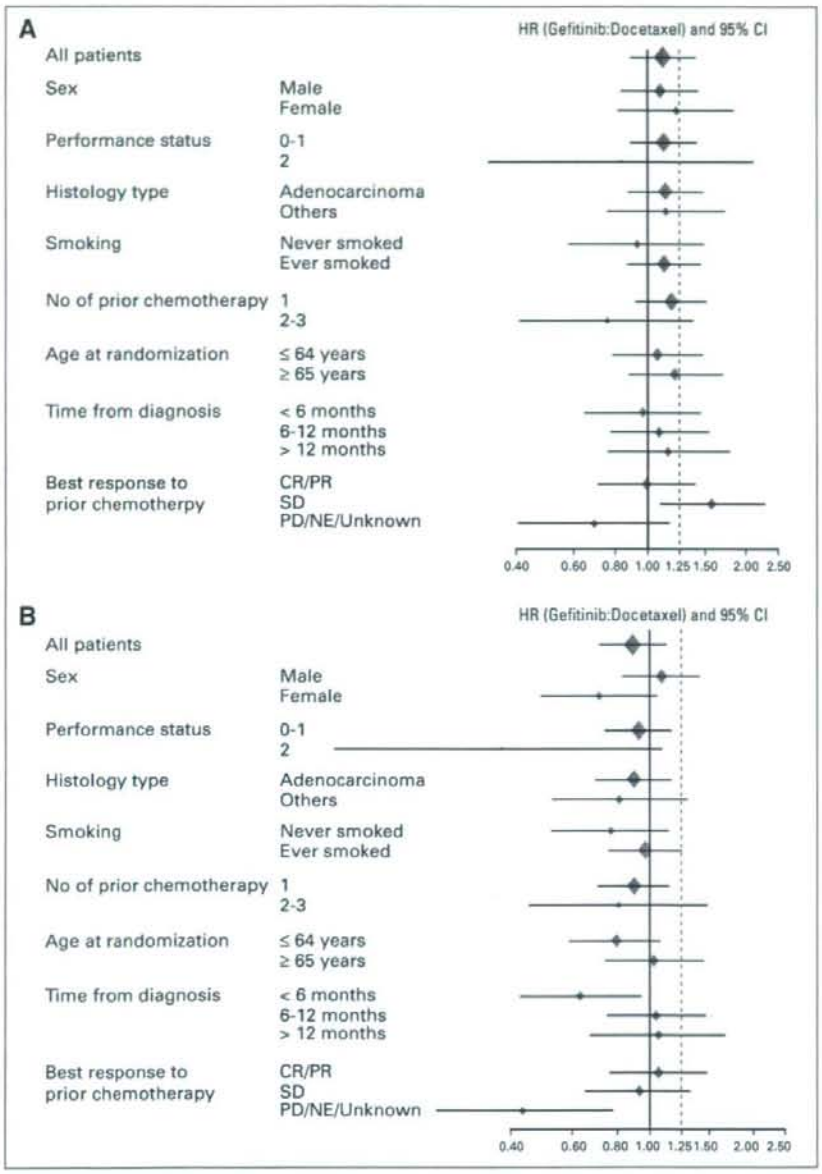

Fig 3. Forest plots of (A) overall survival and (B) progression-free survival that compare treatment groups within clinically relevant subgroups. HR, hazard ratio; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not assessable.

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

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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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®).

