Table 3. Phase III studies of gefitinib.

Author/study	Treatment arms	Number	ORR (%)	PFS (months)	MST (months)	Comments	Ref.
Chemotherapy with gefitinib in the first-line treatment of non-small-cell lung cancer							
Giaccone (INTACT-1)	Gem/cis + gefitinib 250 mg	365	51.2	5.8	9.9	Phase III negative trial, corresponding with the TALENT trial	[13]
	Gem/cis + gefitinib 500 mg	365	50.3 (p = NS)	5.5 (p = 0.76)	9.9 (p = 0.46)		
	Gem/cis + placebo	363	47.2	6.0	10.9		
Herbst (INTACT-2)	Pac/carbo + gefitinib 250 mg	345	30.4	5.3	9.8	Phase III negative trial, corresponding with the TRIBUTE trial	[14]
	Pac/carbo + gefitinib 500 mg	347	30.0 (p = NS)	4.6 (p = 0.06)	8.7 (p = 0.64)	Subset analysis of patients with adenocarcinoma who received 90 days' chemotherapy demonstrated statistically significant prolonged survival, suggesting a gefitinib maintenance effect	
	Pac/carbo + placebo	345	28.7	5	9.9		
Kelly (SWOG 0023)	Gefitinib	118	NA	8.3 (p = 0.17)	23 (p = 0.01)	Phase III trial of maintenance therapy after definitive chemoradiation in stage III NSCLC	[68]
	Placebo	125		11.7	35		
Hida (WJTOG0203)	Chemotherapy + gefitinib 250 mg	300	34.2	4.6 (p < 0.001)	13.68 (p = 0.10)	Phase III trial of sequential therapy Superior overall survival time with adenocarcinoma histology in the gefitinib arm (p = 0.03)	[17]
	Chemotherapy alone	298	29.3	4.2	12.89		
Gefitinib versus BSC in the treatment of advanced non-small-cell lung cancer							
Thacher (ISEL)	Gefitinib	1129	8.0 (p < 0.0001)	3.0* (p = 0.0006)	5.6 (p = 0.09)	Survival advantage seen in nonsmoking and Asian patients; MST, p = 0.03 by Cox's analysis	[12]
	Placebo	563	1.0	2.6*	5.1		
Gefitinib compared with chemotherapy in the treatment of advanced non-small-cell lung cancer							
Douillard (INTEREST)	Gefitinib 250 mg	733	9.10 (p = 0.33)	2.2 (p = 0.47)	7.6 (HR: 1.04)	Effect seen across subgroups: favorable toxicity profile with gefitinib; noninferiority of gefitinib demonstrated	[18]
	Docetaxel 75 mg/m²	733	7.6	2.7	8.0		
Maruyama (V-15-32)	Gefitinib 250 mg	245	22.5 (p = 0.009)	2.0 (p = 0.34)	11.5 (p = 0.33)	Favorable toxicity profile with gefitinib; noninferiority of gefitinib not demonstrated	[19]
	Docetaxel 60 mg/m²	244	12.8	2.0	14.0		

*Time to treatment failure.
†Preliminary (37% maturity).
BSC: Best supportive care; Carbo: Carboplatin; Cis: Cisplatin; EGFR: EGF receptor; Gem: Gemcitabine; HR: Hazard ratio; INTACT: IRESSA NSCLC Trial Assessing Combination Treatment; INTEREST: IRESSA Non-Small-Cell Lung Cancer Trial Evaluating Response and Survival Against Taxotere; IPASS: IRESSA Pan-Asia study; ISTANA: Iressa as Second line Therapy in Advanced Non-Small Cell Lung Cancer-Korea; ISEL: IRESSA® Survival Evaluation in Lung Cancer; MST: Median survival time; NA: Not available; NS: Not significant; NSCLC: Non-small-cell lung cancer; ORR: Overall respone rate; Pac: Paclitaxel; PFS: Progression-free survival; SWOG: Southwest Oncology Group.

Table 3. Phase III studies of gefitinib.

Author/study	Treatment arms	Number	ORR (%)	PFS (months)	MST (months)	Comments	Ref.
Gefitinib compared with chemotherapy in the treatment of advanced non-small-cell lung cancer							
Lee (ISTANA)	Gefitinib 250 mg	82	28.1 ($p = 0.0007$)	3.3 ($p = 0.04$)	N/A	Second-line chemotherapy previously received platinum-based chemotherapy; PFS was longer with gefitinib arm ($p = 0.04$)	[70]
	Docetaxel 75 mg/m²	79	7.6	3.4	N/A		
Mok (IPASS)	Gefitinib 250 mg	606	43.0 ($p = 0.0001$)	5.7 ($p < 0.0001$)	18.6[a]	Open-labeled, randomized, Phase III previously untreated patients with adenocarcinoma who are never- or light-smokers; improved PFS in the gefitinib arm; PFS favoured pac/carbo initially and then gefitinib, potentially driven by different outcomes according to EGFR mutation status	[20]
	Pac/carbo	606	32.2	5.8	17.3[a]		

[a]Time to treatment failure.
[b]Preliminary (37% maturity).
BSC: Best supportive care; Carbo: Carboplatin; Cis: Cisplatin; EGFR: EGF receptor; Gem: Gemcitabine; HR: Hazard ratio; INTACT: IRESSA NSCLC Trial Assessing Combination Treatment; INTEREST: IRESSA Non-Small-Cell Lung Cancer Trial Evaluating Response and Survival Against Taxotere; IPASS: IRESSA Pan-Asia study; ISTANA: Iressa as Second line Therapy in Advanced Non-Small Cell Lung Cancer-Korea; ISEL: IRESSA* Survival Evaluation in Lung Cancer; MST: Median survival time; NA: Not available; NS: Not significant; NSCLC: Non-small-cell lung cancer; ORR: Overall respone rate; Pac: Paclitaxel; PFS: Progression-free survival; SWOG: Southwest Oncology Group.

assigned randomly to a standard treatment (cisplatin plus docetaxel) or a gefitinib-treatment group. It uses PFS as a primary end point. In addition, the North-East Japan Gefitinib Study Group is carrying out a similar clinical trial that targets stage IIIB/IV lung cancer patients assigned randomly into a carboplatin plus paclitaxel treatment or a gefitinib-treatment group and that also uses PFS as a primary end point. The European Organization for Research and Treatment of Cancer are currently testing a Phase III trial of gefitinib or placebo following first-line chemotherapy (EORTC08021) (Table 4).

EGFR in NSCLC

Clinical trial data suggested that gefitinib was more efficacious in patients who were never smokers, female or had adenocarcinoma histology. Since a different 'targeted therapy' (e.g., trastuzumab) was known to be most effective in patients whose tumors had high levels of expression of that drug's target (HER2), an important question was whether responses to gefitinib correlated with levels of EGFR expression [71]. However, analyses of specimens from gefitinib-sensitive and -refractory tumors using immunohistochemistry (IHC) showed no relationship between tumor sensitivity and EGFR expression levels [72–74]. Negative findings regarding the predictive value of EGFR protein expression using IHC in gefitinib-treated patients raised considerable doubt about the role of IHC techniques in patient selection. Recently, Hirsch *et al.* have demonstrated that EGFR immunostaining with the Dako PharmDx kit according to the percentage of cells with positive staining appears to better predict for survival outcome with gefitinib than Zymed antibody according to staining index [75]. With the discovery of EGFR-activating mutations in tumors from most patients who had EGFR TKI-induced tumor responses, skepticism was soon replaced by enthusiasm for molecular profile research in patients treated with EGFR TKIs. There is increasing evidence that EGFR mutations and high *EGFR* gene copy number are associated with higher response rates and longer survival in patients receiving EGFR TKI therapy.

EGFR mutations

In previous studies that investigated the relationship between *EGFR* gene mutations and sensitivity to EGFR TKIs, objective responses were seen in more than 60% of lung cancer patients, with *EGFR* gene mutations receiving EGFR TKI treatment, whereas objective response was seen in only 10% of patients with no mutations (Table 5) [24,76–80]. The response rate of gefitinib of Western NSCLC patients is approximately 10%, much lower than the response rate 20–30% of East Asian patients. This discrepancy may be due to the EGFR mutations [21]. With mutant *EGFR*, the gefitinib response rate of East Asian patients is approximately 60–80%, but goes down to 0–30% in East Asian patients without mutant *EGFR* [60,81]. *EGFR* mutations are mainly present in the first four exons of the gene encoding the tyrosine kinase domain. Approximately 90% of the EGFR mutations are either small deletions encompassing five amino acids from codons 746 through 750 (ELREA) or missense

mutations resulting in leucine to arginine at codon 858 (L858R) [82]. There are over 20 variant types of deletion, for example, larger deletion, deletion plus point mutation and deletion plus insertion. Approximately 3% of the mutations occur at codon 719, resulting in the substitution of glycine to cysteine, alanine or serine (G719X). Furthermore, approximately 3% are in-frame insertion mutations in exon 20. These four types of mutations seldom occur simultaneously. There are many rare point mutations, some of which occur with L858R. Sensitivity of cancers to EGFR TKI was found to be more than 70% in patients with exon 19 and exon 21 mutations. Variations in response rate may arise from different classes of EGFR mutations. Patients with an exon 19 deletion or L858R showed high response rates of 81 and 71%, respectively. By contrast, only approximately 50% of the patients with G719X responded to EGFR TKIs. There have been few reports on insertion mutations associated with clinical effects of EGFR TKIs (Figure 2) [25,59,83–86]. Many investigators have reported that patients with EGFR mutations have a significantly longer survival than those with wild-type EGFR when treated with EGFR-TKIs. However, this point is still controversial because some investigators indicated that patients with EGFR mutations survived for a longer period than those without EGFR mutations even when treated by chemotherapy [87,88].

Table 4. Randomized trials with gefitinib currently in progress.

Study	Population	Treatment arm	Primary end point
WJTOG3405	First-line chemotherapy with EGFR gene mutation	Gefitinib vs cisplatin + docetaxel	PFS
NEJGSG	First-line chemotherapy with EGFR gene mutation	Gefitinib vs carboplatin + paclitaxel	PFS
NCIC BR.19	First-line maintenance after complete resection of stage I-IIIA NSCLC ± adjuvant chemotherapy	Gefitinib vs placebo	OS
EORTC08021	First-line maintenance for advanced NSCLC in patients without disease progression after chemotherapy	Gefitinib vs placebo	OS

EGFR: EGF receptor; NCIC: National Cancer Institute of Canada; NEJGSG: North-East Japan Gefitinib Study Group; NSCLC: Non-small-cell lung cancer; OS: Overall survival; PFS: Progression-free survival; WJTOG: West Japan Thoracic Oncology Group.

EGFR secondary mutations & resistance against EGFR TKIs

Another major issue is that nearly all patients who respond initially to EGFR TKIs later develop drug resistance (Figure 3). The effective period of EGFR TKI varies from 2–4 months to more than 2 years. It has been reported that, in some patients with such acquired resistance, in addition to the original deletion and L858R mutations that elevate sensitivity to EGFR TKIs, an extra secondary mutation occurs with the threonine at codon 790 being changed to a methionine (T790M) [89]. Tumors with T790M are highly resistant to reversible TKIs, such as gefitinib or erlotinib. However, the T790M mutant kinase remains sensitive to irreversible inhibitors, including CL-387,785, EKB-569, and HKI-272 [89–93]. Although the substitution in EGFR with a bulky methionine has been thought to cause resistance by steric interference with binding of TKIs, including gefitinib and erlotinib, Yun *et al.* have reported that the T790M mutation is a 'generic' resistance mutation that will reduce the potency of any ATP-competitive kinase inhibitor (T790M substitution confers resistance by increasing the affinity for ATP) and that irreversible inhibitors overcome this resistance simply through covalent binding, not as a result of an alternative binding mode [94]. Recently, Engelman *et al.* reported that amplification of the *MET* gene is another mechanism of acquired resistance to EGFR TKIs [95,96]. With the use of a 1000-times resistant cell line, HCC827GR, established by exposing it to increasing concentrations of gefitinib, the authors found that phosphorylated forms of MET, ERBB3 and EGFR remain after gefitinib treatment and that the *MET* gene is amplified. Inhibition of *MET* signaling restored the cells' sensitivity to gefitinib. *MET* amplification was also detected in four of 18 (22%) clinical specimens

Table 5. *EGFR* mutations versus wild-type *EGFR* related to response rate, progression-free survival and overall survival in patients treated with gefitinib.

Study	Patients (n)	Mutation (%)	Response rate (mutation/wild-type; %)	PFS (mutation/ wild-type; months)	OS (mutation/ wild-type; months)	Ref.
Cappuzzo *et al.*	89	19	54/5	9.9/2.6	20.4/8.4	[24]
Cortez-Funes *et al.*	83	12	60/9	12.3/3.6	13.0/4.9	[76]
Han *et al.*	90	19	65/14	21.7/1.8	30.5/6.6	[77]
Takano *et al.*	66	59	82/11	12.6/1.7	20.4/6.9	[78]
Mitsudomi *et al.*	59	56	83/10			[79]
Taron *et al.*	68	25	94/13		–/9.9	[80]

OS: Overall survival; PFS: Progression-free survival.

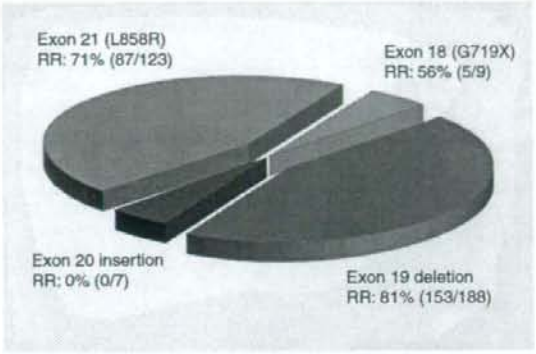

Figure 2. Distribution of EGF receptor mutations and response rates to EGF receptor tyrosine kinase inhibitors.
RR: Response rate.

from patients who had developed resistance to EGFR TKIs. In some specimens, *MET* amplification can occur concurrently with T790M.

EGFR mutation & amplification

There is increasing evidence that *EGFR* mutations and high *EGFR* gene copy number are associated with higher response rates to TKIs and longer survival. Both mutation and amplification of EGFR in lung cancers have been reported in association with clinical responses to TKIs. The *EGFR* locus can undergo both mutation and amplification. Yatabe *et al.* examined the topographical distribution of amplification in three microdissected portions each of 48 individual lung cancers with confirmed mutations [97]. Gene amplification was found in 11 lung cancers. Strikingly, nine of the cancers showed heterogeneous distribution, and amplification was associated with higher histologic grade or invasive growth. They also examined 17 precursor lesions and 21 *in situ* lung adenocarcinomas and found that only one *in situ* carcinoma harbored gene amplification. Taken together, their results show that mutation occurs early in the development of lung adenocarcinoma, and that amplification may be acquired in association with tumor progression. In general, tumors with EGFR mutations tend to have gene amplification. Mutation and amplification are probably both important in determining EGFR 0TKI sensitivity. The FISH scoring system, generated by the Colorado group, stratifies results into six groups by number of copies of the *EGFR* gene and frequency of tumor cells in the sample. These groups include disomy, low trisomy, high trisomy, low polysomy, high polysomy and gene amplification, with high polysomy or gene amplification being considered FISH positive [98,99]. However, the role of high polysomy is unclear.

KRAS mutation

Activating mutation of the *KRAS* gene was one of the earliest discoveries of genetic alterations in lung cancer known as a poor prognostic indicator. It was reported that the occurrence of *EGFR* and *KRAS* mutations are strictly mutually exclusive [100,101]. This finding can be explained by the fact that the KRAS–MAPK pathway is one of the downstream signaling pathways of EGFR. *KRAS* mutations predominantly occur in Caucasian patients with a history of smoking. Pao *et al.* reported that lung cancers with *KRAS* mutations are resistant to EGFR TKIs [102].

Postmarketing surveillance

It was shown that erlotinib, another EGFR TKI, extended the median survival time in the BR.21 trial [8]. In the BR.21 study, patients with NSCLC, after failure of first- or second-line chemotherapy, were randomized to receive erlotinib 150 mg/day or placebo (2:1, respectively). Statistically significant differences were observed for OS (6.7 vs 4.7 months; HR: 0.70; $p < 0.001$) and PFS (2.2 vs 1.8 months; HR: 0.61; $p < 0.001$) in favor of erlotinib. These results led to regulatory approval of erlotinib for NSCLC refractory to chemotherapy. However, gefitinib failed to prolong survival in comparison with placebo in the overall population in the ISEL study, possibly due to the refractory, difficult-to-treat nature of the population [12]. Based on the lack of improvement in survival in response to gefitinib, the FDA has restricted the labeling of gefitinib. Both gefitinib and erlotinib are currently available and are used to treat patients with advanced or metastatic NSCLC in the second- or third-line setting or, sometimes, in the first-line setting for selected patients. Most patients treated with these agents, however, had progressive disease even after showing an initial dramatic response. Among the mechanism of acquired resistance to EGFR TKIs, T790M secondary mutation or amplification of the *MET* oncogene was reported frequently [89,95,96]. However, other secondary mutations have also been reported. Of note, unlike T790M secondary mutation, some mutations, such as E884K or L747S mutations, may result in different sensitivities to gefitinib and erlotinib, resulting in different tumor responses to these two agents. Choong *et al.* reported a case of erlotinib-refractory adenocarcinoma with leptomeningeal metastases that had a L858R+ E884K somatic mutation of the *EGFR* [103]. Gefitinib responded to erlotinib-refractory lung cancer, showing a differential response between erlotinib and gefitinib that was mediated by the *EGFR* mutation E884K. On the other hand, Costa *et al.* reported a case of differential response to erlotinib in *EGFR*-mutated lung cancers with acquired resistance to gefitinib carrying the L747S secondary mutation [104]. Therefore, although half of patients could overcome the resistant T790M secondary mutation by empirical use of irreversible new EGFR TKIs [90], identification of the mechanism of acquired resistance in each patient could guide the proper use of these two different EGFR TKIs.

Safety & tolerability

Compared with conventional chemotherapeutic agents, gefitinib produces relatively few severe side effects, such as hematotoxicity. Gefitinib is generally well tolerated, even in elderly patients or patients with poor performance status. The principal side effects of gefitinib are skin rash, acniform changes of the skin, diarrhea, nausea, vomiting and anorexia. Diarrhea was actually the dose-limiting toxicity in Phase I studies. Most toxicities

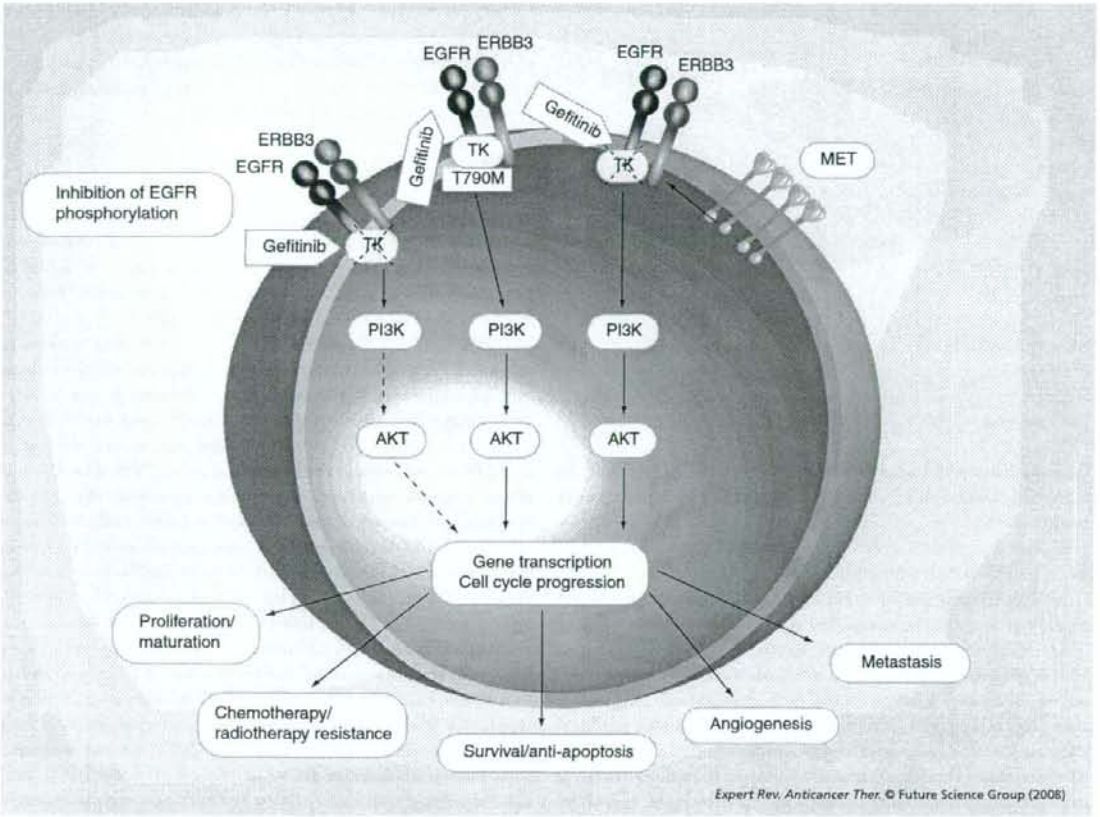

Figure 3. Mechanism of action of gefitinib signal-transduction blockage through EGFR TK and mechanisms of acquired resistance to gefitinib. When gefitinib is administered, EGFR TK is specifically inhibited and the survival signal is blocked leading to apoptosis of cancer cells. When a secondary threonine-to-methionine mutation at codon 790 of the *EGFR* gene (T790M) is acquired, T790M prevents gefitinib from binding EGFR TK. Alternatively, when *MET* is activated by amplification, ERBB3 is phosphorylated by *MET*. Even when EGFR TK is inhibited by gefitinib, activation of the PI3K/AKT pathway is maintained through ERBB3 phosphorylation [113]. EGFR: EGF receptor; TK: Tyrosine kinase.

are common toxicity criteria grade 1 or 2. Interstitial lung disease has been observed in patients receiving gefitinib [105,106]. Worldwide, the incidence of interstitial lung disease is approximately 1% (2% in the Japanese postmarketing experience and ~0.3% in a US expanded-access program), with approximately a third of the cases being fatal. Retrospective studies on the incidence of interstitial lung disease (ILD) and prospective studies involving 3000 subjects were conducted in Japan. The risk factors of ILD have been identified as male gender, prior history of smoking and pre-existing ILD. In addition, a case–cohort study that involved the identification of cohorts among patients receiving treatment for NSCLC to determine their relative risks was conducted [107]. For this study, 4423 subjects were included in the analysis as a cohort. Among them, 122 patients were identified with ILD. The results suggest that, regardless of patients' background, administration of gefitinib carries a 3.23-fold risk of ILD compared with conventional chemotherapeutic agents. The risk factors for ILD incidence do not apply to women, adenocarcinoma patients or nonsmokers – patient groups who are more likely to benefit from gefitinib treatment. In clinical practice, it may be possible to use such risk factors as a reference for selecting appropriate patients for gefitinib treatment to reduce the incidence of ILD. Interestingly, the issue of ILD in patients with NSCLC, after gefitinib or other treatments, appears to be a problem largely limited to Japan. From the AstraZeneca Global Drug Safety Database, the reporting rate of ILD-type events in patients receiving treatment with gefitinib was only 0.23% worldwide, excluding Japan, based on more than 275,000 patients worldwide estimated to have been exposed to gefitinib. Even for neighboring countries, the pattern differs from Japan: the rate for East Asian countries, including Korea and Taiwan, but excluding Japan, was 0.17%.

The reasons for this difference in incidence of ILD between Japan and other countries remain unclear, but may relate to both constitutional and environmental factors specific to Japan or Japanese patients.

Regulatory affairs

Gefitinib is approved in 36 countries worldwide for the treatment of NSCLC (Box 1). Gefitinib was approved for clinical use in Japan on 5 July 2002, ahead of many countries in the world. It was approved by the FDA on 5 May 2003 and, subsequently, by several other countries. However, in the wake of the aforementioned ISEL trials, which indicated the failure to improve survival time with gefitinib in comparison with placebo, an application for approval for gefitinib to the EMEA was withdrawn on 4 January 2005, and the FDA has restricted the labeling of gefitinib. However, an application for approval for gefitinib was subsequently submitted to the EMEA in May 2008 following reporting of the INTEREST trial.

Conclusion

Gefitinib is generally well tolerated, has encouraging efficacy and quality of life benefits and offers hope for patients with advanced lung cancer. Gefitinib is effective as a first-, second- or third-line treatment option for advanced NSCLC. Despite the failure of combining TKIs with chemotherapy in several large Phase III clinical trials, sequential dosing regimens of gefitinib with chemotherapy is still a viable clinical research paradigm (WJTOG0203). In addition, recent results of a randomized Phase III study (IPASS) have shown an improved PFS in the gefitinib arm, indicating the possibility of gefitinib as a first-line therapy in selected patients. As a second-line therapy, gefitinib has been shown to be equivalent to docetaxel in terms of OS, with less toxicity and improved quality of life. There is some evidence that *EGFR* mutations and high *EGFR* gene copy number are associated with higher response rates and longer survival, although this is not always the case, as highlighted by the results of the INTEREST study. In the near future, treatments may be selected based on the results of *EGFR* and *KRAS* mutation status, *EGFR* copy number or, possibly, the type of histology (adenocarcinoma). Ongoing prospective trials in which patients with *EGFR* mutations are randomized to chemotherapy or EGFR TKI should help to determine the importance of mutation testing in selecting therapy for subsets of patients with lung cancer. In summary, gefitinib has provided an important alternative approach for palliation of previously treated advanced disease NSCLC patients, and it is likely that there will be increasing use of first-line gefitinib in subgroups of NSCLC patients based on their clinical and molecular characteristics.

Expert commentary

The use of the TKIs gefitinib and erlotinib grew substantially as agents for second- and third-line therapies, replacing a proportion of injectable chemotherapy agents. Although gefitinib has provided an important alternative approach for palliation of previously treated advanced NSCLC patients and is currently not approved for first-line use, it is likely that there will be increasing use of first-line gefitinib in subgroups of NSCLC patients based on their clinical and molecular characteristics. In prior studies, the predictive factors of gefitinib response were female gender, never-smoking status and adenocarcinoma histology. Indeed, before the emerging understanding of EGFR mutations, these factors were important references for physicians in choosing susceptible patients to gefitinib treatment. Grouping patients into best, intermediate and worst categories with respect to potential benefit from gefitinib has practical implications. Based on currently available information, an example of one of the best groups might include Asian women who have never smoked and have adenocarcinoma. An intermediate group might

Box 1. Countries where gefitinib is approved for use.

- Japan
- Australia
- USA
- Argentina
- Singapore
- South Korea
- Taiwan
- Malaysia
- Mexico
- Philippines
- Canada
- Curacao
- Dominican Republic
- Nicaragua
- Hong Kong
- Israel
- New Zealand
- Honduras
- Guatemala
- Thailand
- United Arab Emirates
- Switzerland
- Indonesia
- India
- Peru
- El Salvador
- Bahrain
- Panama
- Venezuela
- Chile
- Serbia/Montenegro
- Uruguay
- Qatar
- Russia
- China
- Sri Lanka

comprise smokers with adenocarcinoma, and the worst group might consist of male smokers with squamous cell carcinoma. However, clinicians are also faced with the question of whether gefitinib treatment is worthwhile in specific patient subgroups based on their clinical characteristics. It has been reported that gefitinib was more effective in never-smokers than smokers, but it is important to note that the risk of death was reduced even in smokers subsets [17,108]. Thus, at this point, it does not seem that patients should be excluded from gefitinib treatment based solely on clinical considerations. Perhaps, more importantly, we need to gather more information regarding the benefit of chemotherapy versus gefitinib in specific patient populations. The observation of higher response rates with gefitinib in selected groups of patients, as well as the disappointing results with simultaneous chemotherapy and gefitinib in unselected patients, led lung cancer researchers to study the potential predictive value of molecular profiles in patients treated with gefitinib. There is increasing evidence that *EGFR* mutations and high *EGFR* gene copy number are associated with higher response rates and longer survival. By contrast, *KRAS* mutations may predict the worst outcomes on gefitinib. Determining the optimum way to select patients for future therapy seems to be a key factor in improving results for individual lung cancer patients.

Five-year view

Gefitinib was the most commonly prescribed EGFR TKI, and still is in Japan and Asia, but the use of gefitinib as a proportion of all second-line therapies declined rapidly during the period of observation after findings from clinical studies suggested that it did not improve survival and after the subsequent FDA labeling change. On the other hand, erlotinib prescriptions increased substantially. However, sequential dosing regimens of gefitinib with chemotherapy is a viable clinical research paradigm [17], and recent results of a randomized Phase III study (IPASS) have demonstrated improved PFS in the gefitinib arm, indicating the possibility of gefitinib as the first-line therapy in selected patients. In addition, gefitinib has been shown to be equivalent to docetaxel in terms of overall survival with less toxicity and improved quality of life in the second-line therapy (INTEREST). Future research of gefitinib will include potential synergistic effects with chemotherapy using an intermittent combination in selected patients or *EGFR*-mutated patients. In addition, it is possible that, in the next 5 years, gefitinib may have a role in early-stage NSCLC as postoperative adjuvant therapy or neoadjuvant therapy. Currently, allowing for test availability and differing preferences, oncologists use mutational analysis to help them choose among possible treatments and to guide the most rational order that these therapies should be administered for individual patients. The *EGFR* mutation appears to be the most sensitive predictor of response to gefitinib. With the advances in sensitive and specific examination for the detection of *EGFR* mutation, such as high-resolution melting analysis, scorpion arms or mutant-enriched PCR, it is now possible to identify the status of *EGFR* mutation in patients, as long as histological samples are available [81,109-111]. Recently, Maheswaran *et al.* have reported the detection of mutations in EGFR of circulating lung cancer cells [112]. Molecular analysis of circulating tumor cells from the blood may offer the possibility of monitoring changes in epithelial tumor genotypes during the course of treatment. In the near future, treatments will be selected based on the results of *EGFR* and *KRAS* mutation status, *EGFR* copy number or possibly histology (adenocarcinoma vs nonadenocarcinoma). As we now know, however, resistance to gefitinib in patients with the *EGFR* mutation develop eventually. In 50% of these cases, the resistance was due to a second-site point mutation (T790M), 20% was due to *MET* gene amplification and the remainder due to unknown causes. Evaluation of the combination of gefitinib with other targeting agents, such as those that inhibit molecules in the same signalling pathway or angiogenesis inhibitors, may potentially enhance clinical outcome and reduce the emergence of resistance.

Key issues

- Gefitinib has encouraging efficacy, is generally well tolerated and has quality-of-life benefits.
- In prior studies, the predictive factors of gefitinib response were female gender, never-smoking status and adenocarcinoma histology.
- From a clinician's perspective, it would be useful to categorize patients into the best, intermediate, and worst EGF receptor (EGFR)-tyrosine kinase inhibitor treatment-outcome groups. Based on currently available information, an example of one of the best groups might include Asian women who have never smoked and have adenocarcinoma. An intermediate group might comprise of smokers with adenocarcinoma, and the worst group might consist of male smokers with squamous cell carcinoma.
- Sequential dosing regimens of gefitinib with chemotherapy is a viable clinical research paradigm, and recent results of a randomized Phase III study (IPASS) have showed improved progression-free survival in the gefitinib arm, indicating the possibility of gefitinib as the first-line therapy in selected patients. In addition, gefitinib has been shown to be equivalent to docetaxel in terms of overall survival with less toxicity and improved quality of life in second-line therapy (INTEREST).
- Currently, the treatments (cytotoxic chemotherapy vs gefitinib) are selected based on the results of *EGFR* and *KRAS* gene mutation status, *EGFR* gene copy number or, possibly, the type of histology (adenocarcinoma).
- Among those, EGFR mutation appears to be most sensitive predictor of response to gefitinib. However, resistance to gefitinib develops eventually. In 50% of these cases, the resistance was due to a second-site point mutation (T790M), 20% *MET* gene amplification and the remainder unknown causes.
- Evaluation of the combination of gefitinib with other targeting agents may potentially enhance clinical outcome and reduce the emergence of resistance.

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No writing assistance was utilized in the production of this manuscript.

Information resources

- US Food and Drug Administration
  www.fda.gov/default.htm
- Medicine Net
  www.medicinenet.com/gefitinib/index.htm
- National Cancer Institute – Clinical trials
  www.cancer.gov/clinicaltrials
- AstraZeneca Pharmaceuticals information resource
  www.iressa.com

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• of interest
•• of considerable interest

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Epidermal Growth Factor Receptor Mutations in Small Cell Lung Cancer

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Abstract

Purpose: The vast majority of epidermal growth factor receptor (*EGFR*) mutations occur in lung adenocarcinoma, and even rare cases of other subtypes with this mutation, such as adenosquamous cell carcinoma, are associated with adenocarcinoma histology. According to this adenocarcinoma-specific nature of *EGFR* mutation, analysis of *EGFR* mutations with small cell lung cancers (SCLC) may provide a clue to its histogenesis.

Experimental Design: The mutational status of the *EGFR* gene was accessed in a cohort of 122 patients with SCLC; all patients were from a single institute. When the *EGFR* mutated, its gene copy number was also examined.

Results: *EGFR* mutations were detected in five SCLCs (4%). The patients were mainly in the light smoker and histologic combined subtype. All but one of the tumors harbored gene amplifications. Notably, in three tumors of the combined SCLC subtype, both components of adenocarcinoma and SCLC harbored an *EGFR* mutation, whereas gene amplification was detected only in the adenocarcinoma component. A partial response was achieved in a patient (with an *EGFR* mutation) who was treated with gefitinib.

Conclusions: Although *EGFR* mutations are rare in SCLC, a combined subtype of SCLC with adenocarcinoma in light smokers may have a chance of harboring *EGFR* mutations. For patients with an *EGFR* mutation, *EGFR* tyrosine kinase inhibitor can be a treatment option. In terms of molecular pathogenesis, it is suggested that some SCLCs may have developed from pre-existing adenocarcinomas with *EGFR* mutations, but the development may not be simply linear, taking into consideration the discordant distribution of *EGFR* amplification.

The vast majority of epidermal growth factor receptor (*EGFR*) gene mutations are detected in lung adenocarcinoma. A comprehensive analysis by Shigematsu and Gazdar reported that non-adenocarcinomatous lung cancers with *EGFR* gene mutations were restricted to <5% of lung cancers (1). Although it is rare in other histologic subtypes, adenosquamous cell carcinoma showed the highest frequency among lung cancers, followed by squamous cell carcinoma and large cell carcinoma. In contrast, small cell carcinoma was not listed among *EGFR*-mutated lung cancers following a comprehensive examination of 1,380 lung tumors, which suggests a different molecular pathogenesis for this type of cancer. However, two patients (who had never smoked), recently reported having *EGFR* mutations with small cell lung cancers (SCLC; refs. 2, 3). In the first case, published in *The New England Journal of Medicine*, the patient with adenocarcinoma was initially treated with erlotinib. The recurrent tumor in the brain consisted of small cell carcinoma, which also harbored an *EGFR* mutation. Because the mutational status of the *EGFR* gene in the initial adenocarcinoma was not addressed, the clonal relationship between the two tumors was not clear. Another case was also a never-smoker who developed widespread SCLC. Mutational analysis revealed a typical *EGFR* gene deletion at exon 19. The tumor responded well to gefitinib treatment, and both primary and metastatic tumors regressed dramatically (3).

The incidence of *EGFR* mutation is quite high among the Japanese (~30-40% of non-small cell lung cancers on average) in contrast to ~10% of patients in the United States and in European countries (1, 4, 5). The clinicopathologic characteristics of patients with *EGFR* mutations include female sex, not smoking, and less frequent p53 mutation (4-6), which are very different from those of SCLC. It is therefore expected that *EGFR* mutations are very rare or absent in SCLC. A comprehensive analysis of *EGFR* mutations in SCLCs has not been reported in the literature; however, we believe it is important to determine its incidence, especially in mutation-endemic countries. In this study, we comprehensively examined a total of 122 SCLCs to address mutation incidence in SCLC.

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Translational Relevance

It is well known that epidermal growth factor receptor (*EGFR*) mutations are prevalent in female nonsmokers. However, *EGFR* mutations have recently been reported in some patients with small cell lung cancers (SCLC). In this study, we first examined a large series of SCLCs to address mutation incidence. Because the incidence of *EGFR* mutations differs between the United States and Japan, these data are important in determining the significance of ethnicity and frequency of *EGFR* mutations. As a result, a combined subtype of SCLC with adenocarcinoma in light smokers may have a chance of harboring *EGFR* mutations, although *EGFR* mutations are generally rare in SCLC. Notably, one such patient with an *EGFR* mutation achieved a partial response to gefitinib treatment. Although clinical relevance needs to be examined in more patients, *EGFR* tyrosine kinase inhibitor can be a treatment option for patients with SCLCs harboring an *EGFR* mutation.

Materials and Methods

Patients. Among 150 patients that were diagnosed with SCLC in the last 7 years at the Department of Pathology and Molecular Diagnostics, Aichi Cancer Center in Nagoya, Japan, specimens from 122 patients were available for molecular genetic analysis, and these were the subject for the current study. This series included 102 specimens obtained by biopsy, and 20 from surgically resected tumors. Histologic diagnosis of SCLC was based on the standard criteria defined by WHO classification (7). The study was a part of a comprehensive lung cancer research program, which had been approved by the institutional review board.

EGFR *mutation analysis.* All the specimens were fixed with formalin, and the *EGFR* mutation was analyzed with the method described previously, using an unstained paraffin section (8). This technique allows the detection of tumor cells constituting as little as 5% of a mixture of tumor cells with normal tissue using a single paraffin section. When frozen tissues were available, the mutational status of *EGFR* was accessed with standard reverse transcription-PCR coupled direct sequencing, as described previously (4), in addition to DNA-based analysis. In this assay, the mutational status of the L858R point mutation and the deletion of exon 19 were obtained when we examined paraffin sections, whereas direct sequencing using RNA revealed the mutational status of the whole tyrosine kinase domain.

Copy number analysis of EGFR. Gene amplification was analyzed by fluorescence *in situ* hybridization, using the LSI EGFR SpectrumOrange/CEP 7 SpectrumGreen probe (Vysis; Abbott Laboratories) according to the manufacturer's protocol. Fluorescence *in situ* hybridization was done on serial paraffin sections in the same tissue areas as the gene dosage analysis. A more than 4-fold increase of *EGFR* gene signals relative to CEP7 signals was considered a gene amplification. The results were confirmed by TaqMan-based gene dosage analysis as described previously (9).

Statistical analysis. Fisher's exact test for independence and unpaired *t* tests were used to show the correlation of clinicopathologic variables with EGFR mutation. $P < 0.05$ was considered statistically significant.

Results

SCLCs with EGFR *mutation.* Among 122 SCLCs examined (Table 1), we found *EGFR* mutations in five cases (4%). The mutations included L858R point mutations (three patients), a G719A point mutation (one patient), and a 15-bp deletion in exon 19 (one patient). Both frozen and paraffin tissues of 10 tumors, 2 of which harbored the above *EGFR* mutation, were available for analysis. They were examined using both reverse transcription-PCR coupled sequencing and assays for paraffin sections. The results were identical to those of the other analysis.

Clinicopathologic features of SCLCs with EGFR *mutations.* *EGFR* mutations were restricted to a very minor proportion (5 of 122; 4%) of SCLCS, and the clinicopathologic features of the patients with the mutation showed a trend similar to those of patients without the mutation. There were no significant differences in age, sex, and clinical stage at presentation. In contrast, accumulated smoking dose (pack-years) in patients with the mutation was much lower, and the difference was statistically significant (unpaired *t* test, $P = 0.02$). Indeed, three of the five patients with *EGFR* mutations were smokers with less than 40 pack-years. It is of note that one of the five patients was treated with gefitinib, and partial response was observed (case 2).

Morphologic features of SCLC with EGFR *mutations.* There are two subtypes of SCLC in the current WHO classification; thus, we examined whether the morphologic subtypes were associated with *EGFR* mutations. The combined subtype constituted a minor proportion (15 of 122, 12%) in this series, and three of them were positive for *EGFR* mutations (Table 1). Preferential mutation in the combined type were statistically significant (Fisher's exact test, $P < 0.01$). In two cases of the combined subtype (cases 1 and 3), SCLC components consisted of only a part of the nodule, and adenocarcinoma components constituted the predominant part. The representative morphologic features are displayed in Fig. 1. The other combined subtype (case 5) showed a mixture of SCLC and adenocarcinoma components throughout the tumor.

EGFR *amplification in SCLCs.* We have recently reported that *EGFR* amplification occurs in association with *EGFR* mutation (9). We therefore examined the EGFR gene copy number in the five SCLCs with *EGFR* mutations. Four of them showed gene amplification (Table 2), and the signals of the EGFR gene were loosely clustered (Fig. 2), suggesting a high degree of amplification, as is the case in homogeneously staining region patterns. Notably, three cases of combined SCLC subtypes harbored *EGFR* amplifications only in the adenocarcinoma component, but not in the SCLC component (Fig. 2).

Discussion

SCLC is a distinct neoplasm in terms of clinical aggressiveness, despite its high response to both chemotherapy and irradiation therapy. This aggressive cancer does not confer to

Table 1. Clinicopathologic features of SCLCs with and without *EGFR* mutations

	Mutated	Wild-type	*P*
No. of patients (total, $N = 122$)	5	117	
Age (median)	69	67	n.s.
Sex (female/male)	2/3	14/103	n.s.
Smoking history (median pack-years)	30	54	0.020
Disease stage (limited/extended disease)	4/1	81/33	n.s.
Histologic type (conventional/combined)	2/3	105/12	0.013

Abbreviation: n.s., not significant.

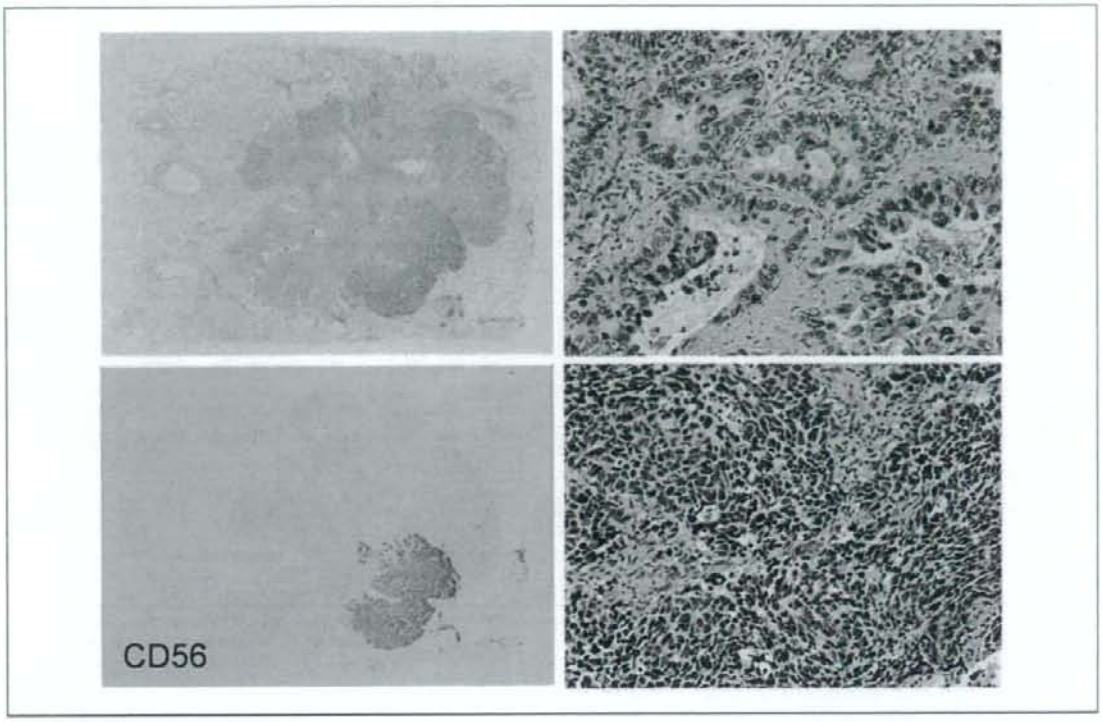

Fig. 1. Representative morphology of combined small cell carcinoma and adenocarcinoma (case 3). Approximately two-thirds of the area of the nodule (*top left*) consisted of an adenocarcinoma component, whereas the other area showed SCLC. Discrete expression of CD56 (neural cell adhesion molecule) corresponds to the component of SCLC (*bottom left*). High-power views of each component of adenocarcinoma (*top right*) and SCLC (*bottom left*). Both components harbor identical L858R *EGFR* mutations, although *EGFR* gene amplification was restricted to the adenocarcinoma component.

the lung, and it can develop in organs other than the lung, all of which share distinctive pathologic and immunohistochemical features, irrespective of their site of origin. These extrapulmonary carcinomas are characterized by frequent admixture with conventional carcinoma of the originating organ, such as adenocarcinoma in gastrointestinal tumors, and squamous cell carcinoma in head and neck cancers. This is true in SCLC. Nicholson et al. reported that 28 of 100 surgically resected SCLCs had a histologic component of non–small cell lung cancers (10). In our study, *EGFR* gene mutation was detected in 5 of 122 SCLCs. Because *EGFR* mutation was quite specific for adenocarcinoma, it is suggested that SCLCs with *EGFR* mutations are associated with adenocarcinoma. Indeed, three of the five combined SCLC had an adenocarcinoma component but not a squamous cell carcinoma component.

It has been suggested that the amine-precursor uptake and decarboxylase cells described by Pearse in 1969 (11) are the putative original cells of small carcinoma. These cells were described as comprising a neuroendocrine system in many organs, and as having ultrastructural features shared by small cell carcinomas. However, this hypothesis cannot explain the existence of combined SCLC, which is an admixture of small cell carcinoma and conventional adenocarcinoma or squamous cell carcinoma. Therefore, a multipotential cancer stem cell capable of divergent differentiation has been suggested as a putative origin of small cell carcinoma. Alternatively, the SCLC component may arise as a consequence of undifferentiated transformation from conventional carcinoma. Case 2 in the present study supported the latter scenario, because SCLC is the only component that metastasized to the lymph nodes. Furthermore, the vast majority of lung cancers harboring *EGFR* mutations are adenocarcinomas, supporting the idea that the adenocarcinomas existed prior to the development of SCLC in at least three of the cases of SCLC with *EGFR* mutations.

However, the results of *EGFR* amplification analyses support the former possibility. In three cases of combined subtype of SCLC with an *EGFR* mutation, only the adenocarcinoma component, not the SCLC component, harbored the amplification. This is in contrast to the uniform detection of *EGFR* mutations in both components. Because *EGFR* mutations in SCLC are rather rare, it is unlikely that the two components are independent of their origin. Rather, it is believed that they originated from a common ancestor. Therefore, it is suggested that the mutation occurred before a point branching off to SCLC and adenocarcinoma components, whereas gene amplification was acquired after that point. Cases 3 and 5 may be considered to have followed this scenario. However, case 1 was inconsistent with it because SCLC emerged after the therapy.

In case 1, the initial adenocarcinoma harbored both *EGFR* mutation and amplification. Subsequently, SCLC, which lacked

gene amplification, developed after the chemotherapy and gefitinib therapy. It was unlikely that the amplification was removed from cancer cells due to therapy. We have recently reported heterogeneous distribution of *EGFR* amplification in lung adenocarcinoma (9), and thus we suggested that only a clone without amplification was selected, survived, and was subsequently transformed to SCLC. The reported SCLC with *EGFR* mutation followed this pattern of progression (2, 3, 12), and lack of *EGFR* expression in SCLC may be a clue to this phenomenon. Under heavy selection pressure by gefitinib therapy, only a clone which is independent of *EGFR*-driven growth signals has a chance to expand. Transformation to SCLC fulfills this condition because *EGFR* expression in the SCLC was at a very low or undetectable level (13–15). Indeed, the SCLC component lacked *EGFR* expression, in contrast to positive expression in the initial adenocarcinoma and adenocarcinoma components (data not shown). This may be another mechanism for tolerance to the *EGFR* tyrosine kinase inhibitor, in addition to secondary genetic alterations.

Clinically, it is noteworthy that a partial response was achieved in one of the patients with an *EGFR* mutation who was treated with gefitinib. Because *EGFR* expression is at a very low or undetectable level in SCLC, it would be expected that *EGFR* tyrosine kinase inhibitors are not effective against SCLC even if the *EGFR* is mutated. However, a similar marked reduction of such cancers by *EGFR* tyrosine kinase inhibitor treatment has also been reported (2, 3). *EGFR* tyrosine kinase inhibitors may be a treatment option for SCLC with *EGFR* mutations, and a mutation test may be helpful to select such patients in addition to clinical characteristics, including the light smoker and histologic combined subtypes.

In summary, we examined 122 SCLCs and found 5 (4%) of them harboring *EGFR* mutations. The SCLCs with *EGFR* mutations were seen in the light smoker and histologic combined subtypes. Because of the specific involvement of *EGFR* mutations in adenocarcinoma, it is suggested that the SCLCs may have developed from pre-existing adenocarcinomas. However, we have concluded that this development may

Table 2. Clinicopathologic features of five SCLCs with *EGFR* mutations

Case	Sex/Age (y)	Pack-years smoking	*EGFR* mutation	*EGFR* amplification	Stage	Sample and histologic subtype	Clinical course
1	F/36	0	L858R	Amplified (>6)*	ED	Resected tumor; combined type (diagnosis of adenocarcinoma with a biopsy prior to surgery)	Stage IV adenocarcinoma was treated with CBDCA and PAC, followed by gefitinib, because of positive EGFR mutation with a biopsy specimen. Partial response was achieved but the tumor regrew. It was surgically resected, and histologically revealed to be combined small and adenocarcinoma
2	M/81	40	G719A	Amplified (>6)	ED	Biopsy specimen; conventional type	Stage IV SCLC was treated with gefitinib, because of the detection of G719A mutation using a lung biopsy specimen. A partial response was obtained
3	M/69	30	L858R	Amplified (>6)*	LD	Biopsy specimen, combined type	A lung cancer ($cT_1N_0M_0$) was surgically removed, and subsequent pathologic examination revealed combined SCLC. Adjuvant chemotherapy (CDDP and CPT-11) were administered. The patient is alive without recurrence
4	F/89	2.5	L858R	Low polysomy	LD	Biopsy specimen; conventional type	A biopsy specimen for lung cancer ($cT_2N_0M_0$) was diagnosed as SCLC. The patient refused any therapy, and was not a part of follow-up
5	M/65	67.5	Ex.19Del	Amplified (>6)*	LD	Resected tumor; combined type (cytological diagnosis of SCLC prior to surgery)	$cT_1N_1M_0$ cancer was treated with CDDP and TXT, followed by surgical resection of the tumor. Combined SCLC was revealed, and the patient was treated with adjuvant chemotherapy and irradiation. Three years later, SCLC recurred

Abbreviations: F, female; M, male; LD, limited disease; ED, extended disease; CBDCA, carboplatin; PAC, paclitaxel; CDDP, cisplatin; CPT-11, irinotecan.
* Only in the adenocarcinoma component.

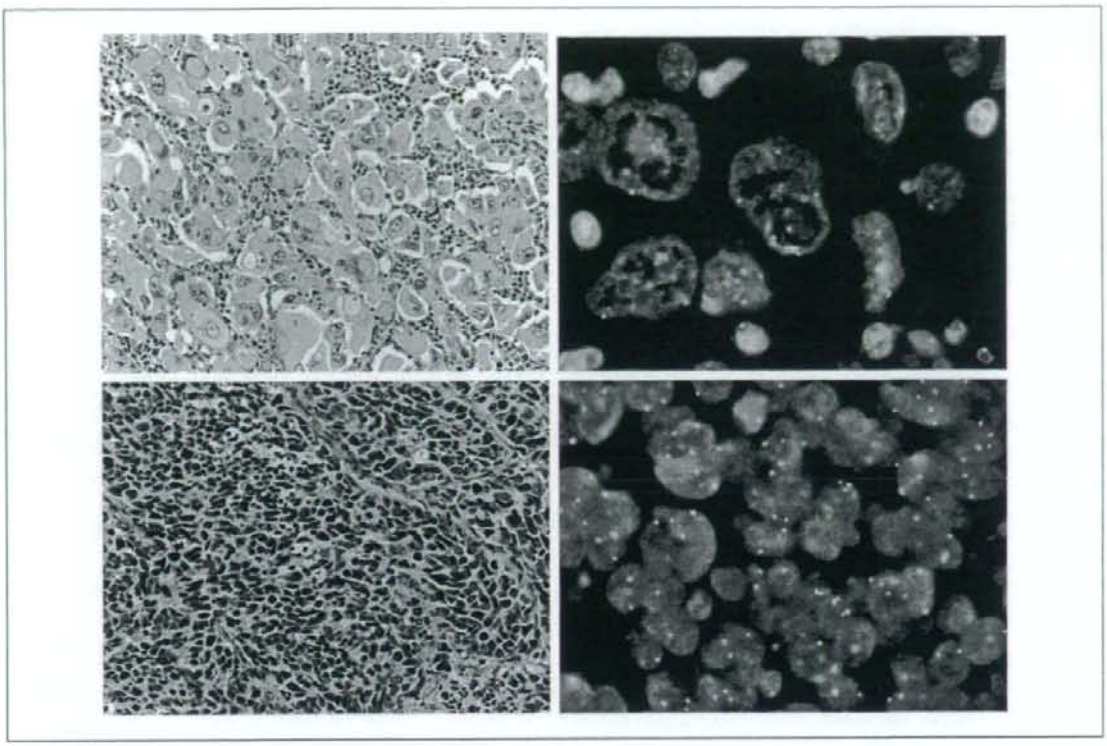

Fig. 2. *EGFR* amplification in SCLC with *EGFR* mutation (case 1). A female nonsmoker who had developed stage IV adenocarcinoma was treated with carboplatin and paclitaxel. The tumor recurred at the neck lymph node (*top left*), which was biopsied. Because molecular analysis using the tissue revealed a L858R mutation, she was subsequently treated with gefitinib. Although the tumor responded initially, rapid regrowth of the lung nodule was evident, and it was removed surgically. The SCLC component constituted most of the regrown nodule. *EGFR* mutation was detected in both adenocarcinomas in the lymph node and in the regrown SCLC, *EGFR* amplification was identified only in the adenocarcinoma but not in the regrown SCLC (*right*).

not be simply linear, considering the discordant distribution of EGFR amplification.

Disclosure of Potential Conflicts of Interest

T. Mitsudomi has a minor conflict with AstraZeneca, Chugai Pharm, Astellas, Daiichi-Sankyo, Sanofi-Aventis, Taiho Pharm, and Bristol Meyers.

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ORIGINAL ARTICLE

Predictors of Survival in Patients With Bone Metastasis of Lung Cancer

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Abstract The prognosis of patients with bone metastasis from lung cancer has not been well documented. We assessed the survival rates after bone metastasis and prognostic factors in 118 patients with bone metastases from lung cancer. The cumulative survival rates after bone metastasis from lung cancer were 59.9% at 6 months, 31.6% at 1 year, and 11.3% at 2 years. The mean survival was 9.7 months (median, 7.2 months; range, 0.1–74.5 months). A favorable prognosis was more likely in women and patients with adenocarcinoma, solitary bone metastasis, no metastases to the appendicular bone, no pathologic fractures, performance status 1 or less, use of systemic chemotherapy, and use of an epithelial growth factor receptor inhibitor. Analyses of single and multiple variables indicated better prognoses for patients with adenocarcinoma, no evidence of appendicular bone metastases, and treatment with an epithelial growth factor receptor inhibitor. The mean survival period was longer in a small group treated with an epithelial growth factor receptor inhibitor than in the larger untreated group. The data preliminarily suggest treatment with an epithelial growth factor receptor inhibitor may improve survival after bone metastasis.

Level of Evidence: Level IV, prognostic study. See the Guidelines for Authors for a complete description of levels of evidence.

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Each author certifies that his or her institution has approved or waived approval for the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

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Introduction

Metastatic bone tumors occur at particularly high rates in cancers of the breast, prostate, lung, and kidney, accounting for 75% of all patients [16]. Many patients with lung cancer are in advanced stages of the disease at the time of diagnosis. The 5-year survival rate for patients with lung cancer is 10% to 20%, as reported by Stanley [15] and Freise et al. [4], indicating a poor prognosis. Although it is reported bone metastasis from lung cancer occurs in 14% to 40% of patients, its clinical features have not been clearly described [9].

When treating skeletal metastasis, it is important to know the prognostic factors and prognosis after bone metastasis. Tokuhashi et al. [17] proposed six factors that predicted survival for tumors metastatic to the spine: general condition, number of extraspinal bone metastases, number of metastases in the vertebral body, metastases to major internal organs, primary site of the cancer, and severity of spinal cord palsy. The grade of malignancy of the primary tumors, visceral metastasis to vital organs, and

number of bone metastases are reportedly important prognostic factors [18, 19]. In a report of 350 patients with bone metastasis, the primary site, performance status (PS), number of bone metastases, metastasis to organs, and previous chemotherapy were important prognostic factors, with lung cancer being the poorest [10]. The Scandinavian Sarcoma Group [5] examined prognostic factors in 460 patients undergoing surgery for bone metastasis and reported poor prognoses in patients with lung cancer as the primary site, pathologic fracture, and metastasis to organs. In another report of 342 patients with vertebral metastasis, the important prognostic factors included PS, metastasis to organs, and the primary site [20]. Prognosis in bone metastasis from lung cancer also was reported as poor. However, these studies [5, 10, 17–20] reported on bone metastasis from various cancers and did not focus on lung cancer alone. Therefore, the prognostic factors and survival rates of patients with bone metastasis from lung cancer remain unclear.

Several recent reports suggest an epithelial growth factor receptor (EGFR) inhibitor has been effective in treating lung cancer [6, 11, 12, 21]. The EGFR inhibitor is a new molecule-targeted agent for lung cancer that is reported to have a considerable effect on females and nonsmokers, especially those with adenocarcinoma [6, 12]. However, its effectiveness in patients with bone metastasis from lung cancer is unknown.

We first assessed the survival rates and explored various prognostic factors of 118 patients with bone metastasis from lung cancer. We then preliminarily ascertained in a small group of patients whether treatment with an EGFR inhibitor had the potential to influence survival.

Table 1. Distribution of patients with skeletal metastases of lung cancer (n = 118)

Prognostic factor	Subgroups	Number of patients
Age (years)	≥ 60	67 (57%)
	< 60	51 (43%)
Gender	Female	41 (35%)
	Male	77 (65%)
Performance status	0,1	67 (57%)
	2, 3, 4	51 (43%)
Subtype	Adenocarcinoma	83 (70%)
	Nonadenocarcinoma	35 (30%)
Surgery for lung cancer	Yes	36 (31%)
	No	82 (69%)
Number of bone metastases	Solitary	19 (16%)
	Multiple	99 (84%)
Appendicular bone metastasis	Yes	21 (18%)
	No	97 (82%)
Pathologic fracture	Yes	15 (13%)
	No	103 (87%)
Brain metastasis	Yes	48 (41%)
	No	70 (59%)
Liver metastasis	Yes	16 (14%)
	No	102 (86%)
Chemotherapy	Yes	67 (57%)
	No	51 (43%)
Radiation	Yes	61(52%)
	No	57 (48%)
Gefitinib	Yes	14 (12%)
	No	104 (88%)

Materials and Methods

We retrospectively reviewed 1157 patients with lung cancer treated at Aichi Cancer Center Hospital between January 1, 1999, and December 31, 2002. Of these, 121 patients (10.4%) were treated for lung cancer that had metastasized to bone. We excluded three patients because of incomplete information; this left 118 patients (77 men, 41 women) who had bone metastasis from lung cancer (Table 1). Fifty-two of the 118 patients met criteria (see below) for administering an oral selective EGFR inhibitor and it was administered to 14 of the 52 patients. It was not administered to the remaining 38 patients because the use of EGFR inhibitor was not available before June 2002 in Japan. Apart from determining survival, our primary outcome was survival in patients receiving an EGFR inhibitor. Based on survival in our hospital [12], the power would be approximately 70% using a two-side type I error of 5% to detect a 30% difference in 1–year survival among the 52 patients who met the criteria for administering EGFR inhibitor.

The mean age of the 118 patients at the time of bone metastasis was 59.6 years (standard deviation [SD], 10.2 years; range, 28–85 years). Lung cancer diagnosis was confirmed by computed tomography, fiberscope examination, and biopsy. Presence or absence of bone metastasis was confirmed by radiography or bone scintigraphy. All patients provided informed consent for participation in this study.

Among the 118 patients, 308 sites with bone metastasis were determined. Sites with high incidence included the rib, vertebra, and pelvis, where there is a high concentration of red marrow (Fig. 1). When bone metastasis was first confirmed by radiography or scintigraphy, 19 patients (16%) had a solitary site of metastasis and 99 patients (84%) had multiple sites. Eight (42%) of the 19 patients had a solitary bone metastasis that developed in other new sites. The remaining 11 patients (58%) remained with a solitary site of metastasis at followup. The minimum followup was

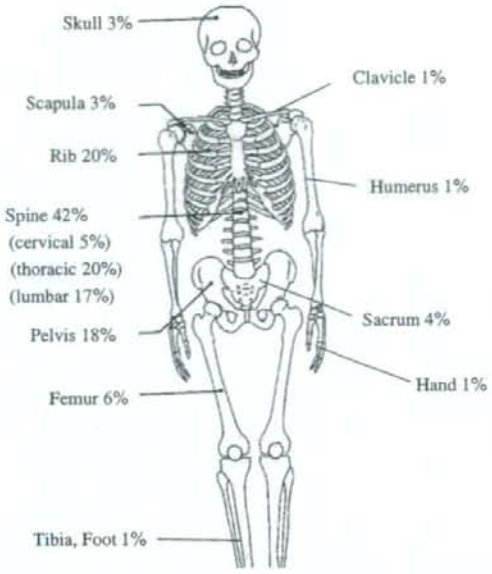

Fig. 1 Anatomic localization of skeletal metastases from lung cancer is shown (n = 118).

0.2 months (mean ± SD, 12.8 ± 14.6 months; range, 0.2–54.0 months)

The time from lung cancer diagnosis to bone metastasis was less than 1 month in 54 patients (46%), of which 12 patients initially had been diagnosed with an unknown primary cancer. For the remaining patients, the time from diagnosis to bone metastasis was 1 to 6 months in 23 patients, 6 months to 1 year in 11 patients, and 1 to 2 years in 10 patients. There were 20 patients (17%) whose lung cancer metastasized to the bone longer than 2 years after diagnosis, among whom the primary site was excised in 19 cases.

The major histologic type of the primary site was adenocarcinoma (83 patients), followed by squamous cell carcinoma (17 patients), small cell and large cell carcinoma (seven patients), and adenosquamous carcinoma (four patients). The primary site already had been excised at the time of bone metastasis in 36 patients (31%), but not in the remaining 82 patients (69%). After bone metastasis, 44 patients (37%) had brain metastasis, 12 patients (10%) had liver metastasis, and four patients (4%) had metastasis to the brain and liver. Approximately 50% of the patients had brain or liver metastasis.

Performance status was evaluated using the method devised by the Eastern Cooperative Oncology Group [14]. Patients with PS 0 are fully active and have no limitation in daily life; patients with PS 1 are restricted in physically strenuous activity but are ambulatory and able to do work of a light or sedentary nature; patients with PS 2 are ambulatory and capable of all self-care but are unable to do work activities; patients with PS 3 are capable of only limited self-care, are confined to bed or chair for greater than 50% of working hours; and patients with PS 4 are completely disabled, cannot do any self-care, and are totally confined to a bed or chair. Seventeen patients had PS 0, 50 patients had PS 1, 17 patients had PS 2, 17 patients had PS 3, and 17 patients had PS 4. Pathologic fractures during the course occurred in 15 patients, among which five underwent surgery for femoral pathologic fractures. Three patients were treated by intralesional

Table 2. Data for patients with adenocarcinoma and performance status 1 or less (n = 14) with user of gefitinib

Patient number	Age (years)	Gender	Performance status	Metastasis to appendicular bone	Pathologic fracture	Solitary or multiple	Radiation	Chemo therapy	Outcome	Survival period (days)
1	42	Female	0	–	–	Multiple	–	+	Dead	898
2	72	Female	1	–	–	Solitary	–	+	Alive	736
3	57	Male	0	–	–	Multiple	+	+	Dead	467
4	68	Female	0	–	–	Multiple	–	+	Alive	903
5	56	Male	1	–	–	Solitary	–	+	Alive	251
6	72	Male	1	+	–	Multiple	+	+	Dead	531
7	66	Male	0	–	–	Multiple	–	+	Dead	427
8	65	Male	0	–	–	Multiple	+	+	Dead	387
9	72	Female	1	–	–	Solitary	+	+	Dead	431
10	69	Male	1	–	–	Multiple	+	+	Alive	491
11	62	Female	1	+	–	Solitary	+	+	Dead	448
12	66	Female	1	–	–	Multiple	–	+	Dead	310
13	66	Male	1	–	–	Multiple	–	+	Alive	621
14	54	Female	1	–	–	Solitary	+	–	Alive	577