Thus, both hematologic and nonhematologic toxicities were generally manageable, and in most instances, treatment could be continued in an outpatient setting, resulting in a median of five treatment courses (range, 1-15).

In conclusion, we have presented the results of the first plhase II study of the combination of S-1 and irinotecan for the treatment of chemotherapy-naive patients with advanced NSCLC. This regimen yielded a response rate, progression-free survival, and overall survival similar to or better than those previously reported for platinum-based regimens. In addition, this regimen was well tolerated and could be administered in an outpatient setting. Given its efficacy and favorable toxicity profile, the combination of S-1 and irinotecan is a promising alternative for treatment of advanced NSCLC and a feasible nonplatinum option to which molecularly targeted agents can be added. The chemotherapy regimens of S-1 plus platinum derivatives have been studied (11). We are currently conducting a randomized phase III trial comparing carboplatin/S-1 with carboplatin/paclitaxel for chemonaive advanced NSCLC. We firmly believe that further trials comparing S-1 plus irinotecan with platinum-based doublet chemotherapy (perhaps carboplatin/S-1) are warranted.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin 2007;57:43–66.
2. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. BMJ 1995;311:899–909.
3. Clinical practice guidelines for the treatment of unresectable non-small-cell lung cancer. Adopted on May 16, 1997 by the American Society of Clinical Oncology. J Clin Oncol 1997;15:2996–3018.
4. Socinski MA, Crowell R, Hensing TE, et al. Treatment of non-small cell lung cancer, stage IV: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007;132:277–89S.
5. Shirasaka T, Nakano K, Takechi T, et al. Antitumor activity of 1 M tegafur-0.4 M 5-chloro-2,4-dihydroxypyridine-1 M potassium oxonate (S-1) against human colon carcinoma orthotopically implanted into nude rats. Cancer Res 1996;56:2602–6.
6. Takechi T, Nakano K, Uchida J, et al. Antitumor activity and low intestinal toxicity of S-1, a new formulation of oral tegafur, in experimental tumor models in rats. Cancer Chemother Pharmacol 1997;39:205–11.
7. Robben NC, Pippas AW, Moore JO. The syndrome of 5-fluorouracil cardiotoxicity. An elusive cardiopathy. Cancer 1993;71:493–509.
8. Kato T, Shimamoto Y, Uchida J, et al. Possible regulation of 5-fluorouracil-induced neuro- and oral toxicities by two biochemical modulators consisting of S-1, a new oral formulation of 5-fluorouracil. Anticancer Res 2001;21:1705–12.
9. Shirasaka T, Shimamoto Y, Fukushima M. Inhibition by oxonic acid of gastrointestinal toxicity of 5-fluorouracil without loss of its antitumor activity in rats. Cancer Res 1993;53:4004–9.
10. Kawahara M, Furuse K, Segawa Y, et al. Phase II study of S-1, a novel oral fluorouracil, in advanced non-small-cell lung cancer. Br J Cancer 2001;85:939–43.
11. Ichinose Y, Yoshimori K, Sakai H, et al. S-1 plus cisplatin combination chemotherapy in patients with advanced non-small cell lung cancer: a multi-institutional phase II trial. Clin Cancer Res 2004;10:7860–4.
12. Fukuoka M, Niitani H, Suzuki A, et al. A phase II study of CPT-11, a new derivative of camptothecin, for previously untreated non-small-cell lung cancer. J Clin Oncol 1992;10:16–20.
13. Negoro S, Masuda N, Takada Y, et al. Randomised phase III trial of irinotecan combined with cisplatin for advanced non-small-cell lung cancer. Br J Cancer 2003;88:335–41.
14. Takiuchi H, Narahara H, Tsujinaka T, et al. Phase I study of S-1 combined with irinotecan (CPT-11) in patients with advanced gastric cancer (OGSG 0002). Jpn J Clin Oncol 2005;35:520–5.
15. Yamada Y, Yasui H, Goto A, et al. Phase I study of irinotecan and S-1 combination therapy in patients with metastatic gastric cancer. Int J Clin Oncol 2003;8:374–80.
16. Goto A, Yamada Y, Yasui H, et al. Phase II study of combination therapy with S-1 and irinotecan in patients with advanced colorectal cancer. Ann Oncol 2006;17:968–73.
17. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.
18. D'Addario G, Pintilie M, Leighl NB, Feld R, Cerny T, Shepherd FA. Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. J Clin Oncol 2005;23:2926–36.
19. Vanhoefer U, Harstrick A, Achterrath W, Cao S, Seeber S, Rustum YM. Irinotecan in the treatment of colorectal cancer: clinical overview. J Clin Oncol 2001;19:1501–18.
20. Houghton JA, Cheshire PJ, Hallman JD II, et al. Evaluation of irinotecan in combination with 5-fluorouracil or etoposide in xenograft models of colon adenocarcinoma and rhabdomyosarcoma. Clin Cancer Res 1996;2:107–18.
21. Inokuchi M, Yamashita T, Yamada H, et al. Phase I/II study of S-1 combined with irinotecan for metastatic advanced gastric cancer. Br J Cancer 2006;94:1130–5.
22. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92–8.
23. Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol 2003;21:3016–24.
24. Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. Ann Oncol 2007;18:317–23.
25. Hotta K, Fujiwara Y, Matsuo K, et al. Recent improvement in the survival of patients with advanced nonsmall cell lung cancer enrolled in phase III trials of first-line, systemic chemotherapy. Cancer 2007;109:939–48.

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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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A B S T R A C T

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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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,[3] 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.[7] 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).[8,11]

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.

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 (≥ 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 pharmDx™ 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 < 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, 11 v 12 months[3]), and the study plan was to recruit 481 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 ≥ 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 ≥ 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 ≥ 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.

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.

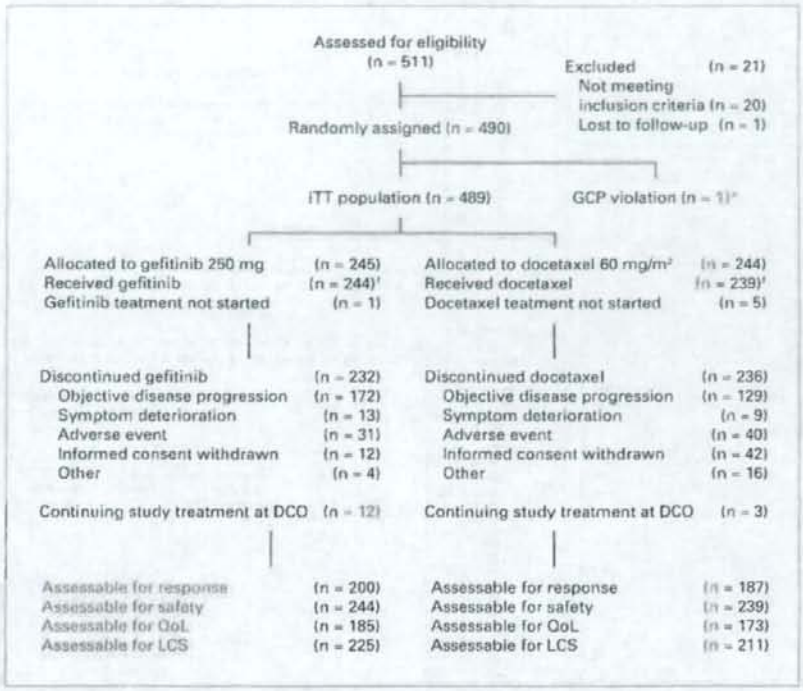

Fig 1. Study flow. (*) Allocated to the docetaxel group. (†) The safety analysis, conducted according to treatment received, was performed on the population. ITT, intent to treat; GCP, Good Clinical Practice; DCO, data cutoff date for overall survival (October 31, 2006); QoL, quality of life; LCS, Lung 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 ≤ 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	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	140	57.1	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

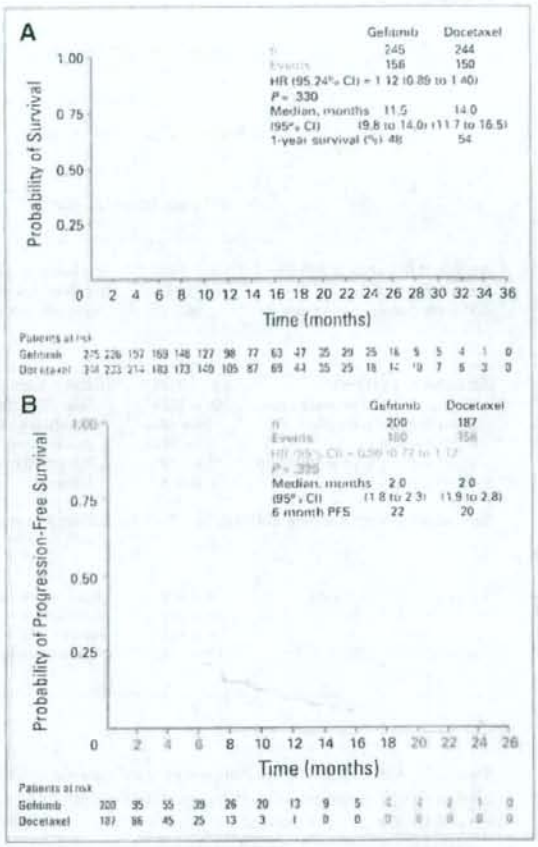

Fig 2. (A) Overall survival in the intent-to-treat population. (B) Progression-free survival (PFS) in the assessable-for-response population. HR, hazard ratio.

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							
	Treatment Arm				Analysis		
	Gefitinib		Docetaxel				
Rate	Total No. of Assessable Patients	%	Total No. of Assessable Patients	%	OR	95% CI	P
Response	[illegible]		187				
Overall		22.5		12.8	2.14	1.21 to 3.78	.009
Disease control		34.0		33.7	[illegible]	[illegible]	.735
Improvement							
FACT-L	[illegible]	[illegible]	173	13.9	1.80	1.09 to 2.98	.023
TOI	[illegible]	20.5	173	8.7	2.72	1.44 to 5.16	.002
LCS	[illegible]	[illegible]	211	[illegible]	[illegible]	0.72 to 1.81	[illegible]

Abbreviations: OR, odds ratio; FACT-L, Functional Assessment of Cancer Therapy–Lung (Japanese version 4A, which includes two additional cancer-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.

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[15]) 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).[1,2,11]

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

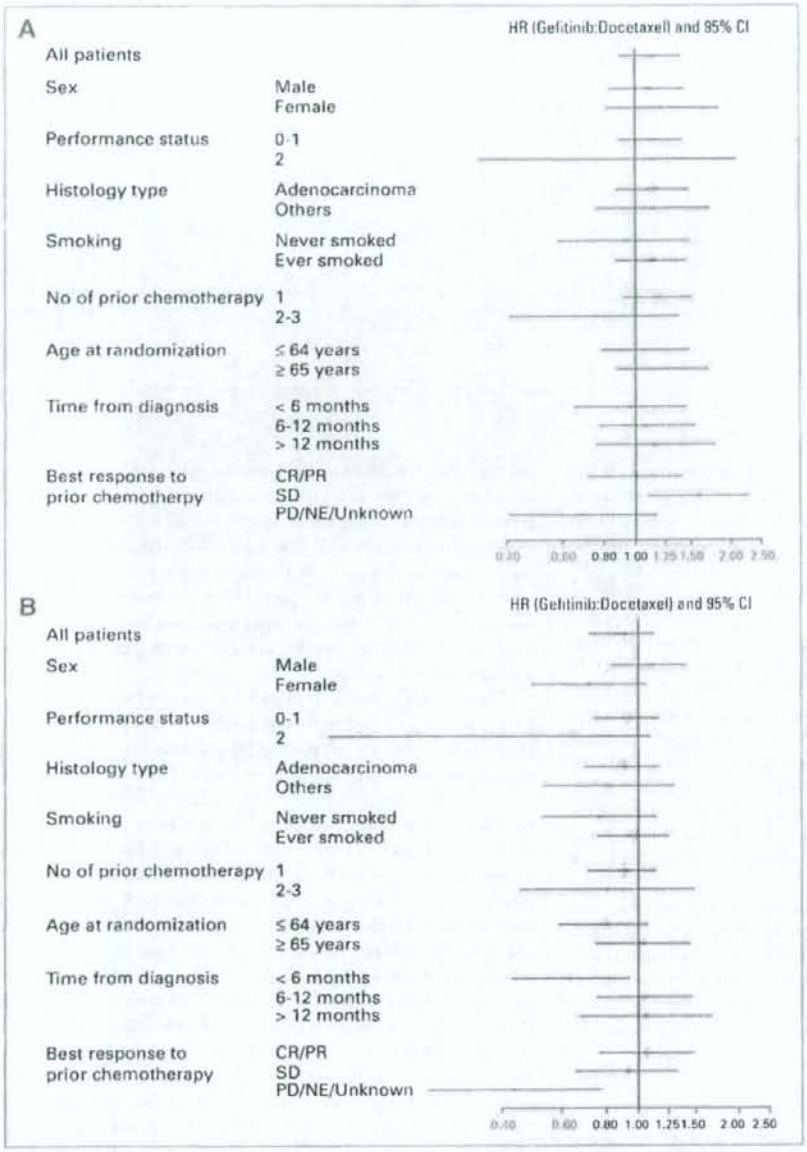

Fig 3. Forest plots of (A) overall survival and (B) progression-free survival that compare treatment groups within clinically relevant subgroups. HR, hazard ratio; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not assessable.

previously to experience improved clinical benefit with gefitinib.[2,1,7,8,10] 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 Association for Safety Population

Category	Patients			
	Gefitinib (n = 244)		Docetaxel (n = 230)	
	No.	%	No.	%
Adverse events	242	99.2	228	99.1
Treatment-related adverse events	233	95.5	223	97.0
Treatment discontinuation because of an adverse event	33	13.5	40	17.4
NCI-CTC adverse event grades 3 to 4	99	40.6	185	80.4
Serious adverse events	42	17.2	31	13.5
Death as a result of a serious adverse event	4	1.6	0	0
ILD events	14	5.7	7	3.0

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 = 229)			
	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 (93.4%[1] and 81.5%[3]). 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.

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1. Mukohara T, Takeda K, Miyazaki M, et al: Japanese experience with second-line chemotherapy with low-dose (60 mg/m2) docetaxel in patients with advanced non-small-cell lung cancer. Cancer Chemother Pharmacol 48(6):356-360, 2001

2. Hanna N, Shepherd FA, Fossella FV, et al: Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 22:1589-1597, 2004

3. Shepherd FA, Dancey J, Ramlau R, et al: Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 18:2095-2103, 2000

4. Nakamura Y, Kunitoh H, Kubota K, et al: Retrospective analysis of safety and efficacy of low-dose docetaxel 60 mg/m2 in advanced non-small-cell lung cancer patients previously treated with platinum-based chemotherapy. Am J Clin Oncol 26:459-464, 2003

5. Shepherd FA, Rodrigues PJ, Ciuleanu T, et al: Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 353:123-132, 2005

6. Fossella FV, Devore R, Kerr RN, et al: Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. J Clin Oncol 18:2354-2362, 2000

7. Kris MG, Natale RB, Herbst RS, et al: Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: A randomized trial. JAMA 290:2149-2158, 2003

8. Fukuoka M, Yano S, Giaccone G, et al: Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. J Clin Oncol 21:2237-2246, 2003

9. Nishiwaki Y, Yano S, Tamura T, et al: [Subset analysis of data in the Japanese patients with NSCLC from IDEAL 1 study on gefitinib]. Gan To Kagaku Ryoho 31:567-573, 2004

10. Thatcher N, Chang A, Parikh P, et al: Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: Results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet 366:1527-1537, 2005

11. Chang A, Parikh P, Thongprasert S, et al: Gefitinib (IRESSA) in patients of Asian origin with refractory advanced non-small-cell lung cancer: Subset analysis from the ISEL study. J Thorac Oncol 1:847-855, 2006

12. Cappuzzo F, Hirsch FR, Rossi E, et al: Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer. J Natl Cancer Inst 97:643-655, 2005

13. Cufer T, Vrdoljak E, Gaafar R, et al: Phase II, open-label, randomized study (SIGN) of single-agent gefitinib (IRESSA) or docetaxel as second-line therapy in patients with advanced (stages IIIB to IV) non-small-cell lung cancer. Anticancer Drugs 17:401-409, 2006

14. Non-Small-Cell Lung Cancer Collaborative Group: Chemotherapy in non-small-cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 311:899-909, 1995

15. Kudoh S, Takeda K, Nakagawa K, et al: Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small-cell lung cancer: Results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). J Clin Oncol 24:3657-3663, 2006

16. Douillard J-Y, Kim ES, Hirsh V, et al: Phase III, randomized, open-label, parallel group study of oral gefitinib (IRESSA) versus intravenous docetaxel in patients with locally advanced or metastatic non-small-cell lung cancer who have previously received

[illegible] Cancer 5:2, 2007 [illegible]

17. Yoshida [illegible]

18. [illegible] mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 350:2129-2139, 2004

19. [illegible]

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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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JOURNAL OF CLINICAL ONCOLOGY 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 (≥ 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 ≤ 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* ≥ 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 ≥ 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 ≥ 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.

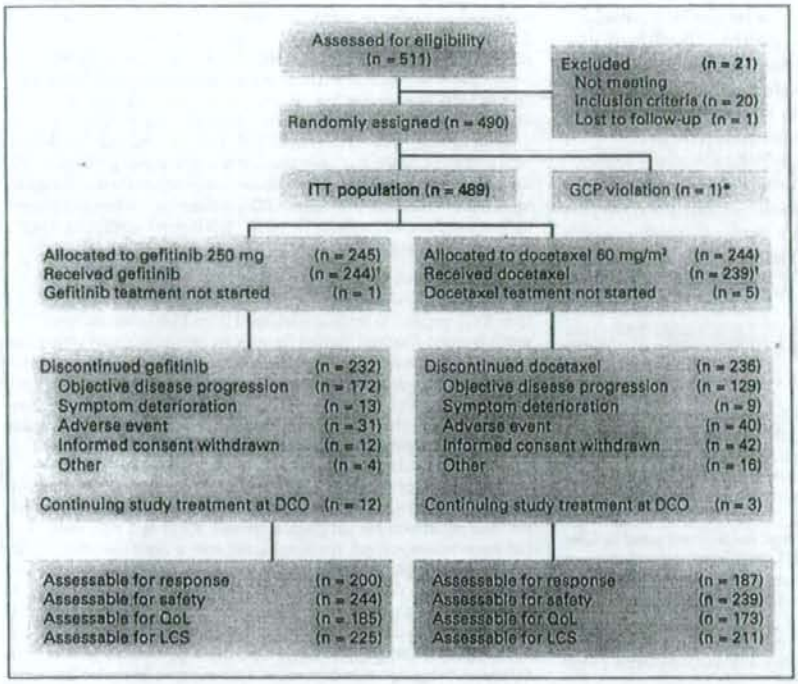

Fig 1. Study flow. (*) Allocated to the docetaxel group. (†) The safety analysis, conducted according to treatment received, was performed on this population. ITT, intent to treat; GCP, Good Clinical Practice; DCO, data cutoff date for overall survival (October 31, 2006); QoL, quality of life; LCS, Lung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

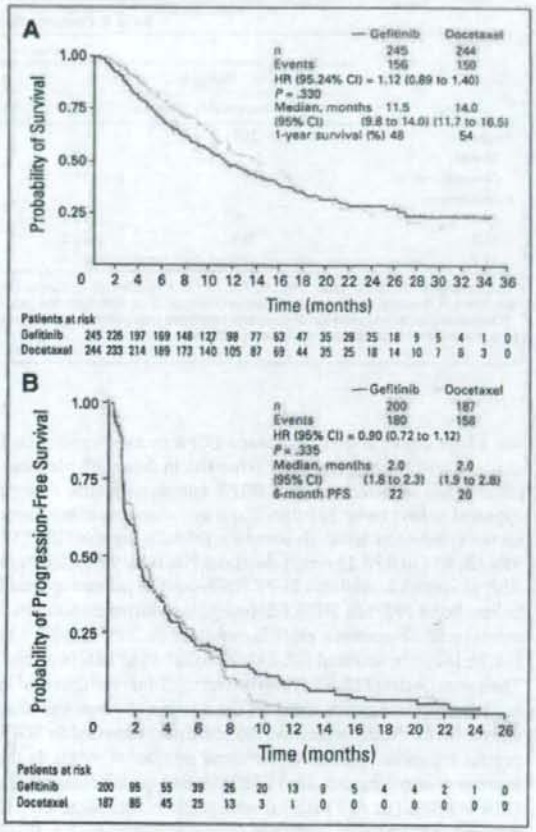

Fig 2. (A) Overall survival in the intent-to-treat population; (B) Progression-free survival (PFS) in the assessable-for-response population. HR, hazard ratio.

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 — %	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

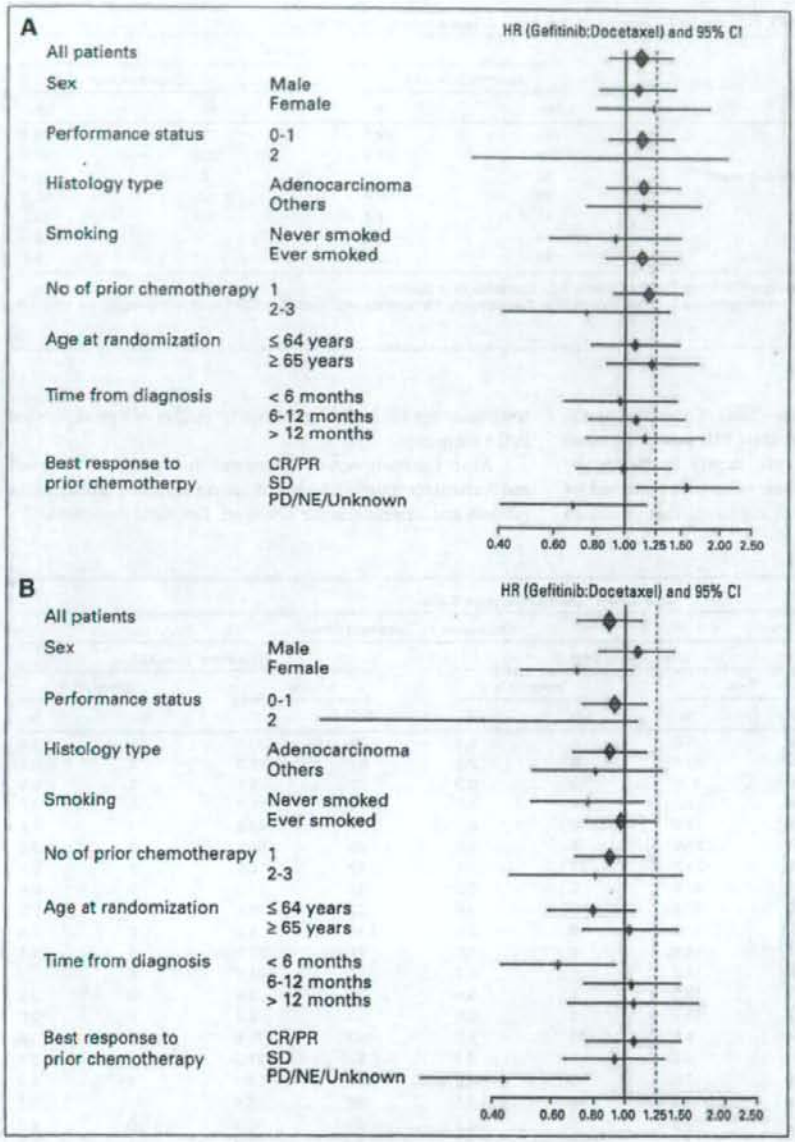

Fig 3. Forest plots of (A) overall survival and (B) progression-free survival that compare treatment groups within clinically relevant subgroups. HR, hazard ratio; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not assessable.

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

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REFERENCES

1. Mukohara T, Takeda K, Miyazaki M, et al: Japanese experience with second-line chemotherapy with low-dose (60 mg/m2) docetaxel in patients with advanced non-small-cell lung cancer. Cancer Chemother Pharmacol 48(5):356-360, 2001
2. Hanna N, Shepherd FA, Fossella FV, et al: Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 22:1589-1597, 2004
3. Shepherd FA, Dancey J, Ramlau R, et al: Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 18:2095-2103, 2000
4. Nakamura Y, Kunitoh H, Kubota K, et al: Retrospective analysis of safety and efficacy of low-dose docetaxel 60 mg/m2 in advanced non-small-cell lung cancer patients previously treated with platinum-based chemotherapy. Am J Clin Oncol 26:459-464, 2003
5. Shepherd FA, Rodrigues PJ, Ciuleanu T, et al: Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 353:123-132, 2005
6. Fossella FV, Devore R, Kerr RN, et al: Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. J Clin Oncol 18:2354-2362, 2000
7. Kris MG, Natale RB, Herbst RS, et al: Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: A randomized trial. JAMA 290:2149-2158, 2003
8. Fukuoka M, Yano S, Giaccone G, et al: Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. J Clin Oncol 21:2237-2246, 2003
9. Nishiwaki Y, Yano S, Tamura T, et al: [Subset analysis of data in the Japanese patients with NSCLC from IDEAL 1 study on gefitinib]. Gan To Kagaku Ryoho 31:567-573, 2004
10. Thatcher N, Chang A, Parikh P, et al: Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: Results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet 366:1527-1537, 2005
11. Chang A, Parikh P, Thongprasert S, et al: Gefitinib (IRESSA) in patients of Asian origin with refractory advanced non-small-cell lung cancer: Subset analysis from the ISEL study. J Thorac Oncol 1:847-855, 2006
12. Cappuzzo F, Hirsch FR, Rossi E, et al: Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer. J Natl Cancer Inst 97:643-655, 2005
13. Cufer T, Vrdoljak E, Gaafar R, et al: Phase II, open-label, randomized study (SiGN) of single-agent gefitinib (IRESSA) or docetaxel as second-line therapy in patients with advanced (stages IIIB to IV) non-small-cell lung cancer. Anticancer Drugs 17: 401-409, 2006
14. Non-Small-Cell Lung Cancer Collaborative Group: Chemotherapy in non-small-cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 311:899-909, 1995
15. Kudoh S, Takeda K, Nakagawa K, et al: Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small-cell lung cancer: Results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). J Clin Oncol 24: 3657-3663, 2006
16. Douillard J-Y, Kim ES, Hirsh V, et al: Phase III, randomized, open-label, parallel-group study of oral gefitinib (IRESSA) versus intravenous docetaxel in patients with locally advanced or metastatic non-small-cell lung cancer who have previously received

platinum-based chemotherapy (INTEREST). Eur J Cancer 5:2, 2007 (suppl)

17. Yoshida S: The results of gefitinib prospective investigation. Med Drug J 41:772-789, 2005

18. Lynch TJ, Bell DW, Sordella R, et al: Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 350:2129-2139, 2004

19. Sequist LV, Joshi VA, Janne PA, et al: Response to treatment and survival of patients with non-small-cell lung cancer undergoing somatic EGFR mutation testing. Oncologist 12:90-98, 2007

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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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Questionnaire Survey of Treatment Choice for Breast Cancer Patients with Brain Metastasis in Japan: Results of a Nationwide Survey by the Task Force of the Japanese Breast Cancer Society

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Objective: A nationwide survey was performed to investigate the current patterns of care for brain metastasis (BM) from breast cancer in Japan.
Method: A total of 351 survey questionnaires were sent to community or academic breast oncologists who were members of the Japanese Breast Cancer Society as of December 2005. The questionnaire consists of 40 multiple choice questions in eight categories.
Results: Of 240 institutions sent survey questionnaires, 161 (67.1%) answered; 60% of institutions answered with '<5' patients with BM every year; almost half (83 of 161) screened for BM in asymptomatic patients; surgical resection was rarely performed, as ~75% of institutions (118 of 160 institutions) answered 'none or one case of surgery per year'; 27% (41 of 154) preferred stereotactic radiosurgery (SRS) over whole-brain radiotherapy (WBRT) as the initial treatment in all cases, although ~70% (100 of 154) of them answered 'depend on cases'. The preference for SRS over WBRT mainly depends on the impressions of breast oncologists about both safety (late normal tissue damage and dementia in WBRT) and efficacy (better local control by SRS). Eighty-one percent (117 of 144) of institutions did not limit the number of SRS sessions as far as technically applicable.
Conclusion: SRS is widely used as the first choice for BM from breast cancer in Japan. Considerable numbers of Japanese breast oncologists prefer SRS over WBRT as the initial treatment for BM. A randomized trial comparing SRS and WBRT is warranted.

Key words: breast cancer – brain metastasis – stereotactic radiosurgery – whole-brain radiotherapy

INTRODUCTION

Brain metastasis (BM) is one of the most devastating complications of cancer and is usually associated with poor prognosis. The incidence of BM is high among patients with breast cancer, 10–20% in general (1). The incidence of BM in patients with HER2/neu over-expression is considered to be especially high, around 25–40% (2–5).

Whole-brain radiotherapy (WBRT) is the standard treatment for most patients with BM. For patients with a single BM, surgery followed by WBRT is superior to WBRT alone (6,7), although some studies does not support this (8). For patients with limited number (usually one to three) of BM, there is a controversy as discussed later (9). For patients with multiple (usually four or more) BM, WBRT is standard treatment.

Stereotactic radiosurgery (SRS) was developed in 1950s (10) and is now widely used as an alternative to surgery, WBRT and sometimes both. WBRT followed by SRS boost

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