Fig. 5

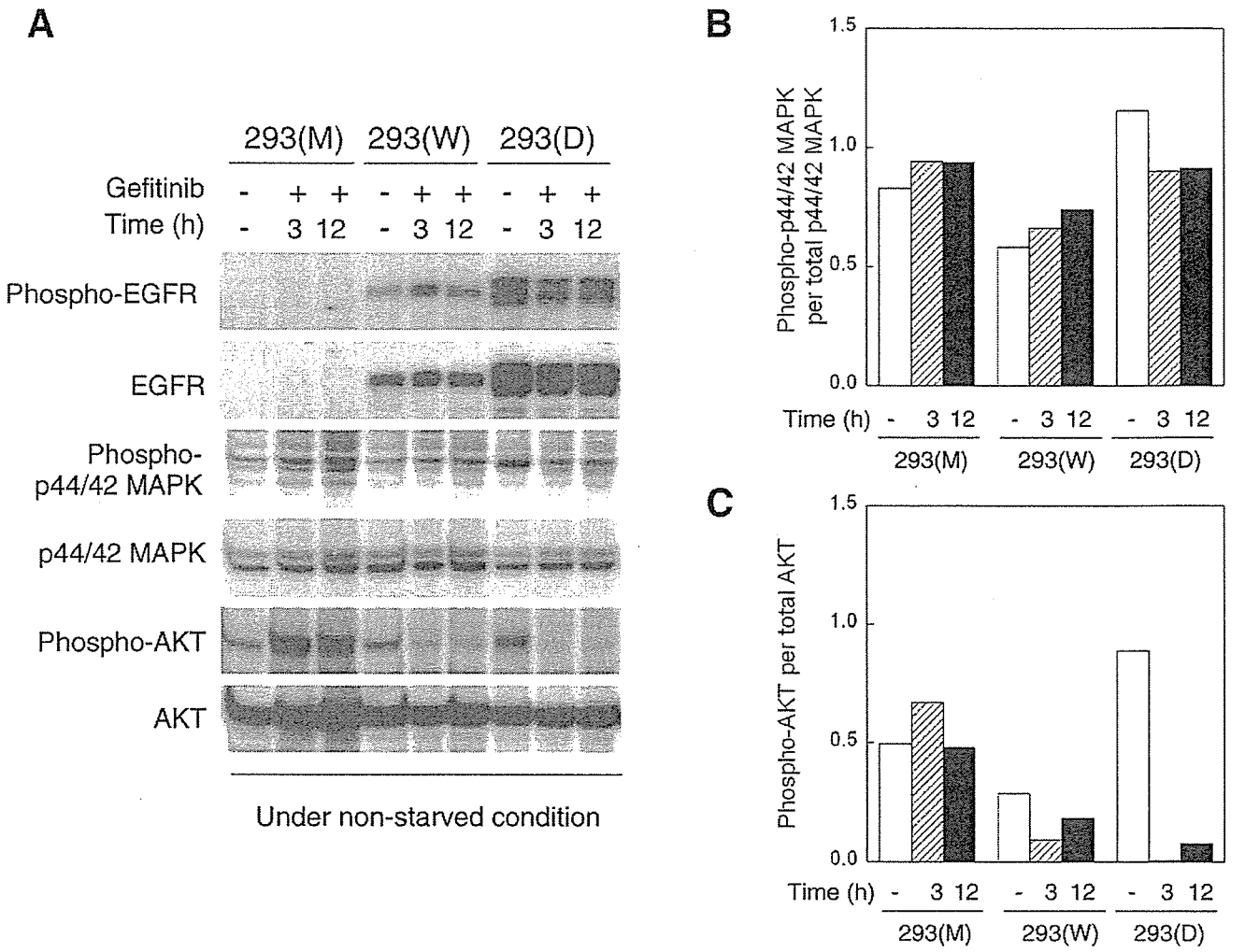

Figure 5. Effect of gefitinib on phosphorylation of EGFR, p44/42 MAPK, and AKT in the EGFR-transfected 293 cells under nonstarved conditions. *A*) The 293(M), 293(W), and 293(D) cells were incubated with gefitinib (0.01 μM) for 3 h or 12 h under nonstarved conditions. After two washes with ice-cold PBS(+), monolayer cells were lysed. Equivalent amounts of protein were separated by 2–15% gradient SDS-PAGE for EGFR or 10–20% for p44/42 MAPK, phospho-p44/42 MAPK, AKT, and phospho-AKT, and then subjected to immunoblot analysis. *B*) Histogram of the degree of p44/42 MAPK activation expressed as phospho-p44/42 MAPK per total p44/42 MAPK. *C*) Histogram of the degree of AKT activation expressed as phospho-AKT per total AKT.

Fig. 6

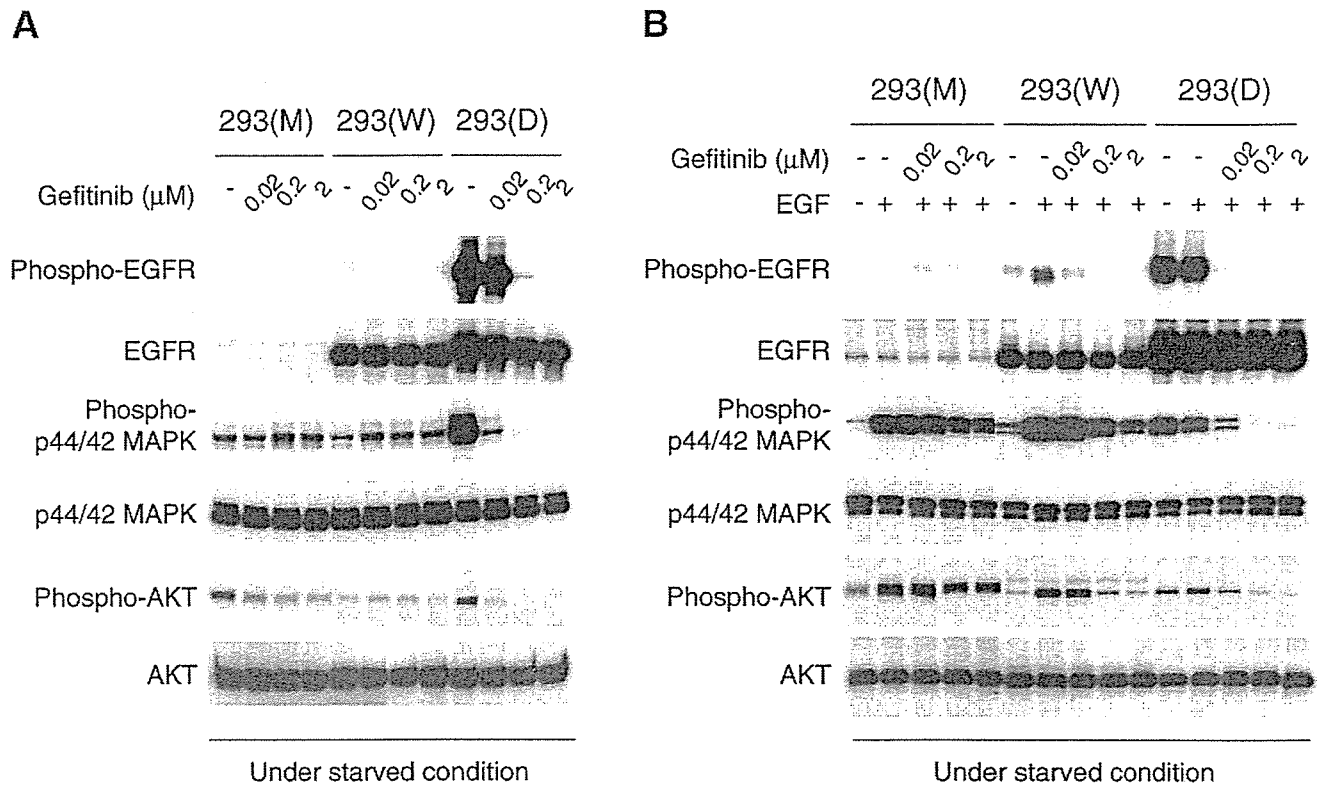

Figure 6. Effect of gefitinib on phosphorylation of EGFR, p44/42 MAPK, and AKT in the EGFR-transfected 293 cells under serum-starved conditions. ***A***) The 293(M), 293(W), and 293(D) cells were incubated with gefitinib (0.02, 0.2, 2 μM) for 3 h under serum-starved conditions. After two washes with ice-cold PBS(+), monolayer cells were lysed. Equivalent amounts of protein were separated by 2–15% gradient SDS-PAGE for EGFR or 10–20% for p44/42 MAPK, phospho-p44/42 MAPK, AKT, and phospho-AKT, and then subjected to immunoblot analysis. ***B***) The transfected cells were incubated with gefitinib (0.02, 0.2, 2 μM) for 3 h under serum-starved conditions and stimulated with EGF (100 ng/ml) for 10 min. Immunoblot analysis was performed as described above.

Fig. 7

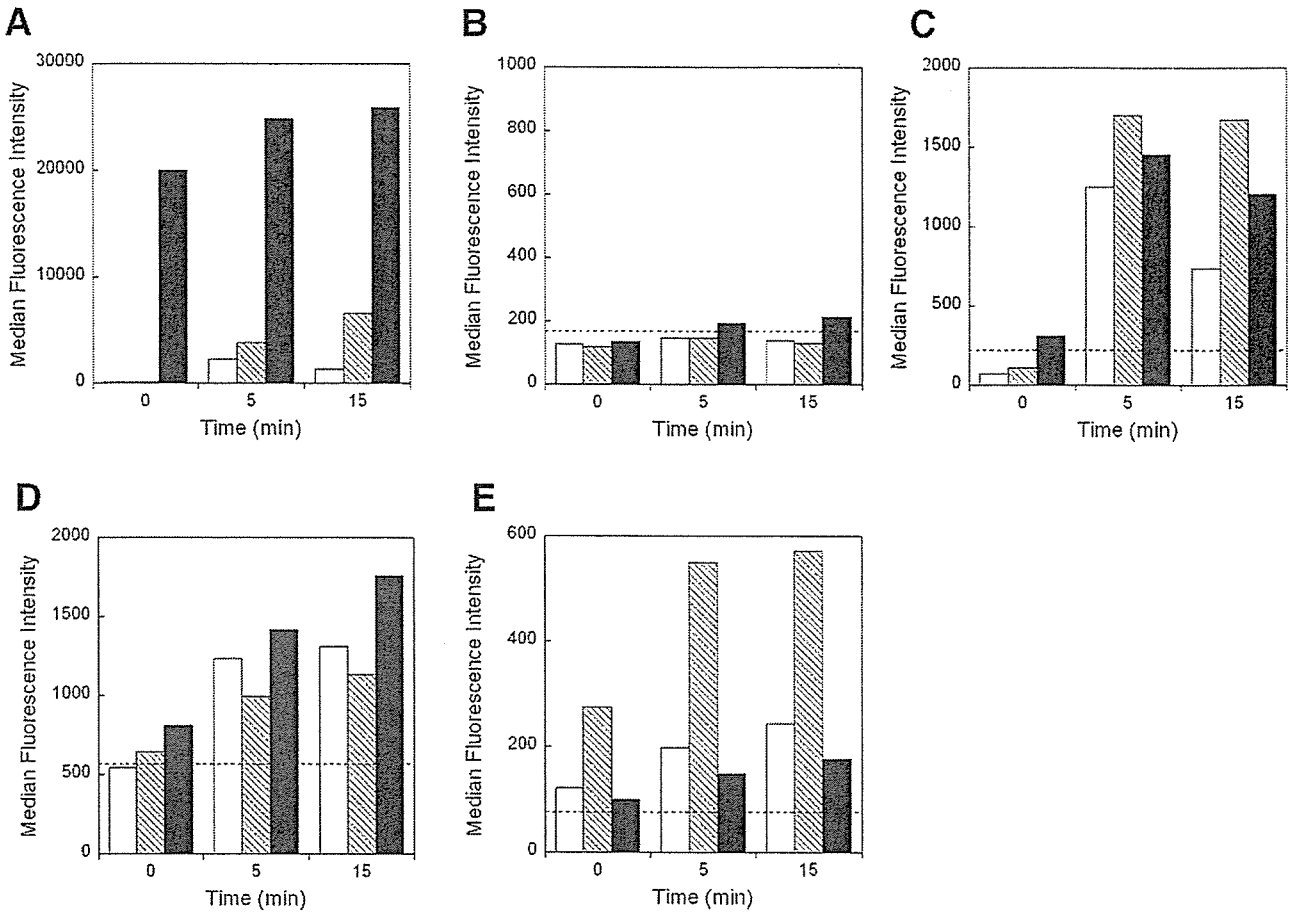

Figure 7. Monitoring of phosphoproteins after EGF stimulation in the EGFR-transfected 293 cells. The phosphoproteins in the 293(M) (open bars), 293 (W) (hatched bars), and 293(D) (solid bars) cells were analyzed by bead-based multiplex assay at the indicated intervals after addition of EGF (100 ng/ml) under serum-starved conditions. After two washes with ice-cold PBS(+), monolayer cells were lysed. The fluorescence intensity of phosphoproteins in the transfected cells was counted by bead-based multiplex assay. ***A***) phospho-EGFR; ***B***) phospho-IκB-α; ***C***) phospho-p44/42 MAPK; ***D***) phospho-ATF-2; ***E***) phospho-JNK. The dotted line shows the signal intensity of nontreated HeLa cells as a background control.

Fig. 8

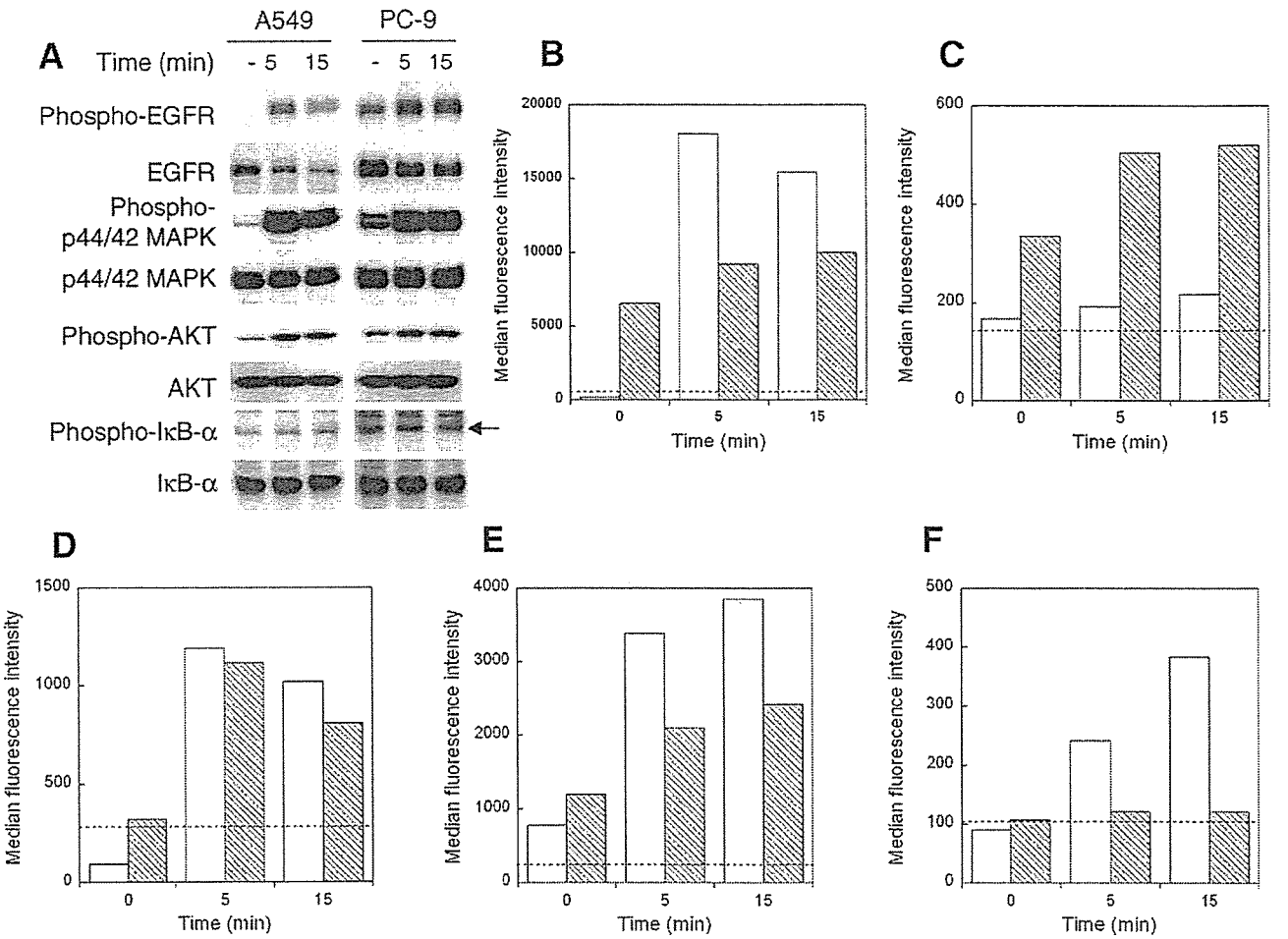

Figure 8. Monitoring of phosphoproteins after EGF stimulation in NSCLC cells. The phosphoproteins in NSCLC cells were analyzed for the indicated time intervals after addition of EGF (100 ng/ml) under serum-starved conditions. ***A***) After two washes with ice-cold PBS(+), monolayer cells were lysed. Equivalent amounts of protein were separated by 2–15% gradient SDS-PAGE for EGFR and phospho-EGFR or 10–20% for p44/42 MAPK, phospho-p44/42 MAPK, AKT, phospho-AKT, IκB-α, and phospho-IκB-α, and then subjected to immunoblot analysis. The fluorescence intensity of phosphoproteins in the A549 (open bars) and PC-9 (hatched bars) cells was counted by bead-based multiplex assay. ***B***) phospho-EGFR. ***C***) phospho-IκB-α, ***D***) phospho-p44/42 MAPK, ***E***) phospho-ATF-2, ***F***) phospho-JNK. The dotted line shows the signal intensity of nontreated HeLa cells as a background control.

Effect of the introduction of minimum lesion size on interobserver reproducibility using RECIST guidelines in non-small cell lung cancer patients

Hirokazu Watanabe,[1,6] Hideo Kunitoh,[2] Seiichiro Yamamoto,[5] Shin Kawasaki,[2] Akira Inoue,[2] Katsuyuki Hotta,[2] Kazu Shiomi,[3] Masahiko Kusumoto,[4] Kazuro Sugimura[1] and Nagahiro Saijo[2]

[1]Department of Radiology, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe 650-0017; [2]Department of Medical Oncology, [3]Thoracic Surgery, and [4]Radiology, National Cancer Center Hospital; and [5]Research Center for Cancer Prevention and Screening, Statistics and Cancer Control, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

(Received September 17, 2005/Revised November 24, 2005/Accepted November 28, 2005/Online publication February 16, 2006)

We evaluated interobserver reproducibility for the response evaluation criteria in solid tumors (RECIST) guidelines and the influence of minimum lesion size (MLS) on reproducibility. The 110 consecutive patients with non-small cell lung cancer were treated with platinum-based chemotherapy. Five observers measured target lesions according to both the World Health Organization (WHO) criteria and RECIST. The percentage changes for unidimensional measurements (UD; RECIST type) and bidimensional measurements (BD; WHO type) were calculated for each patient. Interobserver reproducibility among five observers, that is 10 pairs, was expressed as the Spearman's correlation coefficient for the percentage changes, the proportion of agreement and the kappa statistics for response categories. The same analysis was carried out using MLS. BD was more reproducible than UD (Spearman rank correlation coefficient, 0.84 vs 0.81; proportion of agreement, 84.4% vs 82.5%; kappa value, 0.69 vs 0.61). When MLS was applied to UD, eligible cases decreased by 6.4% and the number of target lesions by 44.6%, whereas interobserver reproducibility for UD improved (Spearman rank correlation coefficient, 0.81–0.84; proportion of agreement, 82.5–84.2%; kappa value, 0.61–0.65). The introduction of MLS to UD could also improve intercriteria reproducibility between WHO and RECIST. It is important to apply the MLS when using RECIST for the comparable interobserver reproducibility attained with WHO. (*Cancer Sci* 2006; 97: 214–218)

Tumor response to chemotherapy was previously evaluated using the WHO criteria, which stipulate bidimensional measurement (BD; WHO type) of lesions.[1] With these standardized criteria for evaluating tumor response, valid and reproducible results could be obtained by all investigators. However, a number of modifications to the WHO criteria have been developed by different institutions, which made it difficult to compare response rates for screening new anticancer agents across different investigators. This has led to the introduction of a new system, the RECIST guidelines,[2] which have been widely accepted as the new standard.

In order to standardize the methodology for evaluating tumor response, RECIST simplified the response evaluation through the use of unidimensional measurements (UD; RECIST type) instead of the BD used by the WHO criteria. Furthermore, the MLS allowable for measurement at baseline study was defined as being no less than double the slice thickness on CT or MRI.

The validity and intercriteria reproducibility between the new RECIST guidelines and the previous WHO criteria have been investigated.[2–7] However, to the best of our knowledge, no analysis of the influence of MLS on interobserver reproducibility, specified for measurability in tumor response evaluation according to the RECIST guidelines, has been published in the literature.

The purpose of the present study was therefore to evaluate interobserver reproducibility in tumor response evaluation using RECIST, intercriteria reproducibility between WHO and RECIST, and whether this reproducibility is affected by the application of MLS.

Materials and Methods

Patient population

This is a retrospective study of the radiological findings for patients who underwent chemotherapy for advanced NSCLC. The subjects were patients treated during clinical trials at the Medical Oncology Division of the National Cancer Center Hospital in Tokyo, Japan, between January 1999 and January 2001. All clinical trials were conducted in accordance with the Helsinki Declaration and the protocols were approved by the institutional review board. Written informed consent was obtained from each patient for the treatment protocols, which included the secondary use of treatment-associated documents. Patients were staged according to the Union Internationale Contra le Cancer TNM classification of malignant tumors.[8] The 110 eligible patients included those histologically or cytologically diagnosed with NSCLC. Patients were required to undergo CT scans periodically for evaluating tumor response prior to and once after

[6]To whom correspondence should be addressed. E-mail: h-watanabe@kcc.zaq.ne.jp
Abbreviations: BD, bidimensional measurements; CR: complete response; CT, computed tomography; MLS, minimum lesion size; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; RECIST, response evaluation criteria in solid tumors; SD, stable disease; TNM, tumor node metastases; UD, unidimensional measurements; WHO, World Health Organization.

doi: 10.1111/j.1349-7006.2006.00157.x
© 2006 Japanese Cancer Association

treatment, to have at least one bidimensionally measurable lesion, and to be treated with chemotherapy in clinical trials.

Patients treated in clinical practice were considered to be unsuitable and excluded from this study as tumor response evaluation in the clinical practice of oncology is not always carried out according to predefined criteria, but rather is made by subjective medical judgment based on clinical and laboratory data. In addition, tumor response evaluation is not always carried out by CT examination, and the intervals between tumor evaluations can be irregular.

Image analysis

Almost all images were acquired with a TCT-900S Superhelix (Toshiba Medical, Tokyo, Japan), with the remainder scanned on an X-Vigor helical CT scanner (Toshiba Medical). Helical CT was carried out with fixed scanning parameters, including a table speed of 15 mm/s, a pitch ratio of 1:1.5 per rotation time 1 s, and the same contrast agent for both baseline and follow-up evaluations. Image reconstruction was carried out at intervals of 10 mm.

On chest CT obtained during baseline examination before the initiation of chemotherapy, target lesions up to a maximum of five lesions per patient with longest and perpendicular diameters that could be measured accurately were selected by one diagnostic radiologist. In addition, one follow-up chest CT examination, indicating tumors with the greatest response to chemotherapy, was selected retrospectively. Target lesions included primary lung lesion, pulmonary metastases and lymph nodes.

For the target lesions, the two parameters consisting of the longest diameter and the diameter perpendicular to it were measured with electronic calipers on digitized images. Five observers of different backgrounds, blinded to patient profiles, reviewed all patients independently and no attempt was made to arrive at a consensus. These observers included one diagnostic radiologist, one thoracic physician, two medical oncologists and one thoracic surgeon.

Tumor response evaluation

The sum of the longest diameters for all target lesions was calculated for pretreatment and post-treatment UD. Similarly, the sum of the products of the longest diameters and their perpendicular diameters for all target lesions was calculated for pretreatment and post-treatment BD. If there were two or more lesions, the sum of all target lesions was calculated. The baseline sum was used as the reference from which objective tumor response could be calculated. The percentage changes were calculated as post-treatment value divided by pretreatment value for both UD and BD.

Percentage changes were then classified using the current RECIST guidelines and the previous WHO criteria tumor response classification system. Tumor response was categorized into CR, PR, SD and PD based on both RECIST guidelines and WHO criteria. The RECIST PR was defined as a 50% decrease in the percentage changes for UD, and the WHO PR was defined as a 30% decrease in the percentage changes for BD. The RECIST PD was defined as a 20% increase in the sum of the longest diameters, and the WHO PD was defined as a 25% increase in the sum of the products of the two diameters of all lesions or in the product of the diameters of one lesion. For the present study, no minimum interval was required for the confirmation of either CR or PR.

Analysis of intercriteria reproducibility

To examine intercriteria reproducibility, the mean and ranges of differences in the response rate between UD and BD were calculated. We then estimated those between UD-MLS and BD. Interobserver differences among the five observers yielded 20 pair comparisons. Intraobserver differences of the same observer yielded five pair comparisons.

Analysis of interobserver reproducibility

First, to examine the interobserver reproducibility of the percentage changes according to the two different dimensional measurements, we estimated the Spearman's correlation coefficient of the percentage changes among the five observers, calculated for each pair observed (five observers yielded 10 pair comparisons).

Second, to examine the interobserver reproducibility for two tumor response criteria, we estimated the proportion of agreement to the categories of CR, PR, SD and PD for both UD and BD among the five observers (10 pair comparisons). We then calculated the kappa statistics, a measure of agreement in which agreement is taken into consideration by chance, to assess interobserver reproducibility for tumor response categories.[9]

Third, we examined the influence of MLS on the number of eligible cases and target lesions. The same analyses on interobserver reproducibility were conducted applying the MLS. MLS was introduced into the RECIST guidelines, which specify a minimum lesion size of less than double the slice thickness on images. The slice thickness was 10 mm in the present study, so the MLS was set at no less than 20 mm at baseline evaluation before treatment. Cases that only had tumors smaller than the MLS were excluded from the present study. We defined the RECIST guidelines as the evaluation by UD for measurable cases and the WHO criteria as the evaluation by BD for all cases.

SAS version 8.02 (SAS Institute, Cary, NC, USA) was used for all analyses.

Results

Patient population

The characteristics of the 110 patients were as follows: male/female = 80/30, median age = 59 years (range 36–72 years), stage IIIB/IV = 33/77. Chemotherapy regimens are listed in Table 1. A total of 220 CT images were reviewed, comprising 110 CT images each from the baseline study (pretreatment) and from the follow-up (post-treatment) study.

Tumor response evaluation between UD and BD

The tumor response evaluation was categorized into CR, PR, SD and PD without MLS. The response rate results are shown in Table 2. None of the patients were rated CR. The use of UD resulted in response categories by observers A, B, C, D and E of 35, 28, 26, 34 and 36 PR, 73, 79, 81, 73 and 71 SD, and 2, 3, 3, 3 and 3 PD, respectively. The response rate ranged from 23.6 to 32.7%. For BD, the corresponding response categories were 37, 30, 33, 36 and 36 PR, 67, 73,

© 2006 Japanese Cancer Association

Table 1. Characteristics of the 110 patients enrolled in the present study

Characteristic	*n*
No. patients	110
Age (years)	
Median	59
Range	36–72
Sex	
Male	80
Female	30
Disease stage at study entry	
IIIB	33
IV	77
Tumor histology	
Adenocarcinoma	78
Squamous	22
Large-cell	1
Unclassified non-small cell	9
Regimen	
Cisplatin and gemcitabine	21
Cisplatin and paclitaxel	18
Nedaplatin and paclitaxel	15
Cisplatin and vinorelbine	14
Carboplatin and paclitaxel	14
Cisplatin and vindesine	13
Cisplatin, docetaxel and ifosfamide	7
Cisplatin and docetaxel	8

Table 2. Response rate (%) using four different measurements among five observers

Measurement	Observer					Mean
	A	B	C	D	E	
UD	31.8	25.5	23.6	30.9	32.7	28.9
BD†	33.6	27.3	30.0	32.7	32.7	31.3
UD-MLS‡	33.0	27.2	32.0	30.1	32.0	30.9
BD-MLS	35.0	32.0	33.0	33.0	34.0	33.4

†WHO criteria; ‡RECIST guidelines. BD, bidimensional measurement; MLS, minimum lesion size; UD, unidimensional measurement.

68, 68 and 68 SD, and 6, 7, 9, 6 and 6 PD, respectively. The response rate ranged from 27.3 to 33.6%.

Tumor response evaluation between UD-MLS and BD-MLS

When the MLS criteria were applied, the number of eligible cases decreased by 6.4% from 110 to 103, and the number of target lesions decreased by 44.6% from 402 to 223.

The response rate results are shown in Table 2. None of the patients were rated CR. When UD was used with MLS, the respective response evaluations made by observers A, B, C, D and E were 34, 28, 33, 31 and 33 PR, 68, 73, 67, 72 and 68 SD, and 1, 2, 3, 0 and 2 PD. The response rates of UD applying MLS ranged from 27.2 to 33.0%, showing a reduction in interobserver difference compared with those of UD not applying MLS. With BD using the MLS, the corresponding response categories were 36, 33, 34, 34 and 35 PR, 63, 66, 65, 63 and 64 SD, and 4, 4, 4, 6 and 4 PD. The response rate ranged from 32.0 to 35.0%.

Intercriteria reproducibility

The intercriteria reproducibility in the response rates is shown in Table 3. Between UD and BD, the intraobserver difference in the response rates ranged from 0 to 6.4% with a mean of 2.36%, and the interobserver difference ranged from 0 to 10.0% with a mean of 4.25%. Between UD-MLS and BD, the intraobserver difference in the response rates ranged from 0.1 to 2.6% with a mean of 1.26%, and the interobserver difference ranged from 0.1 to 6.4% with a mean of 2.76%.

Correlations between UD and BD

The mean and ranges of interobserver reproducibility among five observers using the two dimensional measurements are shown in Table 4. The mean value of the Spearman rank correlation coefficient for the percentage changes when using UD (0.81) was lower than that using BD (0.85), and the same tendency was observed for the mean value of proportion of agreement for the tumor response categories (82.5%, 908/1100 vs 84.4%, 928/1100) and the mean kappa statistics for the tumor response categories (0.61 vs 0.69). The lowest kappa statistics among the 10 pair comparisons were 0.49 with UD and 0.61 with BD. The kappa statistics obtained with BD were higher than those with UD in nine out of 10 pair comparisons (Fig. 1).

Correlations between UD and UD-MLS

The mean values and ranges of interobserver reproducibility when applying the MLS are shown in Table 4. The mean value of Spearman's correlation coefficient for UD-MLS (0.84) was higher than that for UD (0.81), and the same tendency was observed for the mean value of proportion of agreement for the tumor response categories (84.2%, 867/1030 vs 82.5%, 908/1100) and the mean kappa statistics for the tumor response categories (0.65 vs 0.61). The lowest kappa statistics among the 10 pair-based comparisons was 0.57 with MLS and 0.49 without. When MLS was used together with UD, the kappa statistics increased in eight out of 10 pair comparisons (Fig. 2).

Table 3. Intercriteria reproducibility: difference in the response rate (%) among five observers

Category	UD and BD†		UD-MLS‡ and BD†	
	Mean	Range	Mean	Range
Overall (25 comparisons)	3.87	0–10	2.45	0.1–6.4
Interobserver (20 comparisons)	4.25	0–10	2.76	0.1–6.4
Intraobserver (5 comparisons)	2.36	0–6.4	1.26	0.1–2.6

†WHO criteria; ‡RECIST guidelines. BD, bidimensional measurement; MLS, minimum lesion size; UD, unidimensional measurement.

doi: 10.1111/j.1349-7006.2006.00157.x
© 2006 Japanese Cancer Association

Table 4. Interobserver reproducibility (10 pair comparisons) using four different measurements among five observers

Category	No. patients	Spearman's correlation coefficient		Proportion of agreement (%)		Kappa statistic	
		Mean	Range	Mean	Range	Mean	Range
UD	110	0.81	0.76–0.86	82.5	77.3–89.1	0.61	0.49–0.75
BD†	110	0.85	0.79–0.89	84.4	80.0–89.1	0.69	0.61–0.78
UD-MLS‡	103	0.84	0.75–0.89	84.2	80.6–88.3	0.65	0.57–0.73
BD-MLS	103	0.86	0.80–0.89	84.0	78.6–89.3	0.68	0.58–0.78

†WHO criteria; ‡RECIST guidelines. BD, bidimensional measurement; MLS, minimum lesion size; UD, unidimensional measurement.

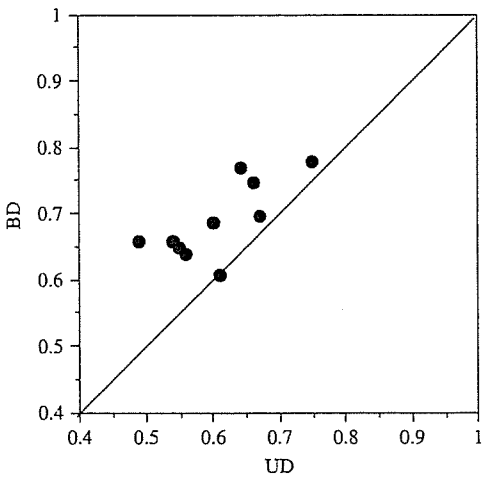

Fig. 1. Scattergram showing the kappa statistics for the use of unidimensional (UD) and bidimensional (BD) measurements. The kappa values for BD were higher than those for UD in nine of 10 pair comparisons.

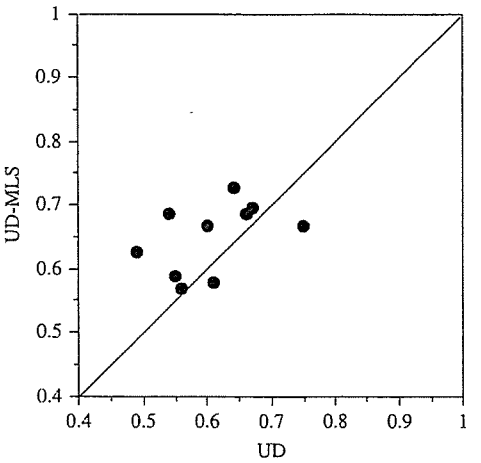

Fig. 2. Scattergram showing the kappa statistics for the use of unidimensional measurement (UD) and UD with minimum lesion size (MLS). When MLS was applied to UD, the kappa values increased in eight of 10 pair comparisons.

Discussion

Standardized tumor response evaluation systems are considered reliable in clinical trials when they are valid and reproducible among different observers. Although the intercriteria reproducibility between the new RECIST guidelines and the previous WHO criteria had been investigated,[2–7] little information was available concerning interobserver reproducibility of tumor response evaluation. In addition, statistical analysis results regarding the effect of MLS on interobserver reproducibility had not been provided in previous reports. This is the first study to investigate interobserver reproducibility of the RECIST guidelines evaluating the MLS.

The importance of interobserver reproducibility for any classification scheme has been discussed previously for other grading systems.[10–12] Clinical investigators must take into account interobserver reproducibility in tumor response evaluation, which can greatly affect the results in clinical trials. Our findings demonstrated that interobserver variability exists for bidimensional measurements, as in studies published previously.[13,14] For example, Hopper *et al.* showed considerable interobserver variability in CT tumor measurements between radiologists interpreting thoracic and abdominal/pelvic CT scans.[13] In another report, the impact of an evaluation committee on patients' overall response status in a large multicenter trial in oncology was evaluated.[14] Major disagreements occurred in 40% of cases and minor disagreements occurred in 10.5% of the cases reviewed. The number of responders was reduced by 23.2% after review by the evaluation committee.

The range of response rates among five observers was clearly narrowed by the MLS (Table 2). The response rates assessed by UD varied from 23.6 to 32.7%. When assessed by BD, the response rates ranged from 27.3 to 33.6%. Response rates assessed with UD-MLS ranged from 27.2 to 33.0%, which was almost identical when BD was used.

The results of the present study also suggested that BD was more reproducible than UD. When MLS was applied to UD, the mean values and ranges of Spearman's correlation coefficient, proportion of agreement and the kappa statistics improved (Table 4). In order to ensure comparable interobserver reproducibility (as was originally achieved with the WHO criteria) it is essential that the MLS be used in combination with UD when using RECIST.

Because of the need to retain some ability to compare results of future therapies with those available currently, no major discrepancy should exist between the old (WHO) and

© 2006 Japanese Cancer Association

new (RECIST) criteria, although measurement criteria would be different. The mean values and ranges of intercriteria reproducibility in the response rates between UD-MLS and BD were lower and narrower than those between UD and BD (Table 3). The introduction of MLS to UD improved the intercriteria reproducibility between WHO and RECIST.

As for intercriteria reproducibility, the mean values and ranges for intraobserver reproducibility were better than those for interobserver reproducibility (Table 3). Erasmus *et al.* have suggested that consistency can be improved if the same reader carries out serial measurements for any one patient.[15]

When MLS is included in the eligibility criteria, the number of patients with measurable lesions is less than that obtained with the previous WHO criteria because patients with only small lesions are excluded from measurement. In the present study, when MLS criteria were used the number of eligible cases decreased by 6.4% from 110 to 103 and the number of target lesions by 44.6% from 402 to 223. This reduction could affect the number of patients enrolled in clinical trials.

The present study had several limitations. First, the study cohort comprised NSCLC patients only and the application of the measurement modalities was limited to chest CT. Second, intraobserver variability between evaluations with different intervals was not investigated. Third, our reference was a 10 mm slice thickness and therefore the minimum lesion size was defined as 20 mm. However, RECIST guidelines allow for a minimum lesion size of 10 mm as a slice thickness of 5 mm measured by helical CT is used. Recently, multidetector CT, which creates a thinner slice thickness, has been developed and is being used in daily clinical practice. Therefore, the addition of the outcomes of patients ineligible for our study as a result of using a thinner slice thickness might change our results and should be evaluated in a further study.

In conclusion, the results of the present study suggest that UD yields poorer interobserver reproducibility of tumor response evaluation than BD; however, if MLS is applied to UD, interobserver reproducibility can improve and become the same as that obtained with BD. The introduction of MLS to UD could also improve intercriteria reproducibility between WHO and RECIST. It is therefore essential that investigators include MLS when using RECIST guidelines to ensure interobserver reproducibility comparable with the WHO criteria.

Acknowledgments

This work was supported by Grants-in-Aid from the Ministry of Health, Labour and Welfare, Japan, and was presented in part at the 38th ASCO Annual Meeting, 19 May 2002.

References

1 Miller AB, Hoogstraten B, Staquet M *et al.* Reporting results of cancer treatment. *Cancer* 1981; **47**: 207–14.
2 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.
3 Watanabe H, Yamamoto S, Kunitoh H *et al.* Tumor response to chemotherapy: The validity and reproducibility of RECIST guidelines in NSCLC patients. *Cancer Sci* 2003; **94**: 1015–20.
4 James K, Eisenhauer E, Christian M *et al.* Measuring response in solid tumors: unidimensional versus bidimensional measurement. *J Natl Cancer Inst* 1999; **91**: 523–8.
5 Sohaib SA, Turner B, Hanson JA *et al.* CT assessment of tumour response to treatment: comparison of linear, cross-sectional and volumetric measures of tumour size. *Br J Radiol* 2000; **73**: 1178–84.
6 Warren KE, Patronas N, Aikin AA *et al.* Comparison of one-, two-, and three-dimensional measurements of childhood brain tumors. *J Natl Cancer Inst* 2001; **93**: 1401–5.
7 Werner-Wasik M, Xiao Y, Pequignot E *et al.* Assessment of lung cancer response after nonoperative therapy: Tumor diameter, bidimensional product, and volume. A serial CT scan-based study. *Int J Radiat Oncol Biol Phys* 2001; **51**: 56–61.
8 Sobin LH, Wittekind CH. *UICC TNM Classification of Malignant Tumours*, 5th edn. New York: John Wiley and Sons, 1997.
9 Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; **33**: 159–74.
10 Al-Aynati M, Chen V, Salama S *et al.* Interobserver and intraobserver variability using the Fuhrman grading system for renal cell carcinoma. *Arch Pathol Lab Med* 2003; **127**: 593–6.
11 Hagen PJ, Hartmann IJ, Hoekstra OS *et al.* Comparison of observer variability and accuracy of different criteria for lung scan interpretation. *J Nucl Med* 2003; **44**: 739–44.
12 Travis WD, Gal AA, Colby TV *et al.* Reproducibility of neuroendocrine lung tumor classification. *Hum Pathol* 1998; **29**: 272–9.
13 Hopper KD, Kasales CJ, Van Slyke MA *et al.* Analysis of interobserver and intraobserver variability in CT tumor measurements. *Am J Roentgenol* 1996; **167**: 851–4.
14 Thiesse P, Ollivier L, Di Stefano-Louineau D *et al.* Response rate accuracy in oncology trials: reasons for interobserver variability. *J Clin Oncol* 1997; **15**: 3507–14.
15 Erasmus JJ, Gladish GW, Broemeling L *et al.* Interobserver and intraobserver variability in measurement of non-small-cell carcinoma lung lesions: Implications for assessment of tumor response. *J Clin Oncol* 2003; **21**: 2574–82.

doi: 10.1111/j.1349-7006.2006.00157.x
© 2006 Japanese Cancer Association

ELSEVIER

Seminars in
Oncology

Geographic Variation in the Second-Line Treatment of Non–Small Cell Lung Cancer

Martin J. Edelman,[a] Ikuo Sekine,[b] Tomohide Tamura,[b] and Nagahiro Saijo[c]

Although there is broad agreement on management options for treating different stages of non–small cell lung cancer (ie, surgery for stage I and II disease, combined treatment modalities for stage III disease, and platinum-based chemotherapy as initial treatment for appropriate patients with stage IV disease), there is considerable geographic variation in practice patterns. These variations reflect a number of factors, including health care economics, the influence of national and regional regulatory bodies, the nature of physician and patient interaction, and probable biological differences between different populations in terms of drug metabolism and inherent susceptibility to both drug activity and toxicity. The approaches taken by three different geographic regions, the United States, European Union, and Japan, are evaluated. Clinically, the most striking differences in activity and toxicity between different regions have been seen with the epidermal growth factor receptor inhibitors gefitinib and erlotinib. Japanese patients experience significantly greater response and a greater degree of interstitial lung disease than patients in the European Union and North America (ie, US and Canada). Similar differences in efficacy and toxicity have also been noted with cytotoxic chemotherapy agents in the first-line setting. These geographic and ethnic differences in toxicity and efficacy will need to be considered in the design and comparison of future clinical trials.
Semin Oncol 33(suppl 1):S39-S44 © 2006 Elsevier Inc. All rights reserved.

Lung cancer is the most lethal malignancy in the developed world, and was expected to account for over one million deaths worldwide in 2005.[1] Non–small cell lung cancer (NSCLC) accounts for approximately 85% of these cases.[2] The vast majority of cases are secondary to tobacco use. Other etiologies include asbestos and radon exposure as well as a genetic contribution.

Although standards of care have been established for different stages of the disease, there is considerable geographic variation in practice patterns. Three major geographic factors influence the choice of second- and third-line therapy. First is the influence of the regulatory agencies that govern the approval of antineoplastic agents. Second is the influence of the specific national healthcare system, including factors governing reimbursement to patients and physicians for treatment. Finally, and most significantly, is the emerging recognition that there are biological differences between different populations in terms of drug metabolism and inherent efficacy. This article will briefly review the approaches taken to second-line therapy in three different areas of the world: the United States, European Union (EU), and Japan.

Overview of Second-Line Therapy

Docetaxel

The first agent to show unequivocal activity in the second-line treatment of NSCLC was docetaxel. A National Cancer Institute of Canada trial compared docetaxel at 75 mg/m^2 or 100 mg/m^2 versus best supportive care. This trial found superior quality and length of life for patients treated with 75 mg/m^2 docetaxel.[3] An industry-sponsored study in the United States compared docetaxel at either 75 or 100 mg/m^2 versus a physician choice of either vinorelbine or ifosfamide. Again, quality of life and survival were superior for docetaxel 75 mg/m^2.[4] The concordant results of these two trials support

[a]University of Maryland Greenebaum Cancer Center, Baltimore, MD.
[b]Division of Thoracic Oncology and Internal Medicine, National Cancer Center Hospital, Tokyo, Japan.
[c]National Cancer Center Hospital East, Kashiwa, Japan.
Dr Edelman has served as a consultant and has received research funding and honoraria from Eli Lilly, Genentech, and Aventis. Drs Sekine, Tamura, and Saijo have received research grant support from Eli Lilly, AstraZeneca, and Bristol-Myers Squibb.
Address reprint requests to Martin J. Edelman, MD, University of Maryland Greenebaum Cancer Center, 22 S. Greene St, Baltimore, MD 21136. E-mail: medelman@umm.edu

0093-7754/06/$-see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1053/j.seminoncol.2005.12.003

the conclusion that docetaxel 75 mg/m^2 every 3 weeks has a clear role in this setting. Docetaxel has been approved for treatment of previously treated NSCLC in the United States, EU, and Japan.

Pemetrexed

Pemetrexed, a new antifolate agent that has shown activity in mesothelioma, has been tested in the second-line treatment of NSCLC. A phase III trial randomizing patients to either pemetrexed (500 mg/m^2 every 3 weeks with vitamin B_{12} and folate supplementation) or docetaxel (75 mg/m^2 every 3 weeks) showed a similar level of activity but superior tolerability.[5] There was considerably less myelotoxicity and alopecia in the pemetrexed arm, and significantly fewer patients required hospitalization after treatment than with docetaxel. Activity, in terms of response rate, median survival time, and 1-year survival rate, was superimposable for pemetrexed and docetaxel. Pemetrexed has been approved in the United States and EU for the second-line treatment of advanced NSCLC.

Gefitinib

Gefitinib was the first drug to receive approval for third-line therapy of NSCLC anywhere in the world (Japan). This approval was controversial as its basis was response rate rather than a more unequivocal outcome of patient benefit, such as survival rate.[6] The drug had previously failed to show benefit (in terms of response or survival) as a first-line treatment when combined with standard chemotherapy.[7,8]

Two large phase II trials of gefitinib monotherapy, the Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL) 1 and IDEAL 2 studies, evaluated the agent in pretreated NSCLC. Both studies determined response and survival. The IDEAL 1 trial, conducted primarily in Japan and Europe, also evaluated the safety profile and symptom improvement, while the IDEAL 2 trial, conducted in North America, evaluated symptom improvement as an additional primary endpoint.[9,10] The response rates for dosages of 250 mg/day and 500 mg/day were 18.4% and 19% in IDEAL 1, and 12% and 9% in IDEAL 2, respectively. Many patients, even those with a poor performance status (ie, performance status 2–3) experienced symptom improvement (most notably in pulmonary symptoms of dyspnea and chest pain) within 2 weeks of starting gefitinib treatment. This improvement in quality-of-life scales, though questionable as there was no randomization against either best supportive care or another agent, was the major impetus for granting conditional approval to market the agent in the United States. Approval was granted under the provision that appropriate randomized trials be conducted. Gefitinib has not received approval in the EU, although it has been approved in Switzerland.

Subset analysis shows that female sex, adenocarcinoma (and, in particular, bronchioloalveolar histology), and nonsmoking status are predictors of response.[10,11] Female sex was a particularly strong predictor in both IDEAL trials. In the primarily North American IDEAL 2 study, 50% of women experienced symptomatic response versus 31% of men ($P = .006$). Radiographic regression was also seen in 19% of women versus only 3% of men ($P = .001$). Two groups in Boston, MA have recently reported that mutations in the aATP-binding pocket of the epidermal growth factor receptor (EGFR) tyrosine kinase (TK) domain predict for clinical benefit from gefitinib.[12,13] While others have confirmed the presence of mutations, the role of mutations versus other alterations in *EGFR* (copy number, expression as measured by fluorescence in situ hybridization) have also been proposed as predictors of response to EGFR TK inhibitors (TKIs). It remains unclear as to whether any of these molecular variables predict independently for outcome.[14]

The role of gefitinib has recently been questioned because of the results of the Iressa Survival Evaluation in Lung Cancer (ISEL) trial.[15] This trial, undertaken in countries in which gefitinib had not received approval (ie, countries other than the United States and Japan) randomized patients between gefitinib and placebo. The ISEL trial was conducted in cooperation with 210 institutes in 28 countries (not including Japan). An advantage was shown in terms of response rate.[15] However, a trend toward improved survival did not achieve statistical significance. The subset analysis in Asian and non-Asian patients showed that female sex and adenocarcinoma histology were more common characteristics in Asian patients (Table 1). The US Food and Drug Administration has recently restricted use of gefitinib to patients who are currently being treated with the agent and who demonstrate benefit, and those enrolled in clinical trials.

Erlotinib

Erlotinib is an agent very similar to gefitinib in terms of structure and activity. It too has been evaluated as a second-line drug in the treatment of NSCLC, showing 'promising results' in terms of response and survival in phase II trials.[16]

However, unlike gefitinib, a phase III trial was unequivocally positive. The National Cancer Institute of Canada led a study (JBR-21) comparing erlotinib with best supportive care in third-line therapy. This large study (more than 700 patients) provided definitive evidence of benefit in terms of survival for this agent.[17] Improvements in response (9% v >1%), median survival (6.7 v 4.7 months; $P < .001$), 1-year survival (31% v 21%), and symptomatology (cough, dyspnea, pain) were observed.[17] Erlotinib has been approved in the United States and EU for the second- and third-line therapy of advanced NSCLC.

Geographic Variations in Treatment

Variations in the efficacy and safety of second-line NSCLC therapies have been observed across geographic regions, and have had an impact on the choice of treatment options within the three key pharmaceutical markets of the United States, the EU, and Japan.

United States

As described above, three agents have been approved by the US Food and Drug Administration for use in the second-line

Table 1 A Comparison of Gefitinib Monotherapy Data Across Geographic Regions

Characteristics	Japanese[40]	Non-Japanese[40]	American[10]	Asian[15]	Non-Asian[15]
No. of patients by gefitinib dose					
250 mg/m²	51	53	102	235	894
500 mg/m²	51	55	114	0	0
Demographics					
Median age (yrs)	60	61	61	61	62
Age range (yrs)	28–77	38–85	30–84	NA	NA
Female (%)	37	22	43	40	31
PS 0–1 (%)	91	83	80	72	64
Stage IV (%)	80	81	89	NA	NA
Adenocarcinoma (%)	76	56	66	64	44
No. of prior chemotherapy regimens (%)					
1	53	59	1	54	48
2	47	41	41	46	52
3 or more	0	0	58	0	0
Treatment efficacy					
Response rate (%)	28	10	10	12	7
Median survival (mos)	12	9.9	6–7	9.5	5.2
1-year survival (%)	50	NA	24–27	44	21
Grade 3–4 toxicity (%)					
Diarrhea	4	3	3	NA	NA
Skin rash	3	5	2	NA	NA
ALT elevation	7	1	1	NA	NA
Interstitial lung disease	2	0	0	2	0.001

Abbreviations: ALT, alanine aminotransferase; NA, not applicable; PS, performance status.

setting: docetaxel, pemetrexed, and erlotinib. Erlotinib also has approval in the third-line setting. Gefitinib, which had been granted an accelerated approval based on the phase II data from the IDEAL studies,[18] has been re-labeled in light of data from the ISEL trial.[19] At present it may only be prescribed in a non-investigational setting for patients who are already receiving the agent and who have demonstrated benefit.

Agent Selection. Controversy exists over which of the three approved agents should be used in the second-line setting. Several factors enter into consideration in the United States. First, docetaxel has also received approval as a first-line agent and is frequently used in this setting with carboplatin or cisplatin. Therefore, a patient who has already received this agent and has progressed would not be a suitable candidate to receive the drug again in the second-line setting. Second, there are no trials comparing the value (in terms of patient benefit) of any of the second-line agents in this setting. As a result, clinical judgement and economic issues are relevant. Third, there appears to be an emerging trend for physicians to use erlotinib in patients who have demonstrated the greatest degree of benefit, ie, non-smokers, women, those patients with adenocarcinoma histology, and those with Asian ancestry. It is possible that selection of patients in the future will also be driven by objective biological markers, ie, the presence of *EGFR* gene mutations or increased *EGFR* copy number. Pemetrexed is therefore used in the remaining population. For most practitioners the superimposable results in terms of survival for pemetrexed and docetaxel, coupled with its superior toxicity profile, make pemetrexed the preferred agent when both drugs are considered for second-line therapy.

Economics. Economic issues are of considerable importance given the expense of the agents. Most insurance programs in the United States will cover the cost of administration of intravenous agents but vary considerably regarding the coverage for oral agents. The cost of gefitinib (USD $2,000 to $3,000/month) is considerable. An assistance program sponsored by the manufacturer is available.

European Union

It is difficult to separate any side effects or outcome differences between the EU countries and North America. Several of the trials described above, including JBR-21 and the randomized trial of pemetrexed versus docetaxel, were conducted with significant accrual from European countries. Approvals within Europe are granted by the European Medicines Agency; a separate Committee for Proprietary Medicinal Products provides clinical expertise for the review process. Pemetrexed, erlotinib, and docetaxel are the agents currently approved in the EU for use as second-line therapy.

Japan

Japan was the first country to approve gefitinib for use in the treatment of lung cancer. Drug approvals in Japan are granted by the Ministry of Health, Labor, and Welfare. The Japanese have a significant preference for oral medications, a factor that is likely to have contributed to the rapid approval of gefitinib.[20]

Approximately 50% of the patients enrolled into the IDEAL 1 trial were Japanese.[9] The remainder were from Europe, Australia, and South Africa, and were predominantly white. Significant differences emerged regarding both efficacy and toxicity; there was no comparison of survival. The response rate was clearly higher for the Japanese (27.5% v 10.4%; $P = .0023$). There were no pharmacokinetic differences to explain this response difference. However, in a multivariate analysis, ethnicity did not emerge as an independent factor for response. Baseline factors such as performance status, sex, and histology appear to explain the ethnic differences.

In the ISEL study, the response rate and median survival time were 12% and 9.5 months in Asian patients and 7% and 5.2 months in non-Asian patients, respectively (Table 1).[15] Mutations of the *EGFR* gene, recently identified in patients with gefitinib-responsive lung cancer,[12,13] correlated well with clinical response to gefitinib and patient survival in retrospective case series studies.[21,22] The relatively high frequency of the mutations in East Asian patients (27% to 34%), compared with 14% or less in American patients, may explain the geographical difference in the efficacy of gefitinib.[12,23] The frequencies of grade 3–4 common toxicities of gefitinib, including diarrhea, skin rash, and alanine transferase elevation, were the same among the study populations (Table 1).

Treatment-Associated Interstitial Lung Disease. Because of the limited number of patients evaluated in clinical trials, it is sometimes difficult to identify and analyze uncommon toxicity before marketing a drug. Interstitial lung disease (ILD) associated with administration of gefitinib came to light in October 2002, 4 months after approval of this agent in Japan.[24] In the IDEAL studies, two Japanese patients developed grade 3–4 ILD (2%), while no patients outside Japan experienced ILD. In the ISEL study, the incidence of grade 3–4 ILD was 2% in Asian patients and .001% in non-Asian patients. In a retrospective evaluation of 112 Japanese patients, the incidence of ILD was 5.4%. The primary risk factor was a prior history of pulmonary fibrosis.[24] Between July 2002 and December 2004, there were 86,800 patients with NSCLC who were estimated to have received gefitinib in Japan. According to the Ministry of Health, Labor, and Welfare 1,473 patients were suspected of having ILD associated with the use of gefitinib and 588 patients died of ILD.[25] A prospective survey of gefitinib toxicity in 3,354 NSCLC patients treated at 698 hospitals in Japan between June and December 2003 showed that the incidence of ILD was 5.8% and the mortality rate was 2.5%.[26] Risk factors for the development of ILD identified in the Japanese population were preceding pulmonary fibrosis, smoking history, poor performance status, and male sex.[24,26,27] ILD tends to appear rapidly after initiation of therapy.[28]

In an analysis by the US Food and Drug Administration comparing the incidence of ILD associated with gefitinib treatment in North America and Japan, there was an incidence of approximately 2% from a Japanese postmarketing experience and 0.3% in approximately 23,000 patients in the United States expanded-access program.[18]

It is interesting to note that ILD has been associated with weekly docetaxel therapy in Japanese patients. In a phase II study, docetaxel as a single agent was administered at a dose of 35 mg/m^2 on days 1, 8, and 15 every 4 weeks in 48 patients with advanced or recurrent NSCLC. Of these, 33 patients had had no prior chemotherapy and 15 had received one prior chemotherapy treatment. Patients who had previously undergone thoracic radiotherapy, who had preceding ILD or pulmonary fibrosis, or who had severe pulmonary emphysema were excluded from the study. Of the 48 patients in the study, five (10.4%) developed grade 3–4 ILD.[29] The incidence of ILD associated with weekly administration of docetaxel in other countries varies with reports: grade 3–4 pulmonary toxicity was noted in seven of 35 (20%) patients in a Spanish study,[30] one of 63 (1.6%) in a French study,[31] none of 110 patients in an Italian study, and none of 30 patients in an American study.[32,33] It is unclear from these data whether the development of ILD represents a toxicity to which Japanese patients are predisposed, or is a diagnosis that is made more frequently in Japan for other reasons.

Differences in Efficacy and Toxicity. The differences between Western populations and the Japanese (and other non-Western ethnicities) in both the efficacy and toxicity of an anticancer agent are an emerging issue. Two recent trials comparing carboplatin plus paclitaxel with other combinations for first-line therapy of NSCLC were conducted in the United States (by the Southwest Oncology Group) and Japan (Japan Cooperative Oncology Group, Four Arm Comparative Study).[34] The carboplatin plus paclitaxel arm was similar in both studies (differing only by a slightly lower dose of paclitaxel in the Japanese study), and criteria for entry, dose modifications, toxicity, and response assessment were identical. Considerable differences in toxicity and activity were noted between the two studies. The rate of febrile neutropenia was five-fold greater (16% v 3%; $P < .0001$) in the Japanese trial, while the rate of neuropathy was substantially lower (5% v 16%; $P = .001$). The response rates were similar, while the 1-year survival rate was better in the Japanese trial (51% v 37%; $P = .009$).

Distribution of Genetic Polymorphisms for Thymidylate Synthase

Another area of growing interest in this field is the observation that the activity of antifolate agents may be related to germline differences in the expression of the target enzyme, thymidylate synthase (TS). Pemetrexed, though a multitargeted antifolate, appears to have its primary activity at TS. TS expression is controlled in part by the *TS* enhancer region (*TSER*) within the 5′ untranslated region of the *TS* gene. Recent work has shown that the *TSER* is polymorphic with significant ethnic variation and relates to the activity of the agents. Tandem repeats of 28 base pairs have been identified,

Table 2 Geographic Differences in the Incidence of TSER*3 Polymorphism[35]

Population	Individuals Homozygous for *TSER*3* (%)
White	28
African-American	24
Southwest Asian	40
Chinese	67

and expression of the gene is increased with additional repeats. A triple tandem repeat (*TSER*3*) demonstrates 2.6-fold greater expression than the double repeat (*TSER*2*). There is considerable variation in this polymorphism both within and between ethnic groups (Table 2).[35]

Increased expression of this enzyme can alter both the activity and pharmacology of folate antagonist agents. For example, the activity of 5-fluorouracil activity in colon cancer is influenced by the *TSER* polymorphism.[36] Patients homozygous for *TSER*3* show increased intratumoral levels of TS protein. Higher levels of TS are associated with poorer response rates and survival. In lung cancer, there is evidence from Japanese studies that elevated TS levels correlate with increased proliferation and decreased sensitivity to antifolate agents (specifically 5-fluorouracil).[37,38] Preliminary data indicate that *TS* gene polymorphisms are prognostic for patients treated with platinum-based chemotherapy.[39] Studies are currently in preparation to determine whether *TS* gene polymorphisms are a predictive or prognostic factor (or both) for treatment with pemetrexed in NSCLC.

Conclusion

Second- and third-line treatments have now emerged as a standard of care throughout the world. Regulatory agencies in the United States and EU have approved docetaxel, pemetrexed, and erlotinib for second-line use. Japan was the first country to approve an EGFR TKI (gefitinib) for second-line use. There appears to be a substantially greater response to both gefitinib and erlotinib in Japan, but also a significant risk of life-threatening pneumonitis. Moreover, this variation in efficacy and side-effect profile appears to be present in other Asian populations. These ethnic differences may be surrogates for differences in genetic aspects of drug metabolism or potential differences in tumor susceptibility. The findings of a recent 'common arm' study performed in the United States and Japan in first-line therapy, as well as the studies of the two EGF TKIs, clearly demonstrate that the benefits and risks of anticancer agents may differ between populations. It is clear that the benefits and risks of anticancer agents differ between populations.

References

1. Schottenfeld D, Searle JG: The etiology and epidemiology of lung cancer, in Pass HI, Carbone DP, Minna JD, et al (eds): Lung Cancer: Principles and Practice (ed 3). Philadelphia, PA, Lippincott, Williams & Wilkins, 2005, pp 3-24
2. Travis WD: Pathology of lung cancer. Clin Chest Med 23:65-81, 2002
3. Shepherd F, Dancey J, Ramlau R, et al: Prospective randomized trial of docetaxel vs. best supportive care in patients with non–small cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 18:2095-2103, 2000
4. Fossella FV, DeVore R, Kerr R, et al: Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non–small cell lung cancer previously treated with platinum containing chemotherapy regimens. J Clin Oncol 18:2354-2362, 2000
5. Hanna N, Shepherd FA, Fossella FV, et al: Randomized phase III trial of pemetrexed versus docetaxel in patients with non–small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 22:1589-1597, 2004
6. Johnson JR, Williams G, Pazdur R: End points and United States Food and Drug Administration approval of oncology drugs. J Clin Oncol 21:1404-1411, 2003
7. Giaccone G, Gonzalez-Larriba JL, van Oosterom AT, et al: Combination therapy with gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor, gemcitabine and cisplatin in patients with advanced solid tumors. Ann Oncol 15:831-838, 2004
8. Herbst R, Giaccone G, Schiller JH, et al: Gefitinib in combination with paclitaxel and carboplatin in advanced non–small cell lung cancer: A phase III trial–INTACT2. J Clin Oncol 22:785-794, 2004
9. Fukuoka M, Yano S, Giaccone G: Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non–small-cell lung cancer. J Clin Oncol 21:2237-2246, 2003
10. Kris MG, Natale RB, Herbst RS, et al: Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non–small cell lung cancer: A randomized trial. JAMA 290:2149-2158, 2003
11. Herbst RS, Giaccone G, Schiller J, et al: Subset analysis of INTACT results for gefitinib (ZD1839) when combined with platinum based chemotherapy for advanced non–small cell lung cancer. Proc Am Soc Clin Oncol 22:627, 2003 (abstr 2523)
12. Paez JG, Janne PA, Lee JC, et al: EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. Science 304: 1497-1500, 2004
13. Lynch TJ, Bell DW, Sordella R, et al: Activating mutations in the epidermal growth factor receptor underlying responsiveness of non–small-cell lung cancer to gefitinib. N Engl J Med 350:2139-2159, 2004
14. Tsao MS, Sakurada A, Cutz JC, et al: Erlotinib in lung cancer–Molecular and clinical predictors of outcome. N Engl J Med 353:133-144, 2005
15. Thatcher N, Chang A, Parikh P, et al: Results of a phase III placebo-controlled study (ISEL) of gefitinib (IRESSA) plus best supportive care (BSC) in patients with advanced non–small-cell lung cancer (NSCLC) who had received 1 or 2 prior chemotherapy regimens. Proc Am Assoc Cancer Res 2005 (abstr LB-6)
16. Pérez-Soler R, Chachoua A, Hammond LA, et al: Determinants of tumor response and survival with erlotinib in patients with non–small-cell lung cancer. J Clin Oncol 22:3238-3247, 2004
17. Shepherd FA, Rodrigues Pereira J, et al: Erlotinib in previously treated non–small-cell lung cancer. N Engl J Med 353:123-132, 2005
18. Cohen MH, Williams GA, Sridhara R, et al: United States Food and Drug Administration Drug Approval summary: Gefitinib (ZD1839; Iressa) tablets. Clin Cancer Res 10:1212-1218, 2004
19. FDA gefitinib information: Available at: http://www.fda.gov/cder/drug/infopage/gefitinib/default.htm (accessed August 6, 2005)
20. Fujiwara Y: MD reviewers' role in the new anticancer drug approval process in the newly established Japanese regulatory agency, PMDEC (Pharmaceuticals and Medical Devices Evaluation Center). Jpn J Clin Oncol 28:653-656, 1998
21. Takano T, Ohe Y, Sakamoto H, et al: Epidermal growth factor receptor gene mutations and increased copy numbers predict gefitinib sensitivity in patients with recurrent non–small-cell lung cancer. J Clin Oncol 23:6829-6837, 2005
22. Mitsudomi T, Kosaka T, Endoh H, et al: Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non–small-cell lung cancer with postoperative recurrence. J Clin Oncol 23:2513-2520, 2005
23. 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 97:339-346, 2005
24. Takano T, Ohe Y, Kusumoto M, et al: Risk factors for interstitial lung disease and predictive factors for tumor response in patients with advanced non–small cell lung cancer treated with gefitinib. Lung Cancer 45:93-104, 2004
25. Ministry of Health, Labour, and Welfare of Japan: Acute ILD associated with the use of gefitinib reported to Pharmaceuticals and Medical Devices Agency Japan. Available at: http://www.mhlw.go.jp/shingi/2005/01/txt/s0120-4.txt (accessed August 6, 2005)
26. AstraZeneca: Results and discussion on IRESSA Tablet 250 prospective survey. Available at: http://www.mhlw.go.jp/shingi/2005/01/s0120-4.html (accessed August 6, 2005)
27. Seto T, Yamamoto N: Interstitial lung diseases (ILD) induced by gefitinib in patients with advanced non–small cell lung cancer (NSCLC): Results of a West Japan Thoracic Oncology Group (WJTOG) epidemiological survey. Proc Am Soc Clin Oncol 22:632s, 2004 (abstr 7064)
28. Kataoka K, Taniguchi H, Hasegawa Y, et al: Interstitial lung disease associated with gefitinib. Respir Med 2005 [Epub ahead of print]
29. Ariyoshi K, Nakajima S, Nagao K, et al: Phase II trial of weekly RP56976 in patients with non–small cell lung cancer and advanced or recurrent breast cancer. Presented at the Second Annual Meeting of the Japanese Society of Medical Oncology, Tokyo, Japan, March 12-14, 2004
30. Esteban E, Gonzalez de Sande L, Fernandez Y, et al: Prospective randomised phase II study of docetaxel versus paclitaxel administered weekly in patients with non–small-cell lung cancer previously treated with platinum-based chemotherapy. Ann Oncol 14:1640-1647, 2003
31. Gervais R, Ducolone A, Breton JL, et al: Phase II randomised trial comparing docetaxel given every 3 weeks with weekly schedule as second-line therapy in patients with advanced non–small-cell lung cancer (NSCLC). Ann Oncol 16:90-96, 2005
32. Gridelli C, Gallo C, Di Maio M, et al: A randomised clinical trial of two docetaxel regimens (weekly vs 3 week) in the second-line treatment of non–small-cell lung cancer. The DISTAL 01 study. Br J Cancer 91:1996-2004, 2004
33. Lilenbaum RC, Schwartz MA, Seigel L, et al: Phase II trial of weekly docetaxel in second-line therapy for nonsmall cell lung carcinoma. Cancer 92:2158-2163, 2001
34. Gandara DR, Ohe Y, Kubota K, et al: Japan-SWOG common arm analysis of paclitaxel/carboplatin in advanced stage non–small cell lung cancer: A model for prospective comparison of cooperative group trials. Proc Am Soc Clin Oncol 22:618s, 2004 (abstr 7007)
35. Marsh S, Ameyaw MM, Githang'a J, et al: Novel thymidylate synthase enhancer region alleles in African populations. Hum Mutat 16:528, 2000
36. Shintani Y, Ohta M, Hirabayashi H, et al: New prognostic indicator for non–small-cell lung cancer, quantitation of thymidylate synthase by real-time reverse transcription polymerase chain reaction. Int J Cancer 104:790-795, 2003
37. Nakagawa T, Otake Y, Yanagihara K, et al: Expression of thymidylate synthase is correlated with proliferative activity in non–small cell lung cancer (NSCLC). Lung Cancer 43:145-149, 2004
38. Huang CL, Yokomise H, Kobayashi S, et al: Intratumoral expression of thymidylate synthase and dihydropyrimidine dehydrogenase in non–small cell lung cancer patients treated with 5-FU-based chemotherapy. Int J Oncol 17:47-54, 2000
39. Giachino D, Ghio P, Regazzoni S, et al: Pharmacogenetics studies in patients with advanced lung cancer: Prognostic value of the thymidylate synthase 2R/3R polymorphism and predictivity of NER factor XPD K751Q and XRCC1 R399Q polymorphisms following platinum based chemotherapy. Lung Cancer 49:S69, 2005 (suppl 2) (abstr PD-010)
40. Nishiwaki Y, Yano S, Tamura T, et al: Subset analysis of data in the Japanese patients with NSCLC from IDEAL 1 study of gefitinib. Gan To Kagaku Ryoho 31:567-573, 2004

Review Article

Recent trends in the treatment of advanced lung cancer

Nagahiro Saijo[1]

National Cancer Center, Hospital East, Kashiwanoha 6-5-1, Kashiwa-shi, Chiba 277-8577, Japan

(Received January 27, 2006/Accepted February 13, 2006/Online publication March 31, 2006)

Lung cancer is one of the major causes of death in many countries because of high rates of smoking, especially in Asian countries. Lung cancer is divided into two major categories based on their biological characteristics and the selection of treatment methods: non-small cell lung cancer (NSCLC; 85%) and small cell lung cancer (15%). Early detection and complete resection are very important in NSCLC, but the cure rate is not very high, except in stage 1A disease. It is extremely important to understand the biology of lung cancer and to introduce more effective treatments in order to improve the survival of NSCLC patients. Numerous clinical trials involving lung cancer patients have led to 'state-of-the-art' treatments for each stage of the disease. Progress in chemotherapy and molecular target based therapy have altered the standard therapy for NSCLC. (*Cancer sci* 2006; 97: 448–452)

Chemotherapy for advanced non-small cell lung cancer

Platinum-based doublets are considered to be the standard treatments for stage IV non-small cell lung cancer (NSCLC).[1,2] Although the majority of regimens contain cisplatin, carboplatin can be used in combination with paclitaxel because numerous phase III data exist on this combination. The question remains, however, as to whether or not we can treat advanced NSCLC patients with a non-platinum-based regimen. To date, the answer would appear to be that platinum-based therapy is superior, although platinum drugs and/or non-platinum doublets could be used to treat elderly and/or frail patients because of their low renal toxicity. Kosmidis, the chairman of the Hellenic Cooperative Oncology Group, reported the results of their randomized controlled trials looking at the combination of paclitaxel/gemcitabine versus carboplatin + gemcitabine in advanced NSCLC. More than 500 patients were accrued, of which 445 were evaluative. There was no difference in response rate, time to progression or median survival. There was slightly more hematological toxicity with carboplatin and gemcitabine, although it was relatively mild with only 28% having grade 3 and 4 neutropenia. There was slightly more neurotoxicity in the paclitaxel and gemcitabine arm, and the difference was statistically significant. Kosmidis concluded that this was enough evidence to show that non-platinum-based chemotherapy is as good as platinum-based chemotherapy.[3] However, no studies have demonstrated the superiority of a non-platinum doublet over a platinum-based doublet.

Several doublets that include new drugs improve survival, but no one regimen is clearly superior to the others.[1,2] We have conducted a four-arm cooperative study (FACS) in advanced NSCLC. The study was designed to demonstrate non-inferiority of three experimental arms: paclitaxel + carboplatin; gemcitabine + cisplatin; and navelbine + cisplatin in comparison with cisplatin + CPT-11 (control arm). One-year survival (59%) was higher than expected in cisplatin + CPT-11. No statistically significant differences in response rate, time to progression (TTP) or overall survival were observed between the reference and experimental regimens. Non-inferiority of the three experimental arms was not demonstrated. The response duration in the cisplatin + CPT-11 arm was relatively longer than in the other three arms. No statistical test was conducted because these data were obtained from selected populations based on response, such that there is no statistical basis for comparison (Ohe Y *et al.*, unpublished data, 2006). In conclusion, all four platinum-based doublets have similar efficacy for advanced NSCLC but with different toxicity profiles. Cisplatin + CPT-11 is still regarded as the reference regimen in Japan.

The chemotherapy outcomes were compared in Japanese and American NSCLC patients accrued to the FACS trial and the SWOG 0003 trial,[4] respectively. The two trials had similar eligibility and evaluation criteria, although the dose of paclitaxel was 200 mg/m^2 in the Japanese trial and 225 mg/m^2 in the SWOG trial. The purpose of the analysis was to demonstrate similarities and differences in patient characteristics and outcomes between the Japanese and USA trials for advanced stage NSCLC treated by the same regimen, to provide a basis for standardization of the study design/process to facilitate interpretation of future trials, and to take the first step toward possible joint NCI-sponsored studies in lung cancer between Japanese and American investigators. This analysis using carboplatin and paclitaxel as the common arm shows great similarities in patient characteristics between the FACS trial and the SWOG 0003 trial. Frequencies of neutropenia and febrile neutropenia were significantly higher in FACS trials although the paclitaxel dose was lower

[1]To whom correspondence should be addressed. E-mail: nsaijo@east.ncc.go.jp

doi: 10.1111/j.1349-7006.2006.00198.x
© 2006 Japanese Cancer Association

in this group. There may be some differences in population-based pharmacogenomics. Grade 3/4 neuropathy, conversely, was more frequent in the SWOG 0003 trial due to differences in the cumulative paclitaxel dose because of the higher absolute dose and higher median numbers of treatment courses. The response rates were exactly the same, but 1 year survival was better in the FACS trial. These results suggest that future joint Japan–USA clinical trials should consider possible pharmacogenomic differences in drug disposition between Japanese and American populations.[5]

Molecular target-based drugs in advanced recurrent NSCLC

Numerous molecular target-based drugs have been introduced for the treatment of NSCLC, but can they replace current therapy? Can they be used as an adjuvant to current therapy? Can they be combined with other chemotherapeutic agents, radiotherapy and/or surgery?

We hypothesize that incorporation of novel molecular target-based therapies into current treatment paradigms will improve outcomes. However, carefully designed clinical trials and translational science will be required to identify subsets of patients who will benefit.

If we are to use them, we must first answer the following critical questions. Is the target required for a response? Whether or not we know a real and correct molecular target is still questionable. Is the presence of the target sufficient for a response, and can we measure the target in a biologically relevant and/or technologically valid way? Does the agent inhibit the proposed target at the dose and schedule used? Is the target a critical driving force for cell growth in the tumor type in question? The answers to these questions are crucial to treatment with molecular target-based drugs.

Various molecular target-based drugs for advanced NSCLC have been evaluated in randomized controlled trials, but the majority, including a matrix metalloprotease inhibitor, a protein kinase C inhibitor and trastsuzumab, have yielded negative results.[6–8] Gefitinib is an orally available selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor that exhibits antitumor activity in patients with previously treated advanced NSCLC.

Clinical trial of gefitinib and erlotinib

Four open-label multicenter phase I studies have identified diarrhea, skin rash/acne and nausea as common adverse events.[9,10] Two large-scale, multicenter randomized controlled phase II trials, IDEAL 1 and 2, have demonstrated clinically significant antitumor activity of gefitinib monotherapy, and erlotinib has also shown promising antitumor activity.[11] Neither drug showed any additive and/or synergistic effect when combined with platinum-based chemotherapy as a first-line treatment for NSCLC.[12,13]

On December 17, 2004, AstraZeneca announced the preliminary results of their Iressa Survival Evaluation in Lung Cancer (ISEL) study. The study had accrued 1692 patients with advanced recurrent/refractory NSCLC. Unfortunately, Iressa failed to significantly prolong survival compared with a placebo (HR = 0.89, $P = 0.087$) in the overall patient population or among patients with adenocarcinoma (HR = 0.83, $P = 0.089$), although a tendency toward a survival benefit was observed in the gefitinib group.[14] The less than 10% response rate did not result in an overall prolongation of survival. A retrospective analysis of patients treated with gefitinib in clinical practice showed that tumor response predictors included 'adenocarcinoma', 'no history of smoking', 'women', and 'Japanese'. Survival in the gefitinib group in the ISEL study was significantly higher for non-smokers ($P < 0.01$) and Asians ($P < 0.01$) than in the placebo group. The survival curves of the two treatment groups were the same for non-Asians. The data obtained from the ISEL study were not surprising, although most observers had expected positive overall results.

The results of similar randomized trials of erlotinib (BR21) were presented at the American Society Clinical Oncology (ASCO) meeting in 2004. Erlotinib significantly prolonged survival in patients with advanced, previously treated refractory/recurrent NSCLC.[15] The two studies referred to above differed in several respects. Sample size was larger in the ISEL study than in the BR21 study, and 10% of the patients in the latter study had a performance status (PS) of 3, whereas only PS-2 patients were accrued by the ISEL study. The follow-up period of the ISEL study was also relatively short (4 months). The overall percentage of patients with adenocarcinoma and the percentage of non-smokers was 50% and 20%, respectively, in both studies. Data stratification into Asians and non-Asians was only performed in the ISEL study. The stratified survival data for Asians in the BR21, submitted to the US FDA, showed a tendency that was similar to the stratified data in the ISEL study. The survival of non-smokers in the erlotinib group in the BR21 study was extremely good and contributed to the improvement in overall survival in the erlotinib group. How can we explain the discrepancy of the result from the ISEL and BR21 studies? Part of the explanation is that the dose of gefitinib in the ISEL study was low, while the BR21 study used nearly the maximum tolerated dose. Another hypothesis is that patient populations in the ISEL study were inappropriately selected, for example, subjects with poor prognostic factors. The shapes of the survival curves for the Intact 1 and 2, TALENT and TRIBUTE studies and for the non-Asians in the ISEL study suggest that EGFR-TKI does not prolong the survival of non-Asian patients with NSCLC, with or without prior chemotherapy.[12,13,16,17] The stratified survival data of the Asians in the Intact 1 and 2, TALENT and TRIBUTE studies should be analyzed.

In the SWOG 0023 trial, patients with stage III NSCLC received chemoradiation therapy then three cycles of a single agent, docetaxel, followed by either a placebo or gefitinib as maintenance. This trial was projected to have 80% of the patients receiving either placebo or gefitinib with a drop off of 20% during this part of the therapy. The drop off rate before randomization was a bit larger than the expected rate because of progressive disease or death. Investigators asked the Data Safety Monitoring Committee to look at the data to see if they should actually continue the trial because the results of the ISEL study were negative. This early unplanned analysis showed there was no difference in time to progression in either arm and the P-value for difference was 0.54. Similarly, there was no statistically significant difference in

© 2006 Japanese Cancer Association

survival and the *P*-value was 0.09, favoring the placebo group. It was surprising and disappointing that the gefitinib-treated patients were actually experiencing worse survival than the placebo patients. This trial had the power to show a 0.33% advantage for gefitinib and the data were sufficient to state that the likelihood of showing a 33% survival improvement was 0.0015.[18] These data suggested that there is no rationale for using gefitinib in locally advanced NSCLC in the adjuvant setting.

Molecular marker predicting clinical outcome of EGFR-TKI

The activities of epidermal growth factor receptor (EGFR) inhibitors, gefitinib and erlotinib in lung cancer and the correlation of responses to somatic mutations are the focus of translational research performed in 2004 and 2005. This answers the major question; which patients respond and why? We have demonstrated that PC-9 cells with a 15 bp deletion in exon 19 of the EGFR gene are extremely sensitive to EGFR-TKI.[19] In April and May 2004, Paez and Lynch reported that activating mutations in EGFR are present in a subset of NSCLC tumors and that the tumors are highly sensitive to gefitinib and erlotinib.[20,21] EGFR expression levels are not a predictor of response and EGFR amplification may have an impact, but EGFR-TK mutations seem to be better predictors of responsiveness to gefitinib and erlotinib.[22–24] Mutant EGFR are more sensitive to ligand stimulation and are dramatically more sensitive to EGFR-TKIs.[19–21] The incidence of EGFR mutations is reportedly higher in Asians, including Japanese,[25,26] and Mitsudomi has reported cumulative percentages of those with EGFR mutation-positive status in 1104 patients with NSCLC to be 34% among Asians and 8% among non-Asians.[27] Eighty percent of the patients who responded to EGFR-TKI carried an EGFR mutation (non-Asians, 79% [30/35]; Japanese, 81%: [39/48]). Among non-responders, 0% of non-Asians and 21% of Japanese patients carried an EGFR mutation. These data suggest that the presence of an EGFR mutation is a strong predictor of a favorable response to EGFR-TKI. Mutations have been reported to be significantly more frequent in women, in patients with adenocarcinoma, and in never smokers, and these findings are consistent with the clinical predictors of tumor response in patients treated with EGFR-TKI. Mitsudomi recently reported that the del 746–750 mutation might be superior to the L858R mutation for predicting the gefitinib response and those patients with EGFR mutations survived longer after the initiation of gefitinib treatment than those without mutations.

Recently it has been demonstrated that an additional mutation at codon 790 induced resistance to originally sensitive mutant cells.[28,29]

A variety of results were presented at the ASCO 2005 meeting in Orland with regards to molecular analysis of the EGFR gene and protein expression in patients accrued to pivotal studies of EGFR-TKIs.[30] Lynch reported the results of an analytical study using resected specimens and biopsy samples obtained during IDEAL and INTACT studies of gefitinib.[31] Patients with either an EGFR mutation or amplification represented distinct populations. Among cases with mutations, large numbers were female, non-smokers, had adenocarcinoma or bronchioloalveolar carcinoma, were Eastern-Asian and often showed dramatic response rates to gefitinib. Because the number of cases for this analysis was not sufficient, it was impossible to draw any conclusions about the impact of mutation and amplification on survival.

Tsao tried to identify certain relations among the response rate and survival and molecular biological features such as the mutation, protein expression and gene copy numbers in the BR21 study conducted by NCI-Canada clinical trial group, which demonstrated that erlotinib does significantly prolong survival as compared with a placebo. Response rates were higher in patients with EGFR mutations, immunohistochemistry (IHC)-positive tumors and high gene copy numbers, but a statistically significant difference was observed for copy numbers only. Survival benefit was greater in patients who were IHC positive and had high gene copy numbers. However, mutation positive patients did not benefit more than mutation negative patients. From these data, Tsao concluded that mutation analysis is not required for the selection of patients who will receive erlotinib.[32]

There are some controversial data on the relationship between biomarkers and clinical outcome.[33–37] One of the reasons for discrepant data is the validity of techniques including the quality of the samples analyzed. Giaccone conducted a cross validation analysis of EGFR mutations in samples obtained from the Free University (the Netherlands) and the Dana Faber Cancer Institute.[38] The results were discrepant in some samples because of poor quality. Another reason is patient selection because it was impossible to obtain samples from all patients with advanced lung cancer. In the retrospective studies reported to date, only a small proportion of patients have had tumor samples evaluable for each biomarker, making patient selection problematic and prone to the introduction of selection bias. It is therefore extremely important that samples be obtained from all patients in studies evaluating the relationships between clinical outcome and biomarkers such as EGFR expression, amplification and mutation. Of course, the techniques for evaluable biomarkers should be valid. In this regard, the report of Takano is most reliable because they analyzed all the samples from all patients using three techniques: IHC, gene copy number and mutation. There were no problems with patient selection. Because they used surgically resected specimens they were able to obtain adequate specimen amounts. It could be concluded that if the analyses were conducted accurately, EGFR mutational status would be the major predictor of outcome and increased EGFR copy number associated with gefitinib sensitivity would significantly depend on the presence of EGFR mutations.[39] Technical innovations are essential for the reproducible and reliable analysis of samples from advanced disease patients because only small amounts of the specimen could be obtained from inoperable lung cancer patients.

EGFR-TKI seems to be a very promising drug for the treatment of East-Asian patients with NSCLC with and without a history of prior chemotherapy. The response rate has ranged from 20% to 33% clinically, and it was 30% in a prospective phase II trial on 100 previously untreated NSCLC patients. The median survival time of the Japanese population in the IDEAL 1 trial was 13.8 months.[11] To date, no survival

doi: 10.1111/j.1349-7006.2006.00198.x
© 2006 Japanese Cancer Association

data from a phase III study of gefitinib and erlotinib in East Asia are available because no phase III study has been conducted. However, a randomized controlled trial comparing gefitinib and docetaxel as a second-line treatment is in progress in Japan. The trial has a non-inferiority design and a definitive conclusion will be difficult to obtain. An erlotinib phase II evaluation has just finished the accrual of patients in Japan, but government approval will require more time.

The frequency of EGFR mutations and response rate are higher in East-Asian populations than in Western countries. A global randomized controlled trial is scheduled for comparison of first-line standard platinum-based chemotherapy versus gefitinib in East Asians, non-smokers versus light smokers, and patients with adenocarcinoma.

Bevacizumab

Vascular endothelial growth factor (VEGF) was originally described as vascular permeability factor. VEGF is involved in the regulation of new vessel growth, promotion of the survival of immature vasculature and binding to one of two receptors such as FLT-1 or KDR.[40]

Bevacizumab is a monoclonal antibody against VEGF. It is 93% human, it recognizes all isoforms of VEGF-A and has a prolonged half life which makes it very convenient to administer on an every 2- or 3-week basis.

The preliminary randomized phase II trial of ECOG using 7.5 mg/kg or 15 mg/kg of bevacizumab every 3 weeks did meet its primary objective of improvement in time to progression on the high dose arm; 7.4 versus 4.2 months. Also, response and survival were numerically better. Problems with hemoptysis or pulmonary hemorrhage occurred in six patients (four squamous cell and two adeno), four of which actually proved to be fatal.[41] Based on these experiences, the ECOG 4599 trial was designed. The primary objective was to compare survival and secondary objectives were to look at the response rate, time to progression and toxicity.

Eligibility criteria included non-squamous cell carcinoma, no history of major hemoptysis and of neither thrombotic nor hemorrhagic disorders, and no central nervous system metastasis. Patients received standard dose carboplatin and paclitaxel with or without high dose bevacizumab 15 mg/kg every 3 weeks. The sample size was calculated to be over 842, providing the investigators with 80% power to detect a 25% improvement in median survival time from the usual 8–10 months. ECOG had two planned interim analyses at 286 and 455 deaths. The study was closed after the second interim analysis. Response rate was significantly higher in the bevacizumab arm (27%) versus the control arm (10%). Progression free survival also favored the bevacizmab arm. Overall survival was highly statistically significant; 12.5 months in the bevacizumab arm and 10.2 months in the control arm. The hazard ratio was 0.77.[42] Hemorrhage was more common in the bevacizumab arm with a 45% incidence compared to less than 1% in the control arm. There were eight treatment-related deaths in the bevacizumab arm and two in the control arm. These data lead to the conclusion that bevacizumab improves survival compared to platinum and paclitaxel in patients with non-squamous NSCLC, although a small increase in severe bleeding can be expected. ECOG considers paclitaxel, carboplatin with bevacizumab to be a standard for the treatment of this NSCLC subgroup. The study group suggested some future plans for combining bevacizumab with chemotherapy, radiotherapy and other targeted agents in neoadjuvant or adjuvant settings. In Europe, a clinical trial of bevacizumab combined with cisplatin + gemcitabine is ongoing. The critical question is whether or not they can obtain reproducible positive data even if the chemotherapy regimen is changed from pacltiaxel + carboplatin to cisplatin + gemcitabine. In Japan, a combination phase I/II study of bevacizumab with 5FU + LV or FOLFOX recently completed the accrual of patients. Combination treatment using bevacizumab with paclitaxel + carboplatin is scheduled. How to manage severe bleeding, even in selected populations, and the extremely high cost of bevacizumab will be major issues.

References

1 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.
2 Kelly K, Crowley J, Bunn PA Jr *et al.* Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced NSCLC: a SWOG trial. *J Clin Oncol* 2001; **19**: 3210–8.
3 Kosmidis PA, Kalofonos C, Syrigos K *et al.* Paclitaxel and gemcitabine vs carboplatin and gemcitabine, a multicenter, phase III randomized trial in patients with advanced inoperable non-small cell lung cancer. *Proc ASCO* 2005; **23**: 621s(7000).
4 Williamson SK, Crowley JJ, Lara PN *et al.* Paclitaxel/carboplatin (PC) vs PC + tirapazamine in advanced NSCLC: A phase III SWOG trial S0003. *J Clin Oncol* 2003; **20**: 9097–104.
5 Gandara DR, Ohe Y, Kubota K *et al.* Japan-SWOG common arm analysis of paclitaxel/carboplatin in advanced stage non-small cell lung cancer (NSCLC): a model for prospective comparison of co-operative group trial. *Proc ASCO* 2004; **22**: 618s(7007).
6 Shepherd FA, Giaccone G, Seymour L *et al.* Prospective, randomized, double-blind, placebo-controlled trial of marimastat after response to first-line chemotherapy in patients with small-cell lung cancer: a trial of NCI-Canada and EORTC. *J Clin Oncol* 2002; **20**: 4434–9.
7 Adjei AA, Mauer A, Bruzek L *et al.* Phase II study of the farnesyl transferase inhibitor R115777 in patients with advanced NSCLC. *J Clin Oncol* 2003; **21**: 1760–6.
8 Gatzemeier U, Groth G, Butts C *et al.* Randomized phase II trial of gemcitabine-cisplatin with or without trastuzumab in HER2-positive NSCLC. *Ann Oncol* 2005; **15**: 19–27.
9 Ranson M, Hammond LA, Ferry D *et al.* ZD1839, a selective oral epidermal 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* 2002; **20**: 2240–50.
10 Herbst RS, Maddox AM, Rothenberg ML *et al.* Selective oral epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 is generally well-tolerated and has activity in NSCLC and other solid tumors: results of a phase I trial. *J Clin Oncol* 2002; **20**: 3815–25.
11 Fukuoka M, Yano S, Giaccone G *et al.* Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced NSCLC (The IDEAL 1 Trial). *J Clin Oncol* 2003; **21**: 2237–46.
12 Giaccone G, Herbst RS, Manegold C *et al.* Gefitinib in combination with gemcitabine and cisplatin in advanced NSCLC: a phase III trial – INTACT 1. *J Clin Oncol* 2004; **22**: 777–84.
13 Herbst RS, Giaccone G, Schiller JH *et al.* Gefitinib in combination with paclitaxel and carboplatin in advanced NSCLC: a phase III trial – NTACT 2. *J Clin Oncol* 2004; **22**: 785–94.
14 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 randomized, placebo-controlled, multicentre

© 2006 Japanese Cancer Association

study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 2005; **336**: 1527–37.
15 Shepherd FA, Pereira J, Ciuleanu TE *et al.* Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005; **353**: 123–32.
16 Herbst RS, Prager D, Hermann R *et al.* TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced NSCLC. *J Clin Oncol* 2005; **23**: 5892–5899.
17 Gatzemeier U, Pluzanska A, Szczesna A *et al.* Results of a phase III trial of erlotinib (OSI-774) combined with cisplatin and gemcitabine (GC) chemotherapy in advanced NSCLC. *TALENT Trial Proc ASCO* 2004; **22**: 619s(7010).
18 Kelly K, Crowley J, Bunn PA Jr *et al.* Preliminary results of S0023: A randomized phase III trial of cisplatin/etoposide/TRT followed by consolidation docetaxelthan maintenance therapy with gefitinib or placebo in patients with locally advanced inoperable stage III NSCLC. *Proceedings ASCO* 2005; **41**: No. 7058.
19 Arao T, Fukumoto H, Takeda M *et al.* Small in-frame deletion in the EGFR as a target for ZD6474. *Cancer Res* 2004; **64**: 9101–4.
20 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.
21 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.
22 Han SW, Kim TY, 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.
23 Johnson BE, Janne PA. Selecting patients for epidermal growth factor receptor inhibitor treatment: a fish story or a tale of mutations. *J Clin Oncol* 2005; **28**: 6813–6.
24 Giaccone G, Rodriguez JA. EGFR inhibitors: What have we learned from the treatment of lung cancer? *Nature Clin Prac Oncol* 2005; **2**: 554–61.
25 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.
26 Kosaka T, Yatabe Y, Endoh H *et al.* Mutations of the epidermal growth factor receptor gene in lung cancer: Biological and clinical implications. *Cancer Res* 2004; **64**: 8919–23.
27 Mitsudomi T, Kosaka T, Endoh H *et al.* Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non-small-cell lung cancer with postoperative recurrence. *J Clin Oncol* 2005; **23**: 2513–20.
28 Pao W, Miller VA, Politi KA *et al.* Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. *PLoS Med* 2005; **2**: e73.
29 Kobayashi S, Boggon TJ, Dayaram T *et al.* *EGFR* mutation and resistance of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2005; **352**: 786–92.
30 Marchetti A, Martella C, Felicioni L *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* 2005; **23**: 857–65.
31 Bell DW, Lynch TJ, Haserlat SM *et al.* Epidermal growth factor receptor mutations and gene amplification in non-small-cell lung cancer: Molecular analysis of the IDEAL/INTACT gefitinib trials. *J Clin Oncol* 2005; **31**: 8081–92.
32 Tsao M-S, Sakurada A, Cutz J-C *et al.* Erlotinib in lung cancer – molecular and clinical predictors of outcome. *N Engl J Med* 2005; **353**: 133–44.
33 Cappuzzo F, Hirsch FR, Rossi E *et al.* Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer. *J Natl Cancer Inst* 2005; **97**: 643–55.
34 Cappuzzo F, Varella-Garcia M, Shigematsu H *et al.* Increased *HER2* gene copy number is associated with response to gefitinib therapy in EGFR-positive non-small cell lung cancer patients. *J Clin Oncol* 2005; **23**: 5007–18.
35 Hirsch FR, Varella-Garcia M, Bunn PA Jr *et al.* Epidermal growth factor receptor in non-small-cell lung carcinomas: Correlation between gene copy number and protein expression and impact on prognosis. *J Clin Oncol* 2003; **21**: 3798–807.
36 Hirsch FR, Varella-Garcia M, McCoy J *et al.* Increased EGFR gene copy number detected by FISH associates with increased sensitivity to gefitinib in patients with bronchioloalveolar carcinoma subtypes: a Southwest Oncology Group Study. *J Clin Oncol* 2005; **23**: 6838–45.
37 Kaye FJ. A curious link between epidermal growth factor receptor amplification and survival: Effect of 'Allele Dilution' on gefitinib sensitivity? *J Natl Cancer Inst* 2005; **97**: 621–3.
38 Giaccone G, Janmeat M, Ruiz MG *et al.* EGFR mutations do not accurately predict response to erlotinib in first line monotherapy treatment of advanced non small cell lung cancer. *Lung Cancer* 2005; **49**: S244 (P–485).
39 Takano T, Ohe Y, Sakamoto H *et al.* Epidermal growth factor receptor gene mutations and increased copy numbers predict gefitinib sensitivity in patients with recurrent non-small-cell lung cancer. *J Clin Oncol* 2005; **23**: 6829–37.
40 Jain RK. Molecular regulation of vessel maturation. *Nat Med* 2003; **9**: 685–93.
41 Johnson DH, Fehrenbacher L, Novotny WF *et al.* Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2004; **22**: 2184–91.
42 Sandler AB, Gray R, Brahmer J *et al.* Randomized phase II/III trial of paclitaxel plus carboplatin with or without bevacizumab in patients with advanced non-squamous NSCLC: An Eastern Cooperative Oncology Group Trial-E4599. *Proc ASCO* 2005; **23**: 2s (LBA4).

doi: 10.1111/j.1349-7006.2006.00198.x
© 2006 Japanese Cancer Association