and who were included in the safety analysis, interstitial-lung-disease events developed in only 16 (2.6%), 3 of whom (0.5%) died.

In summary, this study shows that first-line therapy with gefitinib as compared with carboplatin–paclitaxel prolongs progression-free survival, increases the objective response rate, and improves quality of life among clinically selected patients with non–small-cell lung cancer. The presence of an *EGFR* mutation was a robust predictor of improved progression-free survival with gefitinib, as compared with carboplatin–paclitaxel, and of the benefit of gefitinib with respect to the objective response rate, indicating that patients in whom an *EGFR* mutation has been identified will benefit most from first-line therapy with gefitinib.

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APPENDIX

Members of the First Line Iressa versus Carboplatin/Paclitaxel in Asia (Iressa Pan-Asia Study [IPASS]) Study Organization were as follows: Steering Committee: T.S. Mok, M. Fukuoka, S. Thongprasert, Y.-L. Wu, C.-H. Yang, D.-T. Chu, N. Saijo, H. Jiang, C.L. Watkins, A.A. Armour (K.F. To, pathologist, advisor to steering committee). **Independent Data and Safety Monitoring Committee:** A. Chang, K. Eguchi, M. Buyse, S. Zuckerman. **International Coordinating Investigators:** T.S. Mok, M. Fukuoka. **Study Personnel:** S. Rigby, study coordinator and study delivery leader; H. Jiang, study physician; P. Magill, study physician; E.L. Duffield, biostatistician. **Investigators:** *China* — C. Bojun, X. Cai, X. Cai, Q. Chen, X. Chen, Y. Chen, Z. Chen, W. Cheng, X. Chongrui, D. Chu, T. Chu, J. Dai, Z. Ding, J. Duan, M. Fan, Y. Fan, J. Feng, X. Fu, M. Gao, A. Gu, J. Gu, Z. Guan, B. Han, A. Hao, Z. He, W. Hong, X. Hong, M. Hou, C. Huang, J. Huang, P. Huang, Y. Huang, Y. Huang, Y. Huang, W. 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REFERENCES

1. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non–small-cell lung cancer. N Engl J Med 2005;353:123-32.
2. Kim ES, Hirsch V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. Lancet 2008; 372:1809-18.
3. Park K, Goto K. A review of the benefit-risk profile of gefitinib in Asian patients with advanced non-small-cell lung cancer. Curr Med Res Opin 2006;22:561-73.
4. 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 2005;366: 1527-37.
5. Kosaka T, Yatabe Y, Endoh H, Kuwano H, Takahashi T, Mitsudomi T. Mutations of the *epidermal growth factor receptor* gene in lung cancer: biological and clinical implications. Cancer Res 2004;64:8919-23.
6. Shigematsu H, Lin L, Takahashi T, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. J Natl Cancer Inst 2005;97:339-46.
7. 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 2004;350:2129-39.
8. Paez JG, Jänne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497-500.
9. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci U S A 2004;101:13306-11.
10. Inoue A, Suzuki T, Fukuhara T, et al. Prospective phase II study of gefitinib for chemotherapy-naive patients with advanced non-small-cell lung cancer with epidermal growth factor receptor gene mutations. J Clin Oncol 2006;24:3340-6.
11. Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med 2009;361. DOI: 10.1056/NEJMoa0904554.
12. Sequist LV, Martins RG, Spigel D, et al. First-line gefitinib in patients with advanced non-small-cell lung cancer harboring somatic EGFR mutations. J Clin Oncol 2008;26:2442-9. [Erratum, J Clin Oncol 2008;26:3472.]
13. Chang G-C, Chen K-C, Yang T-Y, et al. Activity of gefitinib in advanced non-small-cell lung cancer with very poor performance status. Invest New Drugs 2005;23:73-7.
14. Kimura H, Kasahara K, Shibata K, et al. EGFR mutation of tumor and serum in gefitinib-treated patients with chemotherapy-naive non-small cell lung cancer. J Thorac Oncol 2006;1:260-7.
15. Lee DH, Han JY, Lee HG, et al. Gefitinib as a first-line therapy of advanced or metastatic adenocarcinoma of the lung in never-smokers. Clin Cancer Res 2005;11: 3032-7.
16. Yang CH, Yu CJ, Shih JY, et al. Specific EGFR mutations predict treatment outcome of stage IIIB/IV patients with chemotherapy-naive non-small-cell lung cancer receiving first-line gefitinib monotherapy. J Clin Oncol 2008;26:2745-53.
17. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975;31:103-15.
18. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205-16.
19. Cella DF, Bonomi AE, Lloyd SR, Tulsky DS, Kaplan E, Bonomi P. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. Lung Cancer 1995;12:199-220.
20. Cella D, Eton DT, Fairclough DL, et al. What is a clinically meaningful change on the Functional Assessment of Cancer Therapy-Lung (FACT-L) Questionnaire? Results from Eastern Cooperative Oncology Group (ECOG) Study 5592. J Clin Epidemiol 2002; 55:285-95.
21. Newton CR, Graham A, Heptinstall LE, et al. Analysis of any point mutation in DNA: the Amplification Refractory Mutation System (ARMS). Nucleic Acids Res 1989;17:2503-16.
22. Whitcombe D, Theaker J, Guy SP, Brown T, Little S. Detection of PCR products using self-probing amplicons and fluorescence. Nat Biotechnol 1999;17:804-7.
23. Morikawa T, Yoshida M. A useful testing strategy in phase III trials: combined test of superiority and test of equivalence. J Biopharm Stat 1995;5:297-306.
24. Westfall PH, Young SS. Resampling-based multiple testing. New York: Wiley, 1993.
25. Pfister DG, Johnson DH, Azzoli CG, et al. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. J Clin Oncol 2004;22:330-53.
26. 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.
27. Hirsch FR, Varella-Garcia M, Bunn PA Jr, et al. Molecular predictors of outcome with gefitinib in a phase III placebo-controlled study in advanced non-small-cell lung cancer. J Clin Oncol 2006;24:5034-42.
28. Tamura K, Okamoto I, Kashii T, et al. Multicentre prospective phase II trial of gefitinib for advanced non-small-cell lung cancer with epidermal growth factor receptor mutations: results of the West Japan Thoracic Oncology Group trial (WJTOG0403). Br J Cancer 2008;98:907-14.
29. Han S-W, Kim T-Y, Hwang PG, et al. Predictive and prognostic impact of epidermal growth factor receptor mutation in non-small-cell lung cancer patients treated with gefitinib. J Clin Oncol 2005;23: 2493-501.
30. Zhu CQ, da Cunha SG, Ding K, et al. Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR2.1. J Clin Oncol 2008;26:4268-75.
31. Maheswaran S, Sequist LV, Nagrath S, et al. Detection of mutations in *EGFR* in circulating lung-cancer cells. N Engl J Med 2008;359:366-77.

Reasons for response differences seen in the V15-32, INTEREST and IPASS trials

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Abstract | The first phase III study to assess the effect of gefitinib and docetaxel on the survival of Japanese patients with non-small-cell lung cancer who received previous treatment with platinum doublets, the V15-32 trial, did not establish noninferiority of gefitinib over docetaxel in terms of the effect on overall survival, despite the results showing a twofold higher response rate to gefitinib. The overall survival favored docetaxel for the first 18 months and gefitinib thereafter. The INTEREST trial, which compared docetaxel and gefitinib, demonstrated noninferiority of gefitinib, and the survival curves were completely superimposed. In this trial, patients had been recruited from 24 countries from Europe, Asia, and North and South America. Results of the IPASS trial showed superior progression-free survival for gefitinib compared with the combination of carboplatin and paclitaxel as first-line treatment in Asian patients who were nonsmokers and had adenocarcinoma histology. In this Review, we discuss the reasons for the differences in the effects of molecular-targeted drugs and cytotoxic antineoplastic agents observed in these trials. We also highlight the magnitude of the antitumor activity of these two different categories of drugs, and discuss how this could affect future clinical trial design and analysis.

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Introduction

At present, the consensus opinion is that the efficacy of lung cancer chemotherapy with cytotoxic agents has reached a plateau, and it is difficult to expect superior efficacy with any novel cytotoxic anticancer agents that will become available in the near future. It is generally believed that the results seen with different platinum doublet regimens are of a similar magnitude, no matter which combination is used. However, slight differences were seen in results reported by the Eastern Cooperative Oncology Group (ECOG) study,[1] Four Arm Clinical Study (FACS),[2] South Western Oncology Group (SWOG) trial,[3] and Tax 326 study.[4] In the ECOG trial, progression-free survival seen with gemcitabine plus cisplatin was better than in the other treatment arms that included paclitaxel plus cisplatin, docetaxel plus cisplatin and paclitaxel plus carboplatin.[1] In the FACS trial, the overall survival rates observed for carboplatin plus paclitaxel and cisplatin plus vinorelbine were inferior compared with the gemcitabine plus cisplatin and irinotecan plus cisplatin,[2] and overall survival of cisplatin plus docetaxel was significantly better than that of cisplatin and vinorelbine.[3] In everyday clinical practice, treatment arms are selected taking into consideration factors such as the toxicity profile and ease of use on an outpatient basis. The choices of treatment used in combination with radiation therapy and surgery are based on consideration of patient adherence to the drugs administered.

Competing interests
N. Saijo has declared associations with the following companies: AstraZeneca, Bristol-Myers Squibb, Chugai-Roche, and Eli Lilly. H. Kunitoh declared associations with the following companies: AstraZeneca, Bristol-Myers Squibb and Sanofi-Aventis. See the article online for full details of the relationships. M. Takeuchi declared no competing interests.

Clinical outcomes with EGFR inhibitors

EGFR is a member of the HER family, which consists of four members: EGFR/HER1/erbB1, HER2/neu/erbB2, HER3/erbB3, and HER4/erbB4.[5] Once the ligands bind to the extracellular domain of EGFR proteins, the receptors dimerize with other EGFR family members to form homodimers or heterodimers, which induce phosphorylation of the tyrosine kinase EGFR and activation of downstream signal pathways.[6] EFGR–tyrosine kinase inhibitors (EGFR-TKIs) are molecular-targeted drugs that, in general, target the ATP binding site of protein kinases and show competitive inhibition, thereby preventing correct functioning of the receptor in tumor cells. Great advances are expected in the treatment of non-small-cell lung cancer (NSCLC) when these agents become available because they have demonstrated impressive tumor shrinkage in patients with disease refractory to platinum and taxane therapy even in phase I clinical trials.[7,8] It has been difficult to demonstrate any survival benefit of these agents in the clinical setting.[9–13] In phase III studies that compared erlotinib with placebo as second-line and third-line chemotherapy, a survival benefit in favor of erlotinib was demonstrated. In the ISEL (Iressa Survival Evaluation in Lung Cancer) trial that compared gefitinib with placebo in similar populations of patients, no survival advantage was seen with gefitinib; however, significant prolongation of survival

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Key points

- Many unexpected results were observed in the randomized, controlled trials of EGFR-targeted tyrosine kinase inhibitors (TKIs)
- The nature and quantity of antitumor effects are different between cytotoxic chemotherapy and molecular-targeted drugs
- Selection of patients is extremely important for future clinical trials that test EGFR-TKIs
- Results from the IPASS trial demonstrate that EGFR-TKIs provide superior progression-free survival compared with platinum-based doublet chemotherapy in selected patients with non-small-cell lung cancer, especially those with mutated *EGFR*

Table 1 | Data from randomized, controlled trials of EGFR-TKIs for NSCLC treatment

Study	EGFR-TKI agent	Selection of patients	Difference in end points between treatment and control
ISEL[a]	Gefitinib vs placebo	None	Negative
BR.21[a]	Erlotinib vs placebo	None	Positive
INTACT 1&2	Gefitinib vs combination	None	Both negative
TALENT & TRIBUTE[a]	Erlotinib vs combination	None	Both negative
V15-32	Gefitinib vs docetaxel	Japanese	Negative
INTEREST[a]	Gefitinib vs docetaxel	None	Positive
IPASS	Gefitinib vs carboplatin plus PTL	Adenocarcinoma, Asian, nonsmoking	Positive
WJTOG0203	Gefitinib vs platinum doublet (consolidation)	Japanese	Not available

[a]Discrepancies: BR.21 versus TALENT & TRIBUTE; ISEL versus INTEREST. Abbreviations: NSCLC, non-small-cell lung cancer; PTL, paclitaxel, trastuzumab and lapatinib; TKI, tyrosine kinase inhibitor.

time was observed in Asian patients.[14,15] Four large, randomized, controlled trials of standard platinum-based chemotherapy (carboplatin plus paclitaxel or cisplatin plus gemcitabine) with or without EGFR-TKIs yielded negative results in patients with advanced NSCLC who had not received previous chemotherapy.[9–12] In addition, the SWOG trial showed that the intensification with gefitinib after chemoradiotherapy in stage III NSCLC provided significantly poorer survival than in the control group.[13] As the reported response rates to EGFR-TKIs in Western populations are ≤10%, this low percentage does not reflect the prolongation of survival.

By contrast, gefitinib has been found to have outstanding therapeutic effect in a phase II clinical trial of Japanese patients, with reported response rates of 27.5%, median duration of response of 114 days, and median survival time of 13.8 months.[16] Subsequent clinical trials that included Asian populations showed higher response rates and better survival rates associated with this drug compared with placebo;[14,17] however, no such benefit was seen in Western patients.[14] A phase II trial of gefitinib in nontreated, nonselected, Japanese patients with NSCLC produced a similar response rate compared to patients with previous therapy.[18] Analysis of clinical factors has demonstrated that Asian ethnicity, female gender, adenocarcinoma histology and nonsmoking status are favorable factors in relation to the efficacy of EGFR-TKIs.[15,19,20]

In 2004, the presence of activating mutations of *EGFR* in tumor cells was reported to be extremely important for achieving the antitumor effect of EGFR-TKIs.[21,22] In patients with these *EGFR* mutations the response rate to EGFR-TKIs is approximately 80%.[23–31] The response duration ranged from 7.0 months to 10.7 months. The frequency of *EGFR* mutations is higher in Asian populations (30–40%) compared with Western populations (5–10%).[30] A higher frequency of these mutations in Japanese populations was also shown to correlate with the presence of favorable clinical factors such as adenocarcinoma, female gender and nonsmoking status.[26,29,31] Some have suggested that other biomarkers, such as *EGFR* amplification status detected by fluorescent *in situ* hybridization, could also be useful indicators of the response to EGFR-TKIs; however, these biomarkers are not reliable.[29,32] The problem with results obtained using fluorescent *in situ* hybridization is that this technique might detect two genetic abnormalities, namely, *EGFR* amplification and high polysomy. High polysomy is usually not well-correlated with the presence of *EGFR* mutations.[32–34] In Japan, gefitinib has been approved by the Ministry of Health, Welfare and Labour on the basis of data from the IDEAL (phase II) study and data from trials showing the survival benefit of gefitinib in Japanese populations.

Data from the V15-32 study of gefitinib

Two randomized, controlled trials conducted in Western patients have reported the effects of docetaxel in patients with previously treated NSCLC.[35,36] Prolongation of survival was demonstrated in the docetaxel-treated groups compared with groups given best supportive care or treated with ifosfamide and/or vinorelbine. Docetaxel was, therefore, established as the gold standard for second-line chemotherapy in patients with NSCLC.[35,36] No data, however, compared the activities of docetaxel and placebo in the second-line setting in Japan. On the basis of comparative studies of pemetrexed and docetaxel, pemetrexed is now employed more frequently in the US for treating patients with NSCLC in the second-line setting.[37] In Japan, however, pemetrexed has not been approved for use in patients with lung cancer because insufficient studies in Japanese populations have been carried out, even though a clinical phase II study has been completed.[38] There has also been a report describing the superiority of erlotinib in prolonging the survival of previously treated patients with NSCLC compared with best supportive care in the second-line or third-line setting.[39] This drug has just been approved for treatment of lung cancer in Japan.[40]

V15-32 was an open-label, randomized phase III study that compared 250 mg gefitinib with 60 mg/m^2 docetaxel in Japanese patients with NSCLC and a history of failure of one or two chemotherapy regimens (Figure 1).[41] The main purpose of this study was to demonstrate the

noninferiority of gefitinib over docetaxel for overall survival in these patients, according to predefined criteria (that is, upper threshold of the CI of the hazard ratio [HR] less than 1.25). A total of 484 patients were accrued, with 242 in each treatment arm; however, noninferiority of gefitinib for overall survival could not be established (HR 1.12; 95% CI 0.89–1.40), and no significant difference in overall survival was apparent between the two treatment groups ($P=0.330$). A Cox regression analysis, with adjustments for imbalances in the baseline characteristics of the patients, yielded an HR of 1.01 (95% CI of 0.80–1.27), $P=0.914$ (Table 2 and Figure 2).[41] Secondary end points included progression-free survival, time-to-treatment failure, response rate, and disease control rate. These end points were evaluated in the patients who had measurable target lesions at study entry. Gefitinib treatment was associated with a significantly improved overall response rate (22.5% versus 12.8%, $P=0.009$) and time-to-treatment failure (HR 0.63; 95% CI 0.51–0.77, $P<0.001$). No significant differences in progression-free survival (HR 0.90; 95% CI 0.72–1.12, $P=0.335$) or disease control rate (34% versus 33.2%, $P=0.735$) were seen between the two treatment groups.[41] Since cessation of chemotherapy in those without disease progression was included as an event for time-to-treatment failure, comparison of this end point between docetaxel and gefitinib-treated patients would not have much clinical relevance.

Additional analysis of V15-32

On behalf of the Drug Safety Policy Panel and FDA Safety Investigation Committee, Takeuchi stated the following on the basis of results of the V15-32 trial.[42] Firstly, the two groups were well balanced and met the requirements of randomization, which assured the comparability of the groups. Secondly, the hazard ratios in two comparative groups on Cox regression analysis should remain constant regardless of the passage of time. In the current study, it does not seem likely that this prerequisite was met; it is difficult, therefore, to evaluate the therapeutic results from the major outcome of the analysis, because the HRs were assumed to be constant regardless of the passage of time.

To understand how the therapeutic benefit in the gefitinib group, compared with the docetaxel group, changed in a time-dependent manner, Takeuchi conducted a retrospective, exploratory investigation of the effect at various time intervals, using survival rate as the evaluation index. In terms of the survival rate at an early stage of follow-up (that is, less than 1 year) the CI for the therapeutic effect indicated that docetaxel was superior to gefitinib. After about 24 months, however, the results showed a tendency for gefitinib to be superior to docetaxel. The CI was so wide that it was difficult to conclude that gefitinib was indeed superior to docetaxel at this stage (Figure 3).

Interpretation of the results of V15-32

The V15-32 study was the first comparative, large-scale, randomized trial conducted in previously treated patients with NSCLC in Japan. It is highly noteworthy that 490 patients were recruited within a period of about 2.5 years and accurate results were obtained. The median survival rates for docetaxel and gefitinib were 11.5 and 14.0 months, respectively. Despite the problems related to selection of patients, the results showed the high level of medical care in Japan. The initial hypothesis of noninferiority of gefitinib was not established. This finding implies that there might be a high probability of gefitinib being inferior to docetaxel for treating patients with NSCLC in the second-line setting. Docetaxel, therefore, remains the drug of first choice in these patients. As subset analyses could not identify subgroups of patients in whom gefitinib yielded better outcomes than docetaxel, a 'docetaxel-first' policy should be employed even in patients with a favorable risk profile (that is, females, adenocarcinoma histology and never-smokers). The response rates of patients to gefitinib were greater than 20%, and almost double that seen with docetaxel. Although the study was small, some of the patients treated with gefitinib have shown prolonged progression-free survival, and the survival curve of the gefitinib group crossed over the survival curve for the docetaxel group 18 months after treatment initiation.[41] These results strongly suggest that gefitinib could be beneficial in a subset of docetaxel-resistant and docetaxel-intolerant patients. The results of the primary analysis of gefitinib versus docetaxel have neither confirmed nor refuted these effects of gefitinib.[41] For the first 18 months after initiation of treatment, the survival rate was better in the docetaxel group than in the gefitinib group; the reasons for this finding may be hypothesized as follows: first, gefitinib might promote tumor proliferation; second, gefitinib might exert potent toxicity in some patients; and third, the antitumor activity of docetaxel might be superior in the overall population of patients. It is likely that the third reason could explain the better survival rate of the docetaxel group, and the late benefit of gefitinib would not have been expected if the first and second reasons are likely. One could speculate that docetaxel, a cytotoxic agent, would have some effect against the vast majority of the tumors, while gefitinib, a targeted agent, might be totally ineffective in patients not expressing the target. The differences in survival curves in the initial phase of follow-up might have reflected the effect of these 'relatively resistant' cases. Many patients, particularly from the docetaxel group, were actually crossed over to receive the other treatment. This made interpretation of the survival

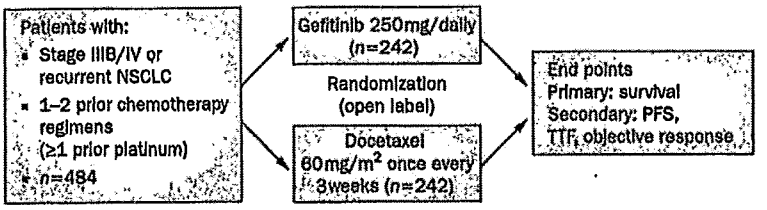
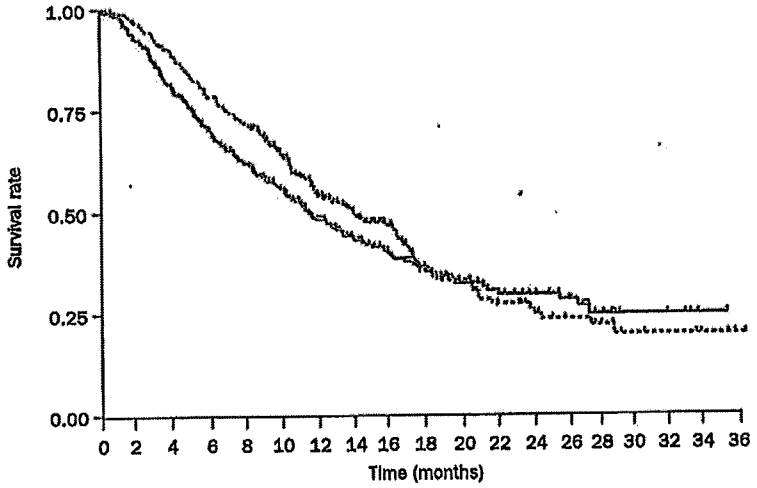


Figure 1 | Schematic diagram to show the randomization schema for the randomized phase III V15-32 trial. Abbreviations: NSCLC, non-small-cell lung cancer; PFS, progression-free survival; TTF, time-to-treatment failure. Data courtesy of AstraZeneca.

Table 2 | Overall survival data (intent-to-treat analysis) from the V15-32 study

Study outcomes	Gefitinib	Docetaxel
Number of patients	245	244
Number of events	156	150
Median (range) survival time (months)	11.5 (9.8–14.0)	14.0 (11.7–16.5)
1-year survival (%)[a]	48	54
Response rate (%)	22.5	12.8

[a]Hazard ratio 1.12 (95% CI 0.89–1.40; P=0.330). Noninferiority could not be demonstrated.



Number of patients at risk

Gefitinib	245	226	197	169	148	127	98	77	63	47	35	29	25	18	9	5	4	1	0
Docetaxel	244	233	214	189	173	140	105	87	69	44	35	25	18	14	10	7	6	3	0

Figure 2 | Table showing the overall survival data for patients treated in the randomized phase III V15-32 trial. Data courtesy of AstraZeneca.

results even more difficult. The decision to treat patients in the docetaxel arm with gefitinib as a post-protocol therapy was probably on the basis of clinical information available; that is, patients with clinical features known to be favorable for the effect of gefitinib were selected. This selection criterion might have offset the survival benefit of gefitinib in the later phase of follow-up.[43]

On 1 February 2007, the Ministry of Health, Labour and Welfare examined the results of the V15-32 trial presented to the Drug Safety Policy Panel, Safety Policy Investigation Committee, and Second Food and Drug Advisory Board of 2006. The results of this meeting were published.[44] First, the safety policy on interstitial pneumonia described in the package insert concerning the adverse events of gefitinib is to be continued. Second, there is no evidence to support the preference of gefitinib over docetaxel for second-line or third-line treatment. Third, to evaluate the clinical efficacy of gefitinib, the difference in the survival curves in the V15-32 study should be analyzed in detail and detailed subset analyses must be conducted. Forth, clinical factors that might affect the drug effects, and the effect of *EGFR* mutations on drug responsiveness, must be evaluated.

Results of the INTEREST trial

The INTEREST trial was a randomized, open-label, parallel-group, phase III trial of gefitinib versus docetaxel in patients with locally advanced or metastatic and/or recurrent NSCLC with a previous history of platinum-based chemotherapy.[45] The phase III study enrolled 1,466 patients from 149 centers in 24 countries. The primary end point was overall survival. The overall survival and 1-year survival rates were 7.6 months and 23%, respectively, in the gefitinib group. The corresponding survival rates were 8.0 months and 34%, respectively, in the docetaxel group. No significant differences in the outcomes between the two treatment arms were noted. The study demonstrated the noninferiority of gefitinib compared with docetaxel. Gefitinib was better tolerated, and the total outcome index of quality of life also favored gefitinib. On the basis of these data, AstraZeneca submitted a marketing authorization application to the European Medicines Agency for gefitinib as an agent for patients with locally advanced or metastatic NSCLC with a previous history of treatment with platinum-containing regimens. It is not known why the INTEREST trial demonstrated positive results, because the response rate to gefitinib is lower in Western patients compared with Japanese patients. The adjusted HR of gefitinib versus docetaxel in the V15-32 study was 1.01, which was almost identical to that in the INTEREST trial (HR = 1.02). This finding suggests that the efficacy of gefitinib was similar to that of docetaxel. Asian patients treated with docetaxel had a better outcome than Asian patients treated with gefitinib in the INTEREST trial. By contrast, Asian patients did not derive a benefit in the placebo arm in the ISEL trial. Since *EGFR* mutation was associated with better response to docetaxel in the INTEREST trial, it is possible that docetaxel worked better in the Asian patients, offsetting gefitinib efficacy in the comparisons and improving the overall outcomes of the Asian subset in the INTEREST and V15-32 studies.

Differences between TKIs and cytotoxic agents

Comparison of cytotoxic agents and molecular-targeted therapeutic drugs reveals that although the former show broader anticancer spectra, their maximal therapeutic quality in responders might be inferior compared with that of molecular-targeted therapeutic agents. Molecular-targeted agents can show narrow antitumor spectra but they can produce a profound effect. In general, the potency of the antitumor effect of the conventional cytotoxic agents is likely to be greater when clinical trials are conducted on large numbers of patients. Molecular-targeted agents exhibit antitumor activity only in those cells that possess the relevant molecular target, hence the effects of these drugs on overall tumor volume reduction would be lower than that of the conventional cytotoxic agents, even when both exert the same response rate.

Thus, the survival rate of patients treated with the molecular-targeted agents might not improve, even if the response rate is twice that of the conventional cytotoxic agents. The results of the V15-32 study indicate

this possibility. Waterfall plot figures have been used frequently for evaluation of the antitumor activities of drugs. The rates of variability in the responses of the tumors of each patient are plotted. If the value is positive the tumor is judged to have increased in size, and if the value is negative the tumor is judged to have reduced in size. The number of patients experiencing even the slightest tumor reduction is often expressed as a percentage. Waterfall plots have been suggested to be suitable for evaluation of the effects of cytotoxic antineoplastic agents against malignant tumors because they suppress tumor growth regardless of the molecular target of each agent. RECIST (Response Evaluation Criteria in Solid Tumors), commonly used all over the world for drug evaluation, have been introduced because it is impossible to measure the size of each tumor accurately. It would be unreasonable to expect highly reliable results from Waterfall plots, as it is not possible to measure tumor size accurately. These plots perhaps suffer from over or underestimation of the effects of drugs. There are occasional reports of analysis of the effects of molecular-targeted agents by the use of Waterfall plots. It has been suggested that cases demonstrating reduction of tumor size can be clearly separated from those not showing a size reduction in the evaluation of the antitumor effects of molecular-targeted drugs, because molecular-targeted drugs are effective only against tumors with expression of the molecular target (Figure 4). If we view the results of V15-32 with this information in mind, it is probable that the magnitude of the antitumor activity of docetaxel overall would be greater than that of gefitinib, which shows significant effect only in a small number or specific subsets of patients. In particular, it would be anticipated that differences in the antitumor activities between conventional cytotoxic agents and molecular-targeted agents would be marked in those patients who do not express the molecular targets.

Patients that may benefit from gefitinib

The high degree of sensitivity to gefitinib of NSCLCs that harbor *EGFR* mutations has been demonstrated in a prospective phase II study: the response rate to gefitinib was about 80%, and both progression-free survival and overall survival were prolonged.[28,31] NSCLC with *EGFR* mutations has also been suggested to be highly sensitive to cytotoxic antineoplastic agents, and it would be necessary to establish the superiority of gefitinib through comparative studies in this group of patients. It is unknown whether gefitinib should be the preferred drug in patients with tumors carrying *EGFR* mutations. According to a report from the National Cancer Center Central Hospital in Japan, the efficacy rates of gefitinib in those with *EGFR* mutations is 82% compared with only 11% in those without such mutations. Thus, the decision to employ gefitinib on the basis of the presence of *EGFR* mutations in the tumors would be incorrect—possibly in as many as 10–20% of the patients.[29] Moreover, determination of the presence of *EGFR* mutations is possible in only 25% of patients with advanced lung cancer, which

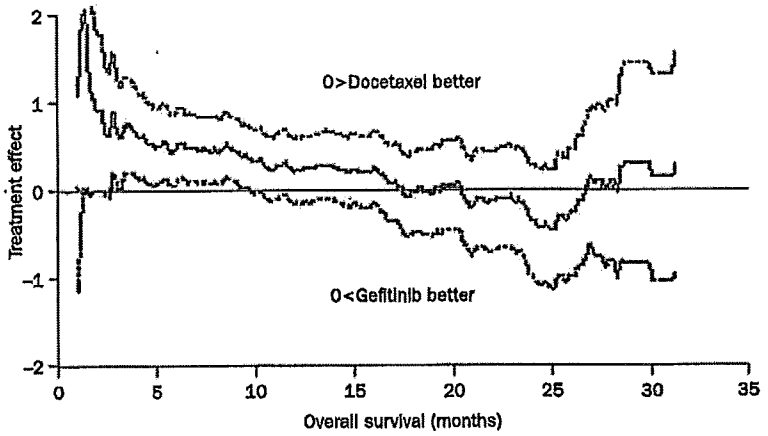


Figure 3 | Retrospective analysis of the survival data from the randomized phase III V15-32 trial. Permission obtained from Takeuchi © Takeuchi, M. *J. Lung Cancer* 7, 1–8 (2007)

poses a problem in selecting the most appropriate treatment.[8] The problem could be resolved if the methodology for the detection of *EGFR* mutations could be improved. It is known that progression-free survival and overall survival end points are favorable among patients who are Asian, are female, have adenocarcinoma histology and are nonsmokers, but the number of patients who meet all of these criteria is limited. Furthermore, when a group of patients who meet at least one of these criteria is selected, the incidence of false-positive and false-negative responses will increase. The results of the V15-32 study suggest that gefitinib should be administered as the drug of first choice only to patients with clear-cut targets, but currently there are no methods to distinguish these patients in a reliable manner.

Results of the IPASS trial

IPASS (IRESSA Pan Asia Study) was a phase III study designed to compare oral gefitinib monotherapy with intravenous carboplatin and paclitaxel chemotherapy as first-line treatment in chemotherapy-naive Asian patients with advanced NSCLC.[46] The eligibility criteria were: age ≥18 years, life expectancy ≥12 weeks, adenocarcinoma histology, never-smokers or light ex-smokers, performance status 0–2, stage IIIB/IV, and presence of measurable disease. A total of 1,217 patients were recruited between March 2006 and October 2007 from nine Asian countries, including China, Japan, Thailand, Taiwan, Indonesia, Malaysia, Philippines, Hong Kong and Singapore. Patients were randomly assigned to receive either 250 mg daily gefitinib ($n=609$) or carboplatin (AUC 5 or 6) and paclitaxel (200 mg/m^2) ($n=608$). The primary end point was noninferiority of these two arms for progression-free survival. The secondary end points were overall survival, objective response rate, quality of life, symptomatic improvement, and toxicity. Association of the efficacy with EGFR biomarkers was also analyzed as an exploratory end point. The study exceeded its primary end point and demonstrated the

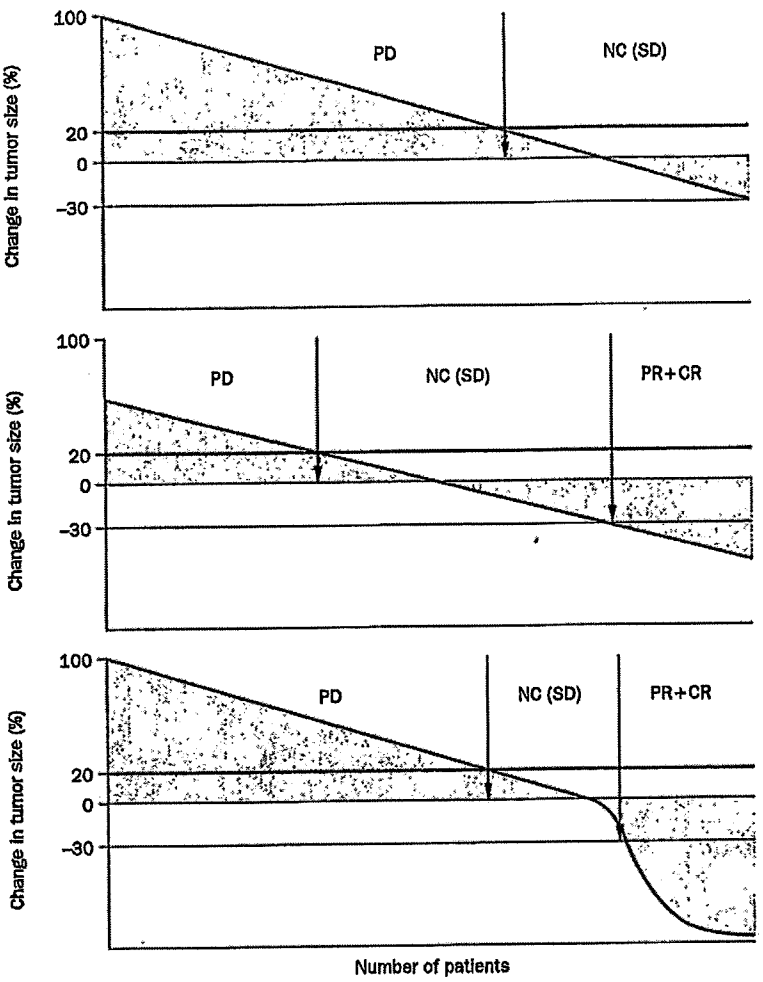


Figure 4 | Waterfall plots showing the differences in the effect of cytotoxic drugs and molecular-target drugs on tumor size. Abbreviations: CR, complete response; NC, no change; PD, progressive disease; PR, partial response; SD, standard deviation. Permission obtained from Takeuchi © Takeuchi, M. *J. Lung Cancer* 7, 1–8 (2007)

superiority of gefitinib over carboplatin and paclitaxel, in terms of progression-free survival, in the first-line setting. The risk of overall progression was reduced by 26% in gefitinib-treated patients compared with those who were administered chemotherapy.[46]

Interestingly, the treatment effect was not constant over time. The progression-free survival curves crossed at 6 months, favoring carboplatin and paclitaxel during the first 6 months and gefitinib thereafter. This evidence suggested there were two different populations of patients with regard to response to the chemotherapy doublet and gefitinib. In exploratory biomarker analyses, the progression-free survival was longer for patients with *EGFR* mutations who received gefitinib, compared to chemotherapy. By contrast, progression-free survival was longer for those in the carboplatin and paclitaxel arm than the gefitinib arm in patients with wild-type *EGFR*. A similar trend was observed in the exploratory analyses based on the *EGFR* copy number status. The target population in the IPASS trials was selected on the basis of clinical characteristics, such as presence or absence of adenocarcinoma histology and smoking history. About 60% of the patients had *EGFR* mutations in the tumor cells. In the 40% of patients without *EGFR* mutations, gefitinib showed no beneficial effect, whereas chemotherapy was effective. This is why the progression-free survival curves in the IPASS study crossed at 6 months after the start of treatment. The response rate to both gefitinib and chemotherapy was higher in those with *EGFR* mutations compared with those without such mutations; however, gefitinib had a greater beneficial effect than chemotherapy in patients with *EGFR* mutations. Another important finding of the IPASS trial was the extremely low response rate to gefitinib in patients with wild-type *EGFR*. The method used for the detection of these mutations was very sensitive, namely the scorpion ARMS method, so that all the mutation-positive patients could be identified. The overall survival data from the IPASS trial are awaited; however, the results of the IPASS trial have demonstrated that molecular-targeted drugs are effective only against tumors with the relevant molecular target, that is, *EGFR* mutations. Conversely, cytotoxic drugs have antitumor activity against tumors regardless of the presence or absence of *EGFR* mutations.

Lessons learned from EGFR-TKI data

Gefitinib has shown dramatic antitumor activity in phase I and II trials. As second-line treatment for Japanese patients with NSCLC, it produced response rates of almost 30%. In a placebo-controlled, comparative trial (ISEL)[14] the effect of gefitinib as second-line and third-line treatment for NSCLC in prolonging survival was proven among Asians, as demonstrated by the high response rates in the predefined subgroup analysis. By contrast, in non-Asians with low response rates, the survival curves of those treated with gefitinib versus no treatment were almost entirely superimposed. Paradoxically, in the BR-21 trial, the overall survival of patients treated with the EGFR-TKI, erlotinib, was significantly better than that of patients administered placebo, despite the low response rate.[39] In the subset analysis of BR-21, the efficacy of erlotinib in terms of survival benefit was reported to be observed in male patients or those with squamous histology, although these factors were associated with lower response rate. One could speculate that erlotinib might be effective in patients with wild-type *EGFR* tumors, although not to the extent to achieve major shrinkage of the tumor. If so, erlotinib could be regarded as a 'less-targeted drug' than gefitinib, since its efficacy is less affected by the target status of the tumor. Dosing strategies of gefitinib (administered at a third of the maximum tolerated dose) and erlotinib (administered at the maximum tolerated dose) are different, which could partly account for the discrepancy. This explanation should be tested in future clinical trials.

Four large, randomized trials, namely Intact 1 and 2, Talent, and Tribute, that compared the effect of a platinum doublet regimen with or without gefitinib or erlotinib yielded negative survival results, probably because of the limited effect of gefitinib or erlotinib.[9–13] The patients

accrued to these trials were not selected according to their *EGFR* mutational status or EGFR histology, smoking and gender status. Another reason might be a competitive cell-cycle effect of anticancer agents and molecular-targeted drugs. Two randomized, controlled trials, namely V15-32 and INTEREST, that compared gefitinib with docetaxel for second-line or third-line treatment NSCLC have been reported.[41,45] Although theV15-32 study did not demonstrate the noninferiority of gefitinib, the INTEREST trial established the noninferiority of this agent despite the low response rate observed in Western patients. It has long been believed that response is a good surrogate for progression-free survival or overall survival. The results of the V15-32 study do not support this hypothesis, and this finding poses a challenge when comparing the effect of molecular-targeted agents with that of cytotoxic antineoplastic agents on the basis of end points such as progression-free survival and overall survival.

The high response rate in the IPASS trial reflected the good progression-free survival for those treated with gefitinib. However, the progression-free survival curves crossed after 6 months, which suggests the existence of two different populations of patients with different effects of molecular-targeted drugs between the two groups. The IPASS trial was a clinical trial in a partially selected population of patients, which suggests the need for more-accurate selection of patients in future clinical trials. Nevertheless, results of the IPASS trial will have some influence on the interpretation of results of ongoing clinical trials. Comparative trials of gefitinib and platinum-based doublets for patients with advanced and/or recurrent disease who harbor *EGFR* mutations will need to be modified as it might be difficult to obtain informed consent from these populations, owing to the finding that progression-free survival is significantly longer in patients treated with gefitinib than in those receiving platinum-based chemotherapy.

Another issue relates to the antitumor activity of cytotoxic drugs against tumors with *EGFR* mutations. In the V15-32 trial, progression-free survival was better in patients with *EGFR* mutations who were treated with either gefitinib or chemotherapy. In the IPASS trial, progression-free survival in those who received gefitinib was quite different between patients with and without *EGFR* mutations. Conversely, progression-free survival tended to be better in patients with *EGFR* mutations than in those without such mutations who were administered platinum-based chemotherapy, although this difference was not significant despite the response rate to platinum-based chemotherapy being significantly higher in patients with *EGFR* mutations. The presence of *EGFR* mutations in the tumor is a predictive factor of response not only to EGFR-TKIs, but also to platinum-based chemotherapy. Thus, the role of *EGFR* mutations as a predictive factor of progression-free survival and overall survival remains unclear in patients treated with platinum-based chemotherapy. Although many randomized trials of EGFR-TKIs in unselected patients with NSCLC have been reported, the results are varied and it is quite difficult to interpret the outcomes of these clinical trials.[47–52]

Conclusions

The results of several randomized, controlled trials of targeted agents and cytotoxic therapies in patients with advanced NSCLC have produced confusing results, perhaps because of the following reasons. First, the modes of action of cytotoxic drugs and molecular-targeted drugs are different, although the differences remain to be precisely elucidated. Second, the majority of clinical trials have been conducted in unselected populations. The IPASS trial was conducted in a partially selected population; however, the additional analysis on the basis of *EGFR* mutations clearly identified the target populations that show response to EGFR-TKI and cytotoxic chemotherapy. Third, although biomarker studies are extremely important, the majority of biomarkers have not been validated and the techniques to assess the EGFR target have not been fully optimized. Data from classical biomarker studies might not be the best data to draw conclusions from because these studies were conducted without selecting patients on the basis of favorable profiles. For the field of personalized medicine with the use of targeted and cytotoxic agents to advance, the scientific and clinical significance of biomarkers should be analyzed more extensively.

Review criteria

Data for this Review were obtained by searching the PubMed database for articles published between 1 January 2000 to 1 November 2008. Only articles published in English were considered. The following search terms were used "non-small-cell lung cancer" "NSCLC", "epidermal growth factor receptor" "EGFR" and "tyrosine kinase inhibitor". When possible primary sources have been cited. Data from searches of the following conferences were also included: ASCO 2004–ASCO 2008 annual meetings, European Society of Medical Oncology 2008 annual meeting, and the 12th World Conference on Lung Cancer 2007.

1. Schiller, J. H. *et al.* Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N. Engl. J. Med.* **346**, 92–98 (2002).
2. Ohe, Y. *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.* **18**, 317–323 (2007).
3. Kelly, K. *et al.* Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: a Southwest Oncology Group trial. *J. Clin. Oncol.* **19**, 3210–3218 (2001).
4. Fossella, F. *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.* **21**, 3016–3024 (2003).
5. Hynes, N. E. & Lane, H. A. ERBB receptors and cancer: the complexity of targeted inhibitors. *Nat. Rev. Cancer* **5**, 341–354 (2005).
6. Yarden, Y. & Sliwkowski, M. X. Untangling the ErbB signalling network. *Nat. Rev. Mol. Cell Biol.* **2**, 127–137 (2001).
7. Ranson, M. *et al.* ZD1849, a selective oral epidermoid growth factor receptor tyrosine kinase

inhibitor, is well tolerated and active in patients with solid, malignant tumors: results of a phase I trial. *J. Clin. Oncol.* **20**, 2240–2250 (2002).
8. Herbst, R. S. *et al.* Selective oral epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 is generally well-tolerated and has activity in non-small-cell lung cancer and other solid tumors: results of a phase I trial. *J. Clin. Oncol.* **20**, 3815–3825 (2002).
9. Giaccone, G. *et al.* Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial—INTACT 1. *J. Clin. Oncol.* **22**, 777–784 (2004).
10. Gatzemeier, U. *et al.*: Results of a phase III trial of erlotinib (OSI-774) combined with cisplatin and gemcitabine (GC) chemotherapy in advanced non-small-cell lung cancer (NSCLC) [Abstract]. *ASCO Meeting Abstracts* **22**, 7010 (2004).
11. Herbst, R. S. *et al.* Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial—INTACT 2. *J. Clin. Oncol.* **22**, 785–794 (2004).
12. Herbst, R. S. *et al.* TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. *J. Clin. Oncol.* **23**, 5892–5899 (2005).
13. Kelly, K. *et al.* Updated analysis of SWOG 0023: A randomized phase III trial of gefitinib versus placebo maintenance after definitive chemoradiation followed by docetaxel in patients with locally advanced stage III non-small-cell lung cancer [Abstract]. *ASCO Meeting Abstracts* **25**, 7513 (2007).
14. Thatcher, N. *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).
15. Han, S. W. *et al.* Predictive and prognostic impact of epidermal growth factor receptor mutation in non-small-cell-lung cancer patients treated with gefitinib. *J. Clin. Oncol.* **23**, 2493–2501 (2005).
16. Fukuoka, M. *et al.* Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial). *J. Clin. Oncol.* **21**, 2237–2246 (2003).
17. Chang, A. *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).
18. Niho, S. *et al.* First-line single agent of gefitinib in patients with advanced non-small-cell lung cancer: a phase II study. *J. Clin. Oncol.* **24**, 64–69 (2003).
19. Lee, D. H. *et al.* Gefitinib as a first-line therapy of advanced or metastatic adenocarcinoma of the lung in never-smokers. *Clin. Cancer Res.* **11**, 3032–3037 (2005).
20. Shigematsu, H. *et al.* Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. *J. Natl Cancer Inst.* **97**, 339–346 (2005).
21. Paez, J. G. *et al.* EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* **304**, 1497–1500 (2004).
22. Lynch, T. J. *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).
23. Johnson, B. E. & Jänne, P. A. Selecting patients for epidermal growth factor receptor inhibitor treatment: A FISH story or a tale of mutations? *J. Clin. Oncol.* **23**, 6813–6816 (2005).
24. Sequist, L. V. *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).
25. Marchetti, A. *et al.* EGFR mutations in non-small-cell lung cancer: analysis of a large series of cases and development of a rapid and sensitive method for diagnostic screening with potential implications on pharmacologic treatment. *J. Clin. Oncol.* **23**, 857–865 (2005).
26. Mitsudomi, T. *et al.* Mutations of the epidermal growth factor receptor gene predicts prolonged survival after gefitinib treatment in patients with non-small-cell lung cancer with postoperative recurrence. *J. Clin. Oncol.* **23**, 2513–2520 (2005).
27. Saijo, N. Advances in the treatment of non-small-cell lung cancer. *Cancer Treat. Rev.* **34**, 521–526 (2008).
28. Inoue, A. *et al.* Prospective phase II study of gefitinib for chemotherapy-naive patients with advanced non-small cell lung cancer with epidermal growth factor receptor gene mutations. *J. Clin. Oncol.* **2**, 3340–3346 (2006).
29. Takano, T. *et al.* Epidermal growth factor receptor gene mutations and increased copy members predict gefitinib sensitivity in patients with recurrent non-small-cell lung cancer. *J. Clin. Oncol.* **23**, 6829–6837 (2005).
30. Mitsudomi, T. & Yatabe, Y. Mutations of the epidermal growth factor receptor gene and related genes as determinants of epidermal growth factor receptor tyrosine kinase inhibitors sensitivity in lung cancer. *Cancer Sci.* **98**, 1817–1824 (2007).
31. Yoshida, K. *et al.*, Comparison of the efficacy between chemotherapy and gefitinib as 1st line setting in patients with EGFR mutation positive NSCLC [Abstract 278P]. *Ann. Oncol.* **19** (Suppl. 8) viii104 (2008).
32. Cappuzzo, F. *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).
33. Hirsch, F. R. *et al.* Increased epidermal growth factor receptor gene copy number detected by fluorescence in situ hybridization associates with increased sensitivity to gefitinib in patients with bronchioloalveolar carcinoma subtypes: a Southwest Oncology Group Study. *J. Clin. Oncol.* **23**, 6838–6845 (2005).
34. Tsao, M. S. *et al.* Erlotinib in lung cancer—molecular and clinical predictors of outcome. *N. Engl. J. Med.* **23**, 133–144 (2005).
35. Fossella, F. V. *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. The TAX 320 Non-Small-Cell Lung Cancer Study Group. *J. Clin. Oncol.* **18**, 2354–2362 (2000).
36. Shepherd, F. A. *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).
37. Hanna, N. *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).
38. Ohe, Y. *et al.* Efficacy and safety of two doses of pemetrexed supplemented with folic acid and vitamin B12 in previously treated patients with non-small-cell lung cancer. *Clin. Cancer Res.* **14**, 4206–4212 (2008).
39. Shepherd, F. A. *et al.* Erlotinib in previously treated non-small-cell lung cancer. *N. Engl. J. Med.* **353**, 123–132 (2005).
40. Tamura, T. *et al.* Evaluation of efficacy and safety of erlotinib as monotherapy for Japanese patients with advanced non-small-cell lung cancer; integrated analysis of two Japanese phase II studies [Abstract]. *J. Thorac. Oncol.* **2** (Suppl. 4), S742 (2007).
41. Maruyama, R. *et al.* Phase III study, V-15-32 of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. *J. Clin. Oncol.* **26**, 4244–4252 (2008).
42. Takeuchi, M. Another statistical analysis on the survival rate at various time intervals in patients accrued to V15–32 studied. Drug Safety Policy Panel, Safety Investigation committee, Second Food and Drug Advisory Board of February 1 2007 (2006).
43. Kunitoh, H. Critical comments on V15–32 study, The 5th Annual Meeting of Japanese Society of Medical Oncology PS-15, (2007).
44. Fushimi, T. Drug Safety Policy Panel, Safety Policy Investigation Committee, Second Food and Drug Advisory Board of Ministry of health Labor and Welfare, February 1, 2007 (2006).
45. Kim, E. S. *et al.* Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. *Lancet* **372**, 1809–1818 (2008).
46. Mok, T. *et al.* Phase III, randomized, open-label, first line study of gefitinib vs carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer (NSCLC) (IPASS) [Abstract LBA2]. *Ann. Oncol.* **19** (Suppl. 8), viii1 (2008).
47. Tsuboi, M. *et al.* Gefitinib in the adjuvant setting: safety results from a phase III study in patients with completely resected non-small-cell lung cancer. *Anticancer Drugs* **16**, 1123–1128 (2005).
48. Giaccone, G. & Rodriguez, J. A. EGFR inhibitors: what have we learned from the treatment of lung cancer? *Nat. Clin. Pract. Oncol.* **2**, 554–561 (2005).
49. Crino, L. *et al.* Gefitinib (IRESSA) versus vinorelbine in chemonaive elderly patients with advanced non-small-cell lung cancer (INVITE): a randomized phase II study: B3–04. *J. Thorac. Oncol.* **2** (Suppl. 4), S341 (2007).
50. Saijo, N. Recent trends in the treatment of advanced lung cancer. *Cancer Sci.* **97**, 448–452 (2006).
51. Lilenbaum, R. *et al.* Randomized phase II trial of single agent erlotinib vs. standard chemotherapy in patients with advanced non-small-cell lung cancer (NSCLC) and performance status (PS) of 2 [Abstract]. *ASCO Meeting Abstracts.* **24**, 7022 (2006).
52. Hida, I *et al.* Randomized phase III study of platinum-doublet chemotherapy followed by gefitinib versus continued platinum-doublet chemotherapy in patients with advanced non-small-cell lung cancer (NSCLC): Results of West Japan Thoracic Oncology Group trial (WJTOG) [Abstract]. *ASCO Meeting Abstracts* **26**, LBA8012 (2008).

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A Phase I Study of Gemcitabine and Carboplatin in Patients with Advanced Non-small Cell Lung Cancer and a Performance Status of 2

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Objective: The aim of this study was to determine the maximum-tolerated dose (MTD) and the recommended dose of combination chemotherapy with gemcitabine (GEM) and carboplatin (CBDCA) in non-small cell lung cancer (NSCLC) patients with a performance status (PS) of 2.
Methods: Chemotherapy-naïve NSCLC patients with PS 2 were enrolled. Chemotherapy consisted of an escalated dose of GEM on days 1 and 8 and CBDCA on day 1 every 3 weeks. Patients were scheduled to receive GEM (mg/m^2)/CBDCA (area under the curve: AUC) at four dose levels: 800/4 (level 1), 1000/4 (level 2), 1000/4.5 (level 3) and 1000/5 (level 4), respectively.
Results: Between February 2004 and August 2006, 13 patients were enrolled in this study. Dose-limiting toxicities (DLTs) were thrombocytopenia, febrile neutropenia and hyponatremia. DLTs were observed in two of six patients at dose level 1 and in three of six patients at dose level 2. Dose level 2 was thus determined to be the MTD. Among 12 evaluable patients, 7 patients had stable diseases and 5 patients had progressive diseases, and the median survival time was 3.8 months.
Conclusions: The MTD and the recommended dose for Phase II studies of this regimen were determined to be GEM 1000 mg/m^2 and CBDCA AUC of 4. Additional objective measures are needed to evaluate patients' risk and benefit in future clinical trials for PS 2 patients.

Key words: non-small cell lung cancer – performance status 2 – gemcitabine – carboplatin – Phase I

INTRODUCTION

Platinum-based combination chemotherapy has been shown to improve survival and quality-of-life (QOL) in patients with advanced non-small cell lung cancer (NSCLC) (1,2). In the 1990s, new chemotherapeutic agents, such as gemcitabine (GEM), vinorelbine, docetaxel, paclitaxel (PTX) and irinotecan, were developed. Currently, platinum-based chemotherapy employing these new agents is accepted as the standard chemotherapy worldwide (3,4). In addition, a meta-analysis demonstrated significant longer progression-free survival of GEM and platinum combination compared with other new agents and platinum combinations (5). Thus, combination chemotherapy with GEM and platinum is now considered as one of the most active regimens for advanced NSCLC.

Like in other types of cancers, performance status (PS) has been shown to be one of the most important prognostic factors for survival in advanced NSCLC (6–8). Patients with impaired PS generally have lower response rate and shorter survival in spite of high risk for severe toxicities (9,10). Historically, clinical trials have excluded patients with Eastern Cooperative Oncology Group (ECOG) PS of 2 or worse. To date, it has not been fully elucidated whether platinum-based combination chemotherapy is feasible and effective in patients with PS 2.

Carboplatin (CBDCA), an analog of cisplatin (CDDP), has lower nephro- and gastrointestinal toxicity and has been widely used as a substitution of CDDP. Several randomized

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trials have shown the equivalence between GEM + CBDCA (GC) and GEM + CDDP (GP) in terms of response rate and survival (11,12). In those trials, toxicities, such as emesis, nephropathy and neuropathy were significantly mild in GC. Although recent meta-analysis disclosed slightly but significant survival advantage of CDDP (13,14), GC can be one of the treatment options, especially for patients who are not suitable to receive CDDP. In a randomized Phase III trial comparing GC with vinblastine + CDDP, GC showed better response rate and survival, and toxicities were similar between the two arms (15). Although 70% of all enrolled patients in the study had PS 2, overall response rate and median survival time (MST) were 27% and 11.6 months in GC arm. These survival data were comparable to those in patients with PS 0 or 1 who treated with platinum-based chemotherapy.

These results suggest the potential benefit of GC in patients with PS 2; however, the optimal dose of GC has not been investigated in patients with impaired PS. Therefore, we conducted a Phase I study to determine the maximum-tolerated dose (MTD) and the recommended dose for Phase II studies of GC in advanced NSCLC patients with PS 2.

PATIENTS AND METHODS

Eligibility

Patients with histologically or cytologically proven advanced NSCLC were eligible for the study. Each patient was required to meet the following criteria: (i) clinical stage IIIB or IV; (ii) ECOG PS of 2; (iii) aged 20–75 years; (iv) measurable lesion; (v) no prior chemotherapy; (vi) adequate hematological function (white blood cell $\geq 3500/mm^3$, hemoglobin ≥ 9.5 g/dl and platelets $\geq 100\,000/mm^3$); (vii) adequate hepatic and renal function (total bilirubin ≤ 1.5 mg/dl, AST and ALT < 100 IU/l and creatinine ≤ 1.5 mg/dl); (viii) $PaO_2 \geq 60$ mmHg; and (ix) written informed consent. Patients with active concomitant malignancy, radiologically apparent interstitial pneumonia or pulmonary fibrosis, serious concurrent illness (e.g. uncontrolled diabetes mellitus, hypertension, angina pectoris, myocardial infarction within 3 months after onset or severe infection), history of severe drug allergy or pregnant/lactating women were excluded. The study protocol was approved by the institutional review board of the National Cancer Center.

Treatment Schedule

This was a Phase I, dose-escalation study planned for GEM on days 1 and 8 and CBDCA on day 1 of a 21-day course. The initial dose level of GEM was 800 mg/m^2 and CBDCA was an area under the concentration–time curve (AUC) of 4 mg min/ml. The actual dose of CBDCA was calculated based on Cockcroft–Gault equation (16) and Calvert formula (17) every course. CBDCA was infused over 60 min, and 60 min after the completion of CBDCA infusion, GEM was administered over 30 min. Prophylactic administration of granulocyte colony-stimulating factor (G-CSF) was not permitted. Administration of G-CSF was permitted for patients with grade 4 neutropenia and/or leukopenia and grade 3 febrile neutropenia. The administration of GEM was omitted on day 8 if patients met one of the following criteria: white blood cell $<2000/mm^3$, neutrophil $<1000/mm^3$, platelets $<50\,000/mm^3$ and PS ≥ 3. No dose modification of GEM was permitted on day 8. If dose-limiting toxicity (DLT) was observed, the dose of each drug was reduced to 80% in the next course of chemotherapy. Treatment was to be performed for at least two courses, unless unacceptable toxicity or disease progression occurred.

The DLT was defined as follows: grade 4 thrombocytopenia, grade 3 or grade 4 febrile neutropenia, grade 3 non-hematological toxicity (except for nausea/vomiting and alopecia) and omission of the treatment on day 8. Dose-escalation schedule is shown in Table 1. Initially, three patients were treated at each dose level. If DLT was not observed in any of three patients, dose escalation was made. If DLT was observed in one or two of three patients, an additional three patients were entered in the same dose level. If DLT was observed in three or more of six patients or all of the initial three patients, we considered that the dose was the MTD. If DLT was observed in one or two of six patients, dose escalation was also made. Dose escalation was decided by the toxic data only in the first course of chemotherapy.

Baseline and Treatment Assessment

Pre-treatment evaluation consisted of complete medical history and physical examination, complete blood cell counts, blood chemistry studies, electrocardiograph, arterial blood gas analysis, chest radiography, computed tomography (CT) of the chest, CT or ultrasound study of the abdomen, CT or magnetic resonance imaging of the brain, and bone scintigraphy. Complete blood cell counts, blood chemistry studies and chest radiography were repeated every week. Creatinine clearance was estimated by the Cockcroft–Gault equation every course. Tumor response was assessed with the Response Evaluation Criteria in Solid Tumor (RECIST) criteria (18). Toxicity was evaluated according to the National Cancer Institute-Common Toxicity Criteria (version 2.0).

Table 1. Dose-escalation schedule

Dose level	Gemcitabine (mg/m^2)	Carboplatin (AUC)	No. of patients
1	800	4	3–6
2	1000	4	3–6
3	1000	4.5	3–6
4	1000	5	3–6

AUC, area under the curve.

RESULTS

Patient Characteristics

Between February 2004 and August 2006, 13 patients were enrolled in this study. However, one patient was excluded from the analysis because of the error in dose calculation. Table 2 shows the characteristics of 12 evaluable patients. Eleven patients were male and one was female. The median age of the patients was 68 years (range, 51–72 years). There were five adenocarcinomas, four squamous cell carcinomas, two large cell carcinomas and one pleomorphic carcinoma. Stage IIIB and IV patients were five and six, respectively, and one patient was a relapse after surgical resection.

Dose Escalation

At the dose level 1, DLT was observed in two of the first three patients: one experienced grade 3 hyponatremia and the other experienced grade 3 febrile neutropenia. Thereafter, we amended the protocol, and grade 3 hyponatremia was excluded from DLT criteria after that. Another three patients were treated at the same dose. Since these patients did not show any additional DLT, the dosage was then escalated to the next step. At the dose level 2, DLT was observed in two of the first three patients: one experienced grade 3 nausea/vomiting and omission on day 8 and the other experienced grade 3 febrile neutropenia and anorexia. Therefore, another three patients were assigned to receive the treatment at the same dose. Out of those three patients, one patient developed grade 4 febrile neutropenia and grade 3 anorexia. Thus, DLT was observed in three of six patients at the dose level 2. As a result, the dose level 2 (GEM, 1000 mg/m^2 and CBDCA, AUC of 4) was determined to be the MTD.

Table 2. Characteristics of evaluable patients ($n = 12$)

Characteristics	No. of patients
Gender	
Male	11
Female	1
Age (years)	
Median	68
Range	51–72
Histology	
Adenocarcinoma	5
Squamous cell carcinoma	4
Large cell carcinoma	2
Pleomorphic carcinoma	1
Stage	
IIIB	5
IV	6
Relapse after surgery	1

Toxicity

The worst grades for each patient in the first cycle are listed in Table 3. Grade 3/4 leukopenia or neutropenia was observed in one patient at level 1 and two patients at level 2. Febrile neutropenia was observed in one patient at level 1 and two patients at level 2. Two patients had grade 3/4 anemia at level 1 and one patient required red blood cell transfusion. No grade 3/4 anemia occurred at level 2. Thrombocytopenia was the principal toxicity of this combination chemotherapy. At level 1, grade 3/4 thrombocytopenias were observed in three patients, and two patients received platelet transfusion. At level 2, two patients experienced grade 3/4 thrombocytopenia requiring no platelet transfusions. Non-hematologic toxicities were generally mild at level 1, however, one patient experienced grade 3 nausea/

Table 3. Toxicities during the first cycle

NCI-CTC grade	Level 1 ($n = 6$)		Level 2 ($n = 6$)	
	G1/2	G3/4	G1/2	G3/4
Hematologic				
Leukopenia	1/2	0/1	2/1	2/0
Neutropenia	1/1	1/0	1/1	2/0
Febrile neutropenia	0/0	1/0	0/0	1/1
Anemia	1/3	1/1	2/3	0/0
Thrombocytopenia	1/2	2/1	1/1	4/0
Transaminase	2/0	0/0	4/2	0/0
Bilirubin	0/0	0/0	0/0	1/0
Creatinine	0/0	0/0	0/0	0/0
Hyponatremia	4/0	2/0	5/0	0/0
Non-hematologic				
Nausea/vomiting	2/0	0/0	3/1	1/0
Anorexia	4/1	0/0	2/1	3/0
Fatigue	1/0	0/0	1/2	1/0
Diarrhea	0/0	0/0	2/0	0/0
Constipation	0/0	0/0	0/1	0/0
Mucositis	0/0	0/0	0/0	0/0
Pneumonitis	0/0	0/0	0/0	0/0
Infection	0/0	0/0	0/0	0/0
Skin rash	1/0	0/0	1/0	0/0
Omission on day 8	0		1	
No. of patients with DLT	2		3	

NCI-CTC, National Cancer Institute-Common Toxicity Criteria; DLT, dose-limiting toxicity.

vomiting and omission of day 8 at level 2. This patient also presented grade 3 hyperbilirubinemia suspected to be drug-induced hepatitis, and died 16 days after the start of the treatment. The worst value of his laboratory data was 6.6 mg/dl in total bilirubin on day 12, 40 IU/l in AST on day 7 and 103 IU/l in ALT on day 7. He had a past history of drug-induced hepatitis related to aspirin. The excluded patient was administered GEM at 800 mg/body. Despite the dose was approximately two-thirds of the planned dose, he experienced grade 3 nausea/vomiting and the treatment was discontinued. The median number of administered cycle was 1. The actual administered cycles were one in seven patients, two in one patient, three in two patients and four in two patients. The reasons for the discontinuation in seven patients who terminated the treatment at one cycle were toxicity for three patients, patient refusal for two patients, treatment delay for one patient and both toxicity and disease progression was for one patient.

Anti-tumor Activity

There were seven stable diseases and five progressive diseases (PD). No partial or complete response was observed (Table 4). Four patients received second-line chemotherapy after GC: docetaxel for two patients and gefitinib for two patients. One patient received gefitinib experienced partial response; however, remaining three patients had PD also in the second-line treatment. The MST was 3.8 months (Fig. 1).

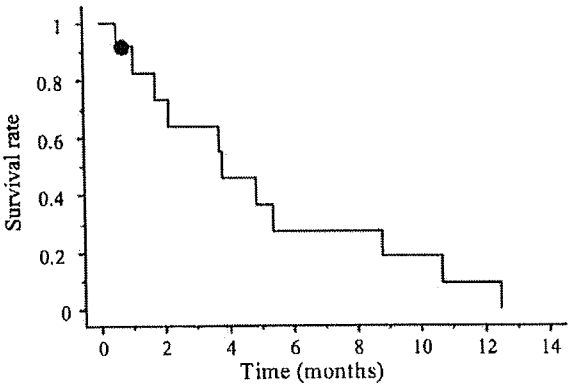

Figure 1. Kaplan–Meier curve of overall survival. Median overall survival time was 3.8 months.

DISCUSSION

This is the first PS 2-specific Phase I study of GC in Japanese patients, and the MTD and recommended dose were determined to be GEM 1000 mg/m^2 and CBDCA AUC of 4.

The recommended dose of CBDCA was lower than other studies conducted in the USA (19,20). With respect to the dose of CBDCA, the method of measuring serum creatinine values is critical. In Japan, most institutions use the enzymatic method, whereas the Jaffe method remains the mainstream in the USA (21). According to the study comparing these two methods, serum creatinine values are higher in the Jaffe method than in the enzymatic method by ~0.2 mg/dl (21). Therefore, at the same AUC, higher CBDCA dose is administered in Japan than in the USA. Incidentally, based on the Calvert formula, a difference of 0.2 mg/dl of creatinine leads to the difference of AUC = 1. In short, the AUC = 4 in Japan roughly corresponds to the AUC = 5 in the USA. For global clinical trials, the difference of methods for measurement of laboratory data also should be paid attention to.

Table 4. Drug delivery and anti-tumor efficacy

Dose level	Number of patients	Median course (range)	Overall response			
			CR	PR	SD	PD
1	6	1 (1–4)	0	0	4	2
2	6	2 (1–4)	0	0	3	3

CR, complete response; PR, partial response; SD, stable diseases; PD, progressive diseases.

PS is one of the most powerful and reliable prognostic factors in advanced NSCLC (6–8), and a worse PS is characterized by lower response rate to chemotherapy and shorter survival (9,10). Median survival of patients with PS 2 is substantially shorter than that of patients with PS 0 or 1. Moreover, patients with PS 2 are at higher risk for severe toxicity than those with better PS. According to the population-based surveys, up to 30–40% of all advanced NSCLC is characterized PS 2 (22,23). Namely, patients with PS 2 constitute a distinctive, non-trivial subgroup in NSCLC. However, little attention has been paid to this special patient population until recently.

The guidelines from the American Society of Clinical Oncology support the single use of third-generation non-platinum agents for patients with PS 2 (24). This recommendation is mainly based on the results of Phase III trials comparing single-agent chemotherapy with best supportive care alone, in which good tolerability and significant survival benefit or improvement of QOL with single-agent chemotherapy have been demonstrated (25–28). However, PS 2 patients accounted for a small proportion of patients in those trials and any conclusive evidence cannot be drawn for the treatment of patients with PS 2. At present, available data from PS 2-specific clinical trials are quite limited. In this context, no consensus has been developed on the standard chemotherapy in patients with PS 2.

The role of adding platinum to third-generation single agents is still unclear. Recently, the Norwegian Lung Cancer Study Group reported the results of a retrospective study that compared the outcome of patients with PS 2 to that of patients with PS 0 or 1 who had participated in randomized trials comparing two third-generation, CBDCA-based

regimens (29). According to the retrospective study, although MST of patients with PS 2 was significantly shorter than that of patients with PS 0 or 1 (4.5 vs. 8.9 months; $P < 0.01$), toxicity was acceptable for patients with PS 2 and they achieved better symptom improvement compared with patients with PS 0 or 1. ECOG conducted the first PS 2-specific randomized trial (19). In the randomized Phase II trial, two platinum-based chemotherapy regimens, PTX + CBDCA (PC) and GP, have been compared, and both regimens were proved feasible with acceptable toxicity. However, survival time was quite limited in both treatment arms: MST was 6.2 months for PC and 6.9 months for GP, respectively. A Greece Group performed a randomized Phase II trial comparing non-platinum single-agent chemotherapy with CBDCA-based chemotherapy (30). In the study, patients were randomly assigned to either GC or GEM alone and MST was 6.7 months for GC and 4.8 months for GEM alone, respectively ($P = 0.49$), whereas neutropenia ($P = 0.007$) and thrombocytopenia ($P < 0.001$) were more common in GC arm. In contrast, according to a subgroup analysis of the Cancer and Leukemia Group B study 9730 comparing PC with PTX alone, patients with PS 2 (107 patients, 18% of the population) achieved significantly better survival when they were treated with PC than those treated with PTX alone (20). Thus, the role of platinum-based chemotherapy for patients with PS 2 is still controversial.

The results could vary even between PS 2-specific trials due to two major reasons. First, determining PS score is inevitably subjective, there is considerable inter-observer variation even between healthcare professionals (31). Second, there can be significant heterogeneity in the PS 2 patient population: the reasons for impaired PS may be due to tumor-related (such as pain, fatigue and weight loss), to pre-existing co-morbidities (such as chronic obstructive pulmonary disease, cardiovascular disease and age-related decline in functional status) or both, furthermore (32). There is a clear need for a more objective classification system that takes into account the individual effects of disease-related symptoms and co-morbidities. The common co-morbidity scales are the Cumulative Illness Rating Scale-Geriatric (CIRS-G) and the Charlson scale. Their prognostic impacts have been validated prospectively (33,34). Moreover, they are more objective than PS. Although our study did not, all future studies for PS 2 patients should use such co-morbidity scales to stratify patients more accurately.

Recently, molecular-targeted agents, especially epidermal growth factor receptor tyrosine kinase inhibitors such as gefitinib or erlotinib, have been tested in clinical trials for patients with poor PS. Inoue et al. (35) conducted a Phase II trial of gefitinib in patients with NSCLC whose tumor harboring EGFR gene mutation. In the study, all patients were not feasible for cytotoxic chemotherapy due to poor PS: 26 of 29 patients were PS 2–4. Overall response rate and MST were 66% and 6.5 months, respectively. In addition, PS improvement rate was 79%, and no treatment-related deaths were observed. These excellent results strongly suggest that stratification with molecular status should be required in the future trial of PS 2 or more.

In this study, we determined the MTD and the recommended dose of GC in Japanese patients with PS 2. Response rate and overall survival of the regimen were disappointing. However, some previous studies clearly support the use of platinum agent in PS 2 patients (19,20). Future clinical trials for PS 2 patients should use more objective criterion such as co-morbidity scales in addition to PS in order to measure patients' risk more accurately. Such studies may reveal that which patients should be treated and not be treated with platinum-based chemotherapy among PS 2 patients.

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Conflict of interest statement

None declared.

References

1. Souquet PJ, Chauvin F, Boissel JP, Cellerino R, Cormier Y, Ganz PA, et al. Polychemotherapy in advanced non small cell lung cancer: a meta-analysis. *Lancet* 1993;342:19–21.
2. 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* 1995;311:899–909.
3. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92–8.
4. Bunn PA, Jr. Chemotherapy for advanced non-small-cell lung cancer: who, what, when, why? *J Clin Oncol* 2002;20:23–33S.
5. Le Chevalier T, Scagliotti G, Natale R, Danson S, Rosell R, Stahel R, et al. Efficacy of gemcitabine plus platinum chemotherapy compared with other platinum containing regimens in advanced non-small-cell lung cancer: a meta-analysis of survival outcomes. *Lung Cancer* 2005;47:69–80.
6. Stanley KE. Prognostic factors for survival in patients with inoperable lung cancer. *J Natl Cancer Inst* 1980;65:25–32.
7. Albain KS, Crowley JJ, LeBlanc M, Livingston RB. Survival determinants in extensive-stage non-small-cell lung cancer: the Southwest Oncology Group experience. *J Clin Oncol* 1991;9:1618–26.
8. Brundage MD, Davies D, Mackillop WJ. Prognostic factors in non-small cell lung cancer: a decade of progress. *Chest* 2002;122:1037–57.
9. Gridelli C, Ardizzoni A, Le Chevalier T, Manegold C, Perrone F, Thatcher N, et al. Treatment of advanced non-small-cell lung cancer patients with ECOG performance status 2: results of an European Experts Panel. *Ann Oncol* 2004;15:419–26.
10. Gridelli C, Maione P, Rossi A, Guerriero C, Ferrara C, Del Gaizo F, et al. Chemotherapy of advanced NSCLC in special patient population. *Ann Oncol17 Suppl* 2006;5:v72–8.
11. Mazzanti P, Massacesi C, Rocchi MB, Mattioli R, Lippe P, Trivisonne R, et al. Randomized, multicenter, phase II study of gemcitabine plus cisplatin versus gemcitabine plus carboplatin in patients with advanced non-small cell lung cancer. *Lung Cancer* 2003;41:81–9.

12. Zatloukal P, Petruzelka L, Zemanova M, Kolek V, Skrickova J, Pesek M, et al. Gemcitabine plus cisplatin vs. gemcitabine plus carboplatin in stage IIIb and IV non-small cell lung cancer: a phase III randomized trial. *Lung Cancer* 2003;41:321–31.
13. Hotta K, Matsuo K, Ueoka H, Kiura K, Tabata M, Tanimoto M. Meta-analysis of randomized clinical trials comparing cisplatin to carboplatin in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2004;22:3852–9.
14. Ardizzoni A, Boni L, Tiseo M, Fossella FV, Schiller JH, Paesmans M, et al. Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. *J Natl Cancer Inst* 2007;99:847–57.
15. Grigorescu AC, Draghici IN, Nitipir C, Gutulescu N, Corlan E. Gemcitabine (GEM) and carboplatin (CBDCA) versus cisplatin (CDDP) and vinblastine (VLB) in advanced non-small-cell lung cancer (NSCLC) stages III and IV: a phase III randomised trial. *Lung Cancer* 2002;37:9–14.
16. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31–41.
17. Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989;7:1748–56.
18. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, 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.
19. Langer C, Li S, Schiller J, Tester W, Rapoport BL, Johnson DH, et al. Randomized phase II trial of paclitaxel plus carboplatin or gemcitabine plus cisplatin in Eastern Cooperative Oncology Group performance status 2 non-small-cell lung cancer patients: ECOG 1599. *J Clin Oncol* 2007;25:418–23.
20. Lilenbaum RC, Herndon JE, 2nd, List MA, Desch C, Watson DM, Miller AA, et al. Single-agent versus combination chemotherapy in advanced non-small-cell lung cancer: the cancer and leukemia group B (study 9730). *J Clin Oncol* 2005;23:190–6.
21. Ando Y, Minami H, Saka H, Ando M, Sakai S, Shimokata K. Adjustment of creatinine clearance improves accuracy of Calvert's formula for carboplatin dosing. *Br J Cancer* 1997;76:1067–71.
22. Buccheri G, Ferrigno D, Tamburini M. Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution. *Eur J Cancer* 1996;32A:1135–41.
23. Radzikowska E, Glaz P, Roszkowski K. Lung cancer in women: age, smoking, histology, performance status, stage, initial treatment and survival. Population-based study of 20 561 cases. *Ann Oncol* 2002;13:1087–93.
24. Pfister DG, Johnson DH, Azzoli CG, Sause W, Smith TJ, Baker S, Jr. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. *J Clin Oncol* 2004;22:330–53.
25. The Elderly Lung Cancer Vinorelbine Italian Study Group. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small-cell lung cancer. *J Natl Cancer Inst* 1999;91: 66–72.
26. Ranson M, Davidson N, Nicolson M, Falk S, Carmichael J, Lopez P, et al. Randomized trial of paclitaxel plus supportive care versus supportive care for patients with advanced non-small-cell lung cancer. *J Natl Cancer Inst* 2000;92:1074–80.
27. Roszkowski K, Pluzanska A, Krzakowski M, Smith AP, Saigi E, Aasebo U, et al. A multicenter, randomized, phase III study of docetaxel plus best supportive care versus best supportive care in chemotherapy-naive patients with metastatic or non-resectable localized non-small cell lung cancer (NSCLC). *Lung Cancer* 2000;27:145–57.
28. Anderson H, Hopwood P, Stephens RJ, Thatcher N, Cottier B, Nicholson M, et al. Gemcitabine plus best supportive care (BSC) vs BSC in inoperable non-small cell lung cancer—a randomized trial with quality of life as the primary outcome. UK NSCLC Gemcitabine Group. Non-Small Cell Lung Cancer. *Br J Cancer* 2000;83:447–53.
29. Helbekkmo N, Aasebo U, Sundstrom SH, von Plessen C, Brunsvig PF, Bremnes RM; Norwegian Lung Cancer Study Group. Treatment outcome in performance status 2 advanced NSCLC patients administered platinum-based combination chemotherapy. *Lung Cancer* 2008;62: 253–60.
30. Kosmidis PA, Dimopoulos MA, Syrigos K, Nicolaides C, Aravantinos G, Boukovinas I, et al. Gemcitabine versus gemcitabine-carboplatin for patients with advanced non-small cell lung cancer and a performance status of 2: a prospective randomized phase II study of the Hellenic Cooperative Oncology Group. *J Thorac Oncol* 2007;2:135–40.
31. Taylor AE, Olver IN, Sivanthan T, Chi M, Purnell C. Observer error in grading performance status in cancer patients. *Support Care Cancer* 1999;7:332–5.
32. Gebbia V, Galetta D, De Marinis F. Non small cell lung cancer patients with ECOG PS2: unsolved questions and lessons from clinical trials. *Ann Oncol* 2005;16(Suppl 4):iv123–31.
33. Firat S, Byhardt RW, Gore E. Comorbidity and Karnofksy performance score are independent prognostic factors in stage III non-small-cell lung cancer: an institutional analysis of patients treated on four RTOG studies. Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 2002;54:357–64.
34. Frasci G, Lorusso V, Panza N, Comella P, Nicolella G, Bianco A, et al. Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2000;18:2529–36.
35. Inoue A, Kobayashi K, Usui K, Maemondo M, Okinaga S, Mikami I, et al. First-line gefitinib for patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy. *J Clin Oncol* 2009;27:1394–400.

original article

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Quality of life and disease-related symptoms in previously treated Japanese patients with non-small-cell lung cancer: results of a randomized phase III study (V-15-32) of gefitinib versus docetaxel

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Background: This report describes quality of life (QoL) findings of a randomized study comparing gefitinib with docetaxel in patients with advanced/metastatic pretreated non-small-cell lung cancer.

Patients and methods: This open-label, phase III study randomized 490 Japanese patients to gefitinib (250 mg/day) or docetaxel (60 mg/m^2/3 weeks), with survival as the primary outcome. Preplanned QoL analyses included Functional Assessment of Cancer Therapy-Lung (FACT-L), Trial Outcome Index (TOI) and Lung Cancer Subscale (LCS) improvement rates, and mean change from baseline.

Results: Gefitinib showed statistically significant benefits over docetaxel in QoL improvement rates (FACT-L 23% versus 14%, $P = 0.023$; TOI 21% versus 9%, $P = 0.002$) and mean change from baseline score [mean treatment difference: FACT-L 3.72 points, 95% confidence interval (CI) 0.55–6.89, $P = 0.022$; TOI 4.31 points, 95% CI 2.13–6.49, $P < 0.001$], although differences did not meet the clinically relevant six-point change. There were no significant differences between treatments in LCS improvement rates (23% versus 20%, $P = 0.562$) or mean change from baseline score (0.63 points, 95% CI −0.07 to 1.34, $P = 0.077$).

Conclusions: Gefitinib improved aspects of QoL over docetaxel, with superior objective response rate and a more favorable tolerability profile and no statistically significant difference in overall survival (although noninferiority was not statistically proven).

Key words: docetaxel, gefitinib, non-small-cell lung cancer, quality of life

original article

introduction

Docetaxel is an established treatment of patients with previously treated advanced non-small-cell lung cancer (NSCLC) worldwide, including Japan; however, this is associated with typical cytotoxic side-effects including hematological toxicity, especially grade 3/4 neutropenia [1, 2]. Alternative agents with an improved tolerability profile, such as the epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) gefitinib, have been investigated in this setting [3–5].

In this randomized phase III study (V-15-32) comparing gefitinib versus docetaxel in previously treated Japanese patients with NSCLC, the primary objective (noninferiority of gefitinib versus docetaxel) was not statistically proven for overall survival (OS) [hazard ratio (HR) 1.12, 95.24% confidence interval (CI) 0.89–1.40], according to the predefined noninferiority criterion (upper CI for HR < 1.25) [6]. However, there were no statistically significant differences in OS ($P = 0.330$) or progression-free survival (PFS; $P = 0.335$) and gefitinib had a superior objective response rate (ORR) and a more favorable tolerability profile than docetaxel. Because of the significant

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burden of disease-related symptoms in patients with advanced NSCLC, improvements in health-related quality of life (QoL) and symptoms are an important additional parameter to guide treatment choice, particularly with the introduction of agents with better tolerability profiles. Here, we report in detail the QoL and symptom analyses of the V-15-32 study.

patients and methods

study design

This phase III study compared the effects of gefitinib versus docetaxel in Japanese patients with advanced/metastatic (stage IIIb/IV) or recurrent NSCLC who failed one or two chemotherapy regimens. Details of the study design and eligibility criteria have been published [6]. The primary end point was OS; the study aimed to show noninferiority of gefitinib versus docetaxel. Secondary end points were PFS, time-to-treatment failure, ORR, disease control rate, QoL, disease-related symptoms, safety, and tolerability.

The study was carried out in accordance with the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice (GCP), applicable regulatory requirements, and the AstraZeneca policy on Bioethics. The study protocol was approved by each institutional review board and written informed consent was obtained from all patients.

QoL assessments and analyses

The Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire was used to assess QoL at baseline and every 4 weeks during study treatment until week 12. The FACT-L questionnaire is a validated, self-report questionnaire comprising physical, functional, social/family, emotional well-being subscales and Lung Cancer Subscale (LCS) [7]. The Trial Outcome Index (TOI), the sum of the physical, functional subscales, and LCS is reported to be a precise indicator of functional outcomes [7]. Disease-related symptoms were assessed weekly using the LCS. As previously reported [8], clinically relevant improvement was defined as change from baseline of ≥+6 for FACT-L or TOI or ≥+2 for LCS, on two visits at least 28 days apart. The assessable for LCS and assessable for QoL populations were subsets of the intent-to-treat (ITT) population with nonmissing baseline and one or more nonmissing post-baseline LCS and QoL assessments, respectively.

Preplanned analyses of FACT-L, TOI, and LCS scores included the following: mean change from baseline and 95% CI of the difference in mean change from baseline scores between the groups (based on the *t*-distribution; calculated as the difference between the mean overall patients on a treatment of the within-patient average change from baseline score); improvement, control (improvement or no change), and worsening rates and the odds ratio between treatments (with 95% CI and *P* value from a logistic regression model without covariates); and HR (gefitinib/docetaxel) for time to worsening (with 95% CI and *P* value using a proportional hazard model without covariates).

Supporting *post hoc* analyses of FACT-L, TOI, and LCS scores included the following: similar analyses using best change from baseline score instead of mean change; mean and best change from baseline for each subscale with two-sample *t*-test comparing treatments; mean and best change from baseline for individual questions; and correlation between mean change and best change from baseline and tumor response.

results

patients

Of 245 gefitinib and 244 docetaxel patients (one patient in the docetaxel arm was excluded due to GCP violation) in the ITT population, 185 (76%) and 173 (71%) patients, respectively, were assessable for QoL and 225 (92%) and 211 (86%) patients, respectively, were assessable for LCS. The demographic characteristics of the assessable for QoL and assessable for LCS populations (Supplemental Table 1, available at *Annals of Oncology* online) were representative of the overall study population [6].

QoL and disease-related symptoms at baseline

The baseline FACT-L, TOI, and LCS scores were similar between treatment groups (Table 1).

compliance and evaluability

Baseline compliance rates [(evaluable questionnaires during the treatment period)/(expected questionnaires) × 100] for gefitinib and docetaxel were high: 92% and 86%, respectively, for FACT-L and 93% and 87%, respectively, for LCS. During the first 12-weeks treatment, compliance rates for gefitinib and docetaxel were between 77% and 89% and 77% and 93%, respectively, for FACT-L completion and between 76% and 98% and 71% and 98%, respectively, for LCS completion, with smaller numbers of patients as time progressed as expected (Supplemental Table 2, available at *Annals of Oncology* online). Evaluability rates [(evaluable questionnaires during the treatment period)/(received questionnaires) × 100] were also high at between 88% and 100% (Supplemental Table 2, available at *Annals of Oncology* online).

QoL and symptom improvement

Significantly, more gefitinib-treated patients experienced a clinically relevant improvement in QoL (FACT-L and TOI) compared with docetaxel (Figure 1). There was no evidence of a difference between treatments in terms of symptom improvement rates measured by LCS (Figure 1).

Table 1. Baseline FACT-L, TOI, and LCS scores (assessable population)

Variable	Gefitinib			Docetaxel		
	n	Median (range)	Mean ± SD	*n*	Median (range)	Mean ± SD
FACT-L	185	98.5 (64.0–100.0)	98.7 ± 17.2	173	98.0 (49.3–138.0)	97.3 ± 17.5
TOI	185	58.4 (26.0–84.0)	58.0 ± 12.4	173	59.0 (28.0–82.0)	57.8 ± 12.6
LCS	225	19.0 (5.0–28.0)	19.4 ± 4.75	211	19.6 (5.0–28.0)	19.4 ± 4.91

SD, standard deviation; FACT-L, Functional Assessment of Cancer Therapy-Lung; TOI, Trial Outcome Index; LCS, Lung Cancer Subscale.

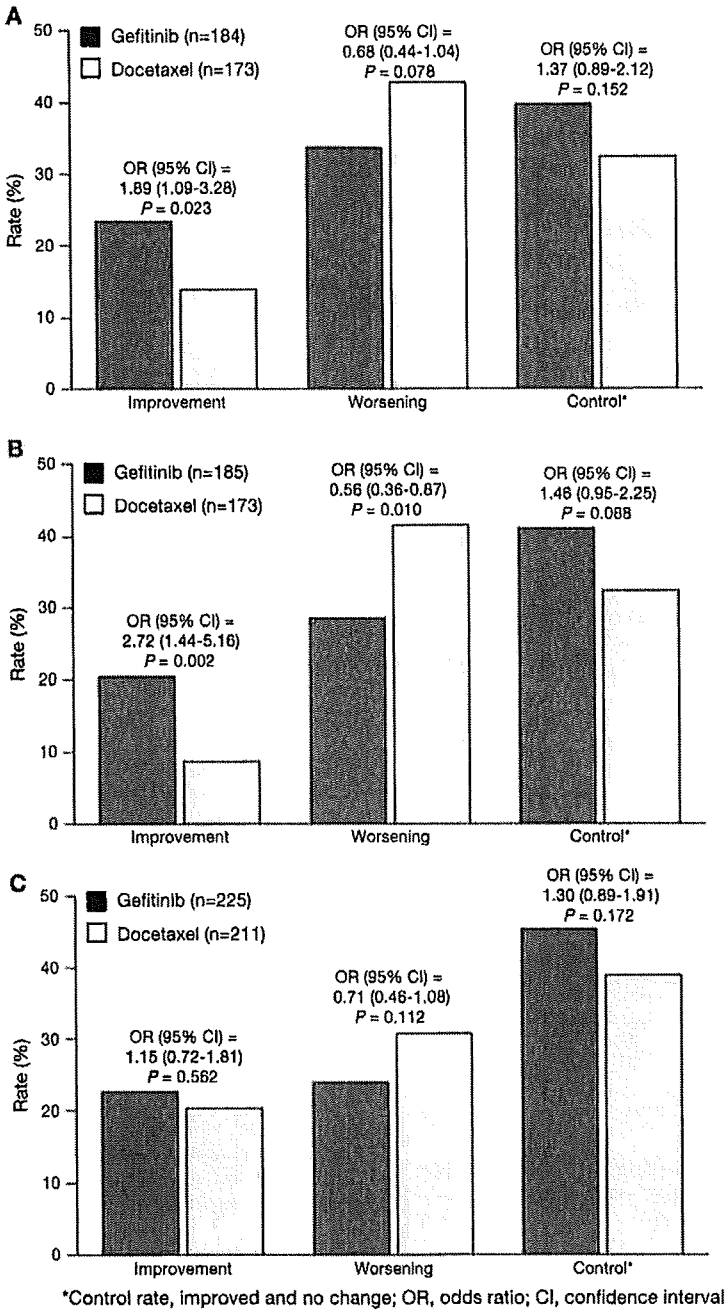

Figure 1. Improvement, worsening and control rates of (A) Functional Assessment of Cancer Therapy-Lung total, (B) Trial Outcome Index, and (C) Lung Cancer Subscale score (assessable population).

Time to worsening was significantly longer on gefitinib than docetaxel for TOI, numerically longer for FACT-L, and slightly longer for LCS (Figure 2).

Mean change from baseline for FACT-L, TOI, and LCS at each visit during the first 12 weeks of treatment is shown in Supplemental Figure 1 (available at *Annals of Oncology* online).

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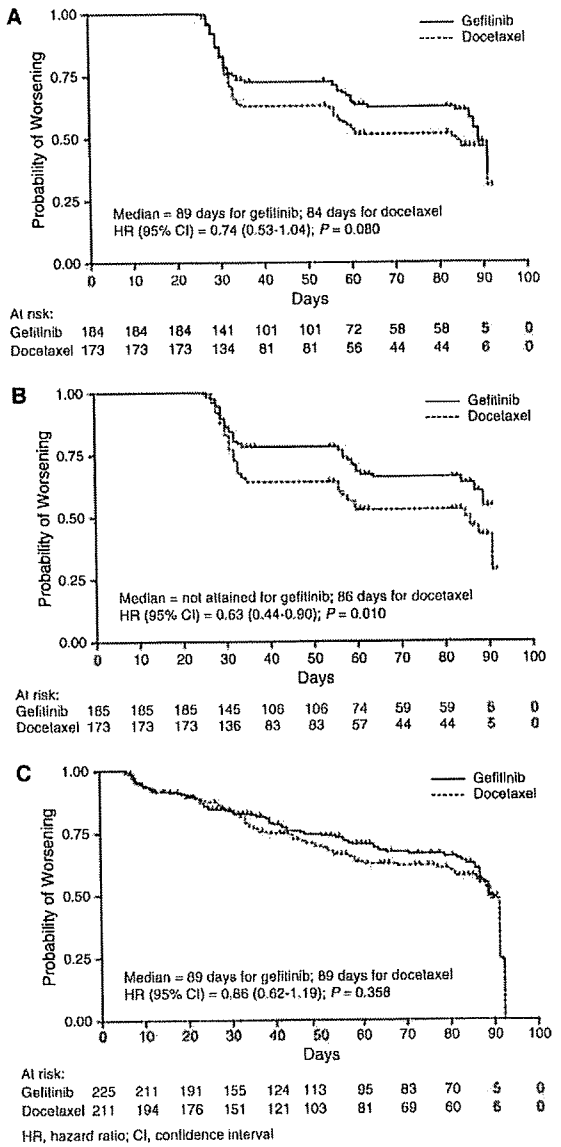

Figure 2. Time to worsening of (A) Functional Assessment of Cancer Therapy-Lung total, (B) Trial Outcome Index, and (C) Lung Cancer Subscale score (assessable population).

Statistically significant differences between treatments in mean change from baseline for QoL score (FACT-L and TOI) in favor of gefitinib were observed, but the differences did not meet the predefined, clinically relevant six-point change (FACT-L: 3.72 points, 95% CI 0.55–6.89, $P = 0.022$; TOI: 4.31 points, 95% CI 2.13–6.49, $P < 0.001$) (Table 2). There was no significant difference between treatments in mean change from baseline for LCS score (0.63 points, 95% CI −0.07 to 1.34, $P = 0.077$) (Table 2).

Table 2. Mean change during the first 12 weeks of treatment (assessable populations)

Variable	Gefitinib			Docetaxel			Difference	*P* value
	n	Mean	SD	*n*	Mean	SD	(95% CI)	by *t*-test
FACT-L	184	0.94	15.48	173	−2.78	14.96	3.72 (0.55 to 6.89)	0.022
TOI	185	0.81	10.22	173	−3.50	10.78	4.31 (2.13 to 6.49)	<0.001
LCS	225	1.38	3.58	211	0.75	3.89	0.63 (−0.07 to 1.34)	0.077

SD, standard deviation; CI, confidence interval; FACT-L, Functional Assessment of Cancer Therapy-Lung; TOI, Trial Outcome Index; LCS, Lung Cancer Subscale.

Post hoc analyses of mean change from baseline in the FACT-L subscales identified significant differences in favor of gefitinib over docetaxel in the physical ($P = 0.002$) and functional well-being subscales ($P = 0.002$) but not in the social/family ($P = 0.494$) or emotional well-being subscales ($P = 0.663$) (Figure 3).

In *post hoc* analyses, individual FACT-L questions with the largest differences between treatments in mean change from baseline (≥0.3 points difference of absolute value, all favoring gefitinib) were 'I am bothered by hair loss' (difference 2.03 points; question not included in calculating FACT-L, TOI, and LCS scores); 'I am content with the quality of my life right now' (0.47 points); 'I am forced to spend time in bed' (0.39 points); 'I am enjoying the things I usually do for fun' (0.33 points); 'I am sleeping well' (0.31 points); and 'I have a good appetite' (0.31 points). No question favored docetaxel by >0.21 points (Supplemental Table 3, available at *Annals of Oncology* online).

The results of *post hoc* analyses of best change from baseline score were consistent with the preplanned mean change from baseline score analyses.

QoL and symptom improvement by objective tumor response

Mean change from baseline in FACT-L, TOI, and LCS improved as best overall objective tumor response improved for both gefitinib and docetaxel (Supplemental Table 4, available at *Annals of Oncology* online). There was a higher correlation between changes and tumor response for gefitinib than docetaxel, which may be caused by more disperse distribution of objective tumor response for gefitinib. Similar results with slightly higher correlations were seen using best change from baseline.

discussion

In this randomized phase III study in previously treated advanced NSCLC, noninferiority of gefitinib versus docetaxel was not statistically proven for OS, although there were no statistically significant differences in OS or PFS between treatments. However, gefitinib demonstrated statistically significant benefits over docetaxel in QoL improvement rates and mean change from baseline QoL score (measured by