Table 2. Phase II studies of gefitinib in selected patients.

Author	Selection	Patients (n)	Response rate (%)	TTP/PFS (months)	MST (months)	1-year survival (%)	Ref.
EGFR selected							
Inoue *et al.*	Mutation	16	75	9.7	NR	NR	[55]
Sutani *et al.*	Mutation	27	78	9.4	15.4	NR	[56]
Asahina *et al.*	Mutation	16	75	8.9	NR	88	[57]
Sunaga *et al.*	Mutation	19	84	13	NR	NR	[58]
Yoshida *et al.*	Mutation	21	90	7.7	NR	NR	[59]
Tamura *et al.*	Mutation	28	75	11.5	NR	79	[60]
Sugio *et al.*	Mutation	16	50	8.8	15.4	NR	[61]
Sequist *et al.* (iTARGET)	Mutation*	31	55	9.2	17.5	73	[62]
Yang *et al.*	Mutation‡	43	84	8.9	24		[63]
	Mutation§	12	16	2.1	6.7		
Cappuzzo *et al.* (ONCOBELL)	FISH	42	48	6.4	NR	64	[25]
Never-smokers							
Lee *et al.*		72	55	5.5	19.7	76	[64]
Cappuzzo *et al.*	Never smoker or FISH)	42	48	6.4	NR	64	[25]
Bronchioloalveolar carcinoma							
West *et al.*		101	17	4	13	51	[65]
Cadranel *et al.*		88	13	2.9	13.3	55	[66]

*EGFR mutations were primarily exon 19 deletions (53%) and L858R (26%), although 21% of mutation-positive cases had less-common subtypes, including exon 20 insertions, T790M/L858R, G719A and L861Q.
‡Del 19 or L858R.
§Other mutations.
EGFR: EGF receptor; MST: Median survival time; NR: Not reported; PFS: Progression-free survival time; TTP: Time to progression.

3 weeks), whereas INTACT-2 used carboplatin and paclitaxel (carboplatin given at AUC of 6 and paclitaxel at 225 mg/m^2 in 3-h infusions every 3 weeks). Chemotherapy was administered for up to six cycles and gefitinib or placebo were continued in nonprogressing patients until progression. A total of 1093 and 1037 patients were entered, respectively, in the two studies in less than 1 year of accrual. These two large randomized studies failed to demonstrate a survival increase with the addition of gefitinib to standard chemotherapy in first-line treatment of advanced NSCLC. A subset analysis of patients with adenocarcinoma who received 90 days of chemotherapy or more in the INTACT-2 study demonstrated statistically significant prolonged survival, suggesting a gefitinib maintenance effect. In general, treatment was well tolerated and the toxicity of chemotherapy did not overlap with gefitinib treatment, which made the studies feasible. However, as expected, gefitinib 500 mg was associated with a higher degree of toxicity, as observed in the IDEAL studies, which led to more dose reductions and treatment interruptions. In none of these studies were patients selected based on EGFR expression or any other marker of efficacy, and this lack of patient selection may have caused the lack of positive outcome. In addition, the antagonistic effect of EGFR TKIs may also halt cells in the G_1 phase of their cycle and, therefore, render them insensitive to chemotherapy. Interestingly, however, the time-to-progression curves and survival curves suggest that maintenance EGFR inhibition may be helpful after termination of chemotherapy. These considerations would suggest that sequential therapies are the best approach to this disease for front-line therapy.

The Southwest Oncology Group trial, SWOG0023, was designed to deliver gefitinib after completion of chemoradiotherapy and consolidation chemotherapy, avoiding a potentially negative interaction with chemotherapy. In this randomized, placebo-controlled trial in unresectable stage III NSCLC, gefitinib maintenance therapy failed to show a survival advantage in an unplanned interim analysis; the inferior survival observed in the gefitinib arm raises the possibility of a deleterious effect [68]. The reasons for this result remain unclear. Recently,

Hida *et al.* reported the results of a randomized Phase III trial (WJTOG0203), which evaluated whether gefitinib improves survival as sequential therapy after platinum-doublet chemotherapy in advanced NSCLC (stage IIIb/IV) [17]. In this study, sequential gefitinib following dual platinum-based induction therapy improved PFS (hazard ratio [HR]: 0.68; 95% confidence interval [CI]: 0.57–0.80; $p < 0.001$), with a trend toward improved overall survival ($p = 0.10$). Furthermore, a prespecified subset analysis showed that gefitinib significantly increased overall survival for patients with adenocarcinoma (n = 467; HR: 0.79; 95% CI: 0.65–0.98; $p = 0.03$) and for smokers (n = 410; HR: 0.79; 95% CI: 0.64–0.98; $p = 0.03$). However, gefitinib failed to show a significant survival advantage in patients with nonadenocarcinoma. These results demonstrate a possible clinical benefit for sequential therapy of gefitinib, especially in adenocarcinoma histology. Regarding the maintenance effects, although no benefit with concurrent EGFR TKI was seen in response rate, PFS or OS in the INTACT 2 and Tarceva responses in conjunction with paclitaxel and carboplatin (TRIBUTE) trials, landmark analyses of them favored patients receiving single-agent TKI maintenance therapy after completion of chemotherapy (Table 3) [14,15].

Gefitinib versus best supportive care

In the ISEL study, 1692 patients from 28 countries (not including Japan) were randomized to receive gefitinib 250 mg/day versus placebo [12]. Approximately 20% of the patients included in the study were Asians. Among the subjects, 1129 were assigned to the gefitinib group and 563 to the placebo group. Although the response rate was similar to that observed with erlotinib in BR.21 [8], in the ISEL study, gefitinib failed to prolong survival in comparison with placebo in the overall population. As for the differences in the ISEL and BR.21 patient populations, 90% of the patients in ISEL were chemorefractory, while patients in BR.21 were not required to be refractory to their previous treatment [8,12]. Median survival was 5.6 months for gefitinib and 5.1 months for placebo ($p = 0.08$; HR: 0.89; 95% CI: 0.77–1.02). Among the 812 patients with adenocarcinoma, median survival times were 6.3 and 5.4 months, respectively ($p = 0.09$; HR: 0.84; 0.49–0.92). However, gefitinib prolonged survival in never-smokers (median survival time [MST]: 8.9 vs 6.1 months; $p = 0.012$) as well as in Asian patients (MST: 9.5 vs 5.5 months; $p = 0.01$) in preplanned subset analyses. Based on these results, the FDA limits the indication of gefitinib to cancer patients who are currently benefiting or have previously benefited from gefitinib treatment or are enrolled in clinical trials as of June 2005.

Gefitinib versus chemotherapy in pretreated advanced NSCLC

Recently, the results of two large Phase III studies were reported (INTEREST and V-15-32). The INTEREST trial compared gefitinib with docetaxel as the second- or third-line therapy in 1466 advanced NSCLC patients with prior treatment of platinum-based chemotherapy [18,69]. Noninferiority of gefitinib in OS was demonstrated (MST: 7.6 vs 8.0 months; HR: 1.020; 95% CI: 0.905–1.150). The one point that should be highlighted in this study is that all of the predictors of efficacy identified in the gefitinib versus placebo studies, including adenocarcinoma, women, Asian and never-smoker, disappear in the comparison with the docetaxel group. The results suggest that these clinical characteristics may be efficacy predictors for docetaxel as well as gefitinib. Gefitinib and docetaxel were equally effective as the second-line therapy for advanced NSCLC patients but gefitinib resulted in an improved quality of life and less toxicity compared with docetaxel. Recently, Douillard *et al.* reported that OS was equally improved with both gefitinib or docetaxel treatments in *EGFR* mutation positive patients compared with *EGFR* mutation-negative patients [69]. On the other hand, PFS was longer with gefitinib than docetaxel in mutation-positive patients [69]. In the V-15-32 trial, however, noninferiority of gefitinib was not demonstrated [19]. The V-15-32 trial, almost identical to the INTEREST trial comparing gefitinib with docetaxel, was a comparative study of 489 patients that was conducted in Japan. The response rate in the gefitinib group was approximately twice as high as in the docetaxel group, but it was impossible to demonstrate noninferiority in OS of gefitinib compared with docetaxel. The survival rate at an early stage, such as less than 1 year, and the CI for therapeutic effects indicated that docetaxel was better than gefitinib. While noninferiority in OS between gefitinib and docetaxel was not demonstrated according to predefined criteria, there was no statistically significant difference in survival between the two arms. This discrepancy in survival between the INTEREST and V-15-32 could be attributable to the smaller patient numbers and imbalances in poststudy treatments in the V-15-32 trial (36% in the gefitinib vs 53% in the docetaxel arm had switched over to the opposite treatment after discontinuation of the study treatment). These two studies established the fact that gefitinib is better tolerated than docetaxel with less toxicities and better quality of life. Recently, Lee *et al.* reported the results of randomized Phase III study (Iressa as Second line Therapy in Advanced NSCLC-Korea [ISTANA]) conducted in Korea [70]. They concluded that PFS was longer with gefitinib compared with docetaxel ($p = 0.04$).

Gefitinib versus chemotherapy as first-line therapy in NSCLC

The result of IPASS has been reported [20]. This large-scale randomized study, which compared gefitinib monotherapy with carboplatin/paclitaxel for previously untreated patients with adenocarcinoma who were never- or light-smokers, was started in April 2004. The results showed improved PFS time in the gefitinib arm; however, the HR was constant over time, initially favoring the carboplatin/paclitaxel arm and later favoring the gefitinib arm, indicating the possibility of gefitinib as the first-line therapy in selected patients. Results of this pivotal trial might establish the role of gefitinib as the first-line therapy in selected patients with advanced NSCLC (Table 3).

Randomized trials currently in progress

At present, the West Japan Oncology Group is conducting a multicenter clinical trial (WJTOG3405) that targets progressive/recurrent lung cancer patients with *EGFR* gene mutations

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*	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*		

*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 response 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.

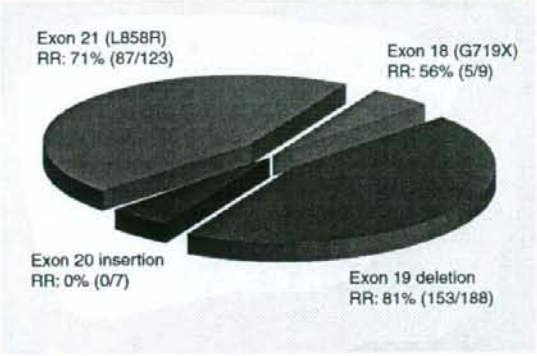

Figure 2. Distribution of EGF receptor mutations and response rates to EGF receptor tyrosine kinase inhibitors.
RR: Response rate.

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

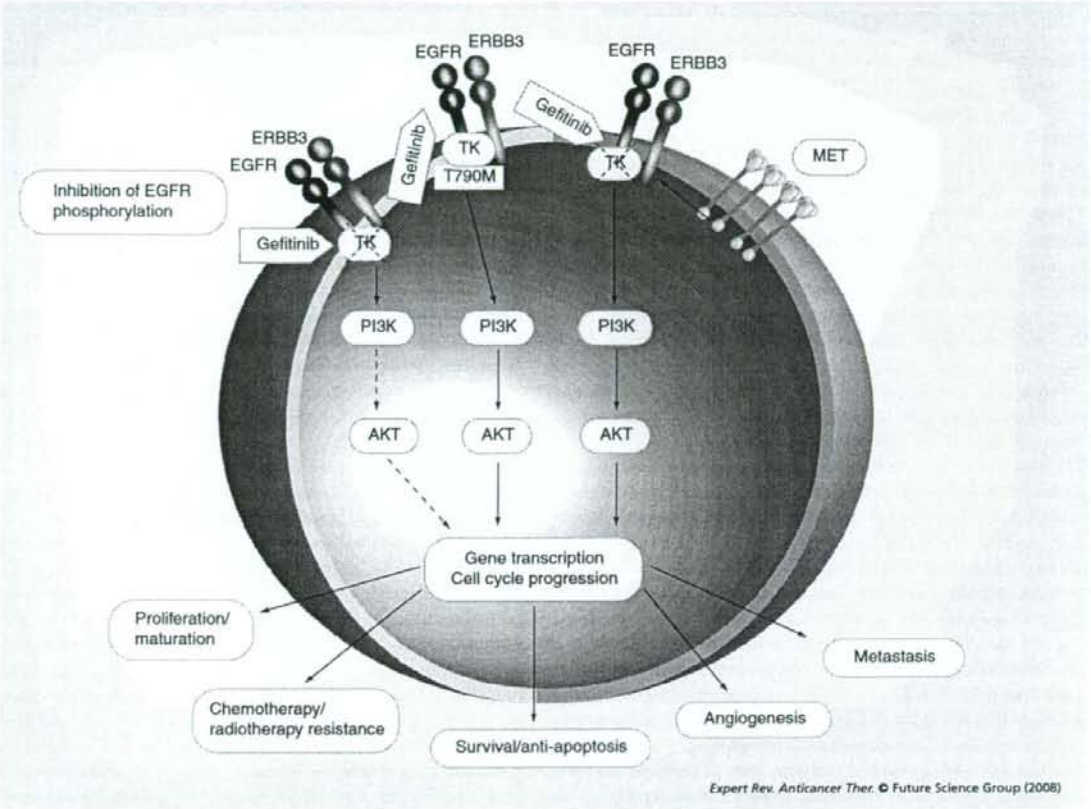

Figure 3. Mechanism of action of gefitinib signal-transduction blockage through EGFR TK and mechanisms of acquired resistance to gefitinib. When gefitinib is administered, EGFR TK is specifically inhibited and the survival signal is blocked leading to apoptosis of cancer cells. When a secondary threonine-to-methionine 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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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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Prognostic factors for lung cancer patients with brain metastases treated with whole brain radiotherapy.

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Sub-category: Local-Regional Therapy
Category: Lung Cancer--Local-Regional and Adjuvant Therapy
Meeting: 2008 ASCO Annual Meeting

Abstract No: 7570
Citation: *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 7570)
Author(s): N. Horiuchi, H. Okamoto, N. Hida, K. Naoki, T. Shimizu, K. Watanabe, A. Ishizaka

Abstract: **Background:** The purpose of this retrospective study was to clarify the role of whole brain radiotherapy (WBRT) in lung cancer patients with brain metastases (BM). **Methods:** Between February 1998 and October 2005, 103 consecutive lung cancer patients received WBRT for BM. The patients included 77 men and 26 women, ranging in age from 34 to 84 years with a median age of 65 years. Thirty- six of the patients had SCLC and 67 had NSCLC. Fifty-two patients had an ECOG performance status (PS) score of 0 to 2, and 51 had a PS score of 3 or 4. Seventy-nine patients (77%) had symptomatic BM, and 72 had multiple BM (70%). The mean dose of brain radiation was 38±8.3 Gy. Following radiation treatment, the median survival time (MST) for all patients was 4.0 months, and the 1-year survival rate was 14%. Multivariate analysis was performed using Cox proportional hazards model to evaluate the following: sex, age (<60 years vs. ≥60 years), histology (SCLC vs. NSCLC), PS score (0-2 vs. 3-4), number of BM (single vs. multiple), the presence or absence of neurological symptoms, the presence or absence of other metastases outside the brain, and lastly, any extracranial disease activity, including active or inactive primary lesions. **Results:** WBRT improved the neurological symptoms in 45 patients out of 75 symptomatic patients (60%). When multivariate analysis was performed, the favorable prognostic factors consisted of females (p=0.017), a PS score 0-2 (p=0.006), and extracranial disease activity including primary lesions (p=0.004). Based on these three prognostic factors, we subdivided the patients into four groups; the low-risk group had no risk factors, the mild-risk group had one, the moderate-risk group had two, and the high-risk group had three. The MST for the four subgroups was as follows: 548 days for the low-risk group, 195 days for the mild-risk group, 95 days for the moderate-risk group, and 58 days for the high-risk group. **Conclusions:** Although WBRT was an effective palliative treatment for lung cancer patients with BM, the MST for the high-risk group was somewhat disappointing. Further studies are necessary to evaluate quality of life and MST with or without WBRT for high-risk group patients with lung cancer.

Abstract Disclosures

Associated Presentation(s):

1. **Prognostic factors for lung cancer patients with brain metastases treated with whole brain radiotherapy.**
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Association between incremental gains in the objective response rate and survival improvement in phase III trials of first-line chemotherapy for extensive disease small-cell lung cancer

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Background: The duration of, resources required for and cost of clinical trials could be reduced if a surrogate end point was to be used in place of survival. We assessed the extent to which the objective response rate (ORR) is predictive of mortality, how much difference in the ORR is needed to predict an obvious survival difference and what factors could affect the association between the two parameters during the first-line treatment of extensive disease (ED)-small-cell lung cancer (SCLC).

Methods: We used the ORRs and median survival times (MSTs) from 48 phase III trials of first-line chemotherapy involving 8779 randomised patients with ED-SCLC in a linear regression analysis. The MST difference was calculated as the difference in MST between the investigational and reference arms; the ORR difference was similarly defined.

Results: ORR difference between the treatment arms was modestly associated with the MST difference in the overall trials ($R^2 = 0.3314$). In contrast, the relationship was stronger among only trials in which prophylactic cranial irradiation was given to those having an objective response to the initial chemotherapy ($R^2 = 0.6279$). In this trial setting, large differences in ORR were needed to predict a survival advantage (1.2-day survival advantage per 2% increase in ORR).

Conclusions: In the first-line treatment of ED-SCLC, a favourable relationship was detected between the two parameters in the selected trial setting. Large ORR differences were needed to predict a survival benefit, clearly suggesting the need for new chemotherapeutic agents.

Key words: lung cancer, objective response, overall survival

original article

introduction

Lung cancer is a leading cause of cancer-related death, and small-cell lung cancer (SCLC) accounts for ~15% of all lung cancer cases. SCLC is clinically categorised according to the disease extent as either limited disease (LD)- or extensive disease (ED)-SCLC. The standard first line of treatment of ED-SCLC is platinum-based chemotherapy with cisplatin–etoposide or cisplatin–irinotecan [1, 2]. The outcome, however, is unsatisfactory, with a median survival time (MST) of ~1 year, indicating the need for novel anticancer agents.

In developing new agents, the most important issue is whether they prolong survival. This is usually evaluated in phase III trials, in which the primary end point is traditionally overall survival (OS). Phase III trials, however, are both expensive and time consuming. Moreover, a recent review of all North American phase III randomised trials for patients with ED-SCLC conducted from 1972 to 1990 determined that only 5 (24%) of 21 trials found a significant, but small, survival advantage, with a survival difference ranging from 0.8 to 3.0 months in the experimental arm compared with the control arm [3]. Considering these findings, early and accurate screening of the agents to be investigated in phase III trials is essential.

As spontaneous cancer regression is a rare event, assuming that tumour regression after treatment is attributable entirely to a treatment effect is reasonable. For this reason, the objective response rate [ORR; complete response (CR) rate and partial response (PR) rate] has historically been considered a clear indicator of antitumour activity and a surrogate for clinical benefit [4]. The ORR has the additional advantage of being an early clinical trial end point, generally reached within just 2–3 months of treatment initiation [5].

The duration, human resources required for and cost of clinical trials could be reduced if a surrogate end point was to be properly used in place of survival. To date, however, (i) the extent to which the OR is predictive of mortality in the first-line treatment of patients with ED-SCLC has not been fully assessed, even though an association itself between OR and OS has been reported [5]. In addition, (ii) how much time of OS increases as ORR increases in this disease has not been formally

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evaluated. Furthermore, (iii) knowing what factors can affect the association between the ORR and OS would be of interest to generate relevant hypotheses in future studies. Here, we investigated the association between ORR and OS to address each of the above-mentioned points.

methods

search for trials

We searched for trials that had been conducted from January 1990 to August 2008, as previous reports relied on studies that had been conducted within the past 15–20 years. To avoid publication bias, published and unpublished trials were identified through a computer-based search of the PubMed database and abstracts from past conferences of the American Society of Clinical Oncology (1998–2008) using the terms lung neoplasm, carcinoma, small cell, chemotherapy and randomised controlled trial. The search was also guided by a thorough examination of reference lists from original articles, review articles, relevant books and the Physician Data Query registry of clinical trials.

selection of trials

Phase III randomised controlled trials were considered if they compared first-line, systemic chemotherapy for ED-SCLC that included cytotoxic agents, providing year of trial initiation. Trials were excluded if they investigated immunotherapeutic regimens or if they enrolled only responders to the initial round of chemotherapy. Trials that were initially designed to assess combined modality treatments, including radiotherapy and surgery concurrently with the initial chemotherapy, were also considered ineligible, whereas those involving the sequential use of these therapies or prophylactic cranial irradiation (PCI) after the induction of chemotherapy were allowed. Some phase III trials included patients with both LD- and ED-SCLC. These were considered eligible only if survival data for the patients with ED-SCLC could be obtained. The definitions of LD- and ED-SCLC varied somewhat in the different groups, but we could not reallocate the patients because of our inability to access each patient database. Instead, we applied the definitions described in each original report to this study. If no relevant descriptions were documented, we assumed that the definitions in the trial were based on the guidelines that existed at the time the trial was initiated [6, 7]. The control arms in each phase III trial were identified based on the statement in each trial.

data abstraction

To avoid bias in the data-abstraction process, four medical oncologists (IO, NO, YF and KH), one of whom holds a board certificate for medical oncology (KH), independently abstracted the data from the trials and subsequently compared the results. The following information was obtained from each report: the year of trial initiation (year when the first patient was accrued), the number of patients enrolled and randomised, the median patient age, the proportion of patients who had a good performance status (PS), the proportion of patients who were male and who had brain metastasis, the chemotherapeutic regimen, the definition of ED, the description of the administration of sequential thoracic irradiation, surgery or PCI as part of the trial design and the MST (per treatment arm). All data were checked for internal consistency, and disagreements were resolved by discussion among the investigators. For trials with more than two treatment arms, we constructed multiple pairs for the investigational and reference arms.

quantitative data synthesis

To investigate the association between differences in ORR and MST, we defined the MST difference as the difference in MST between the investigation and reference arms; similarly, the ORR difference was defined as the ratio of the ORR in the investigation arm to the ORR in the reference arm (all measures in months). The information from the phase III trials was evaluated using a multiple stepwise regression model (with the following stepping method criteria: probability of F to enter of ≤ 0.05 and to remove of ≥ 0.10) to determine whether the following factors independently affected the MST difference: ORR difference, year of study, definition of ED, ratio of patients with a good PS in the investigational arm to those in the reference arm and a trial design including PCI for those with an OR (CR/PR) to the induction of chemotherapy. All analyses were weighted by trial size. The data were used to determine whether each factor had an independent impact on the survival of patients with ED-SCLC who were treated in the phase III studies. All P values corresponded to two-sided tests; significance was set at $P < 0.05$. The strength of each association was defined a priori using commonly accepted criteria for the proportion of variation (R^2) as follows: 0–0.29, little or no association; 0.30–0.69, moderate or weak association and 0.70–1.00, strong association [8].

results

trials included in the analysis

Of the 2166 trials screened, 48 trials for ED-SCLC were identified as having data regarding OS and ORR (Figure 1). A total of 8779 patients were randomly allocated to 100 chemotherapeutic arms. Of these 48 trials, two had three treatment arms and one had four treatment arms; thus, 52 trial pairs were in the investigational arm versus the reference arm (Table 1). Of these trials, most had high proportions of male patients and patients with a good PS. The response criteria were described in 43 of the 52 trials. Approximately half of the trials used the response criteria of the World Health Organisation (WHO). Regarding the chemotherapeutic regimens, cisplatin plus etoposide-containing regimens were most frequently evaluated in both the investigational and reference arms (25 and 27 arms, respectively), while a cyclophosphamide, adriamycin and vincristine regimen was used in 17 and 23 arms, respectively.

degree of association between the MST and ORR differences

We plotted the MST and ORR differences (Figure 2). A modest relationship was detected between the ORR and MST differences ($R^2 = 0.3314$), suggesting that the ORR difference between the investigational and reference arms could predict 33.1% of the variance in the MST difference between the arms.

Next, we assumed that this association would be closer if the trials were limited to those in which the response criteria were clearly defined; the relationship between the two parameters, however, was not as so different as expected ($n = 43$; $R^2 = 0.1949$). In addition, we assessed whether the association could be affected by the type of response criteria, but it was nearly consistent irrespective of using the WHO criteria for response assessment [$R^2 = 0.1340$ ($n = 23$) versus 0.2765 ($n = 20$) for those trials in which the WHO criteria and other criteria were used, respectively].

To rule out potential confounding variables between the ORR difference and other trial characteristics, we conducted a multiple linear regression analysis for the MST difference. The stepwise multiple regression model used excluded all covariates

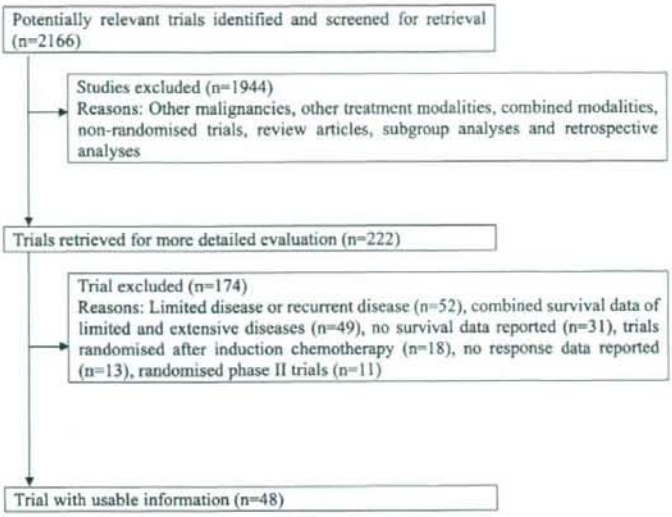

Figure 1. Flowchart showing the review process for the trials.

Table 1. Trial demographics and chemotherapeutic regimens in the 52 trial pairs

Trial characteristics	
Median no. of randomly assigned patients per trial (range)	142 (33–784)
Published year (median, range)	1997 (1990–2008)
Year of trial initiation (median, range)	1990 (1983–2006)
Percentage of patients with a good PS (median, range)	80 (35–100)
Percentage of male patients (median, range)	81 (56–93)
Trials including the administration of PCI to those with an objective response to the initial treatment (yes/no)	20/32
Definition of extensive disease (yes/no)	36/16
Description of the response criteria (yes/no)	43/9
World Health Organisation	23
European Cooperative Oncology Group	2
RECIST	1
Japan Lung Cancer Society	1
Described, but no criteria type documented	16

Good PS was defined as a PS of zero or one.
PS, performance status; PCI, prophylactic cranial irradiation; RECIST, response evaluation criteria in solid tumours.

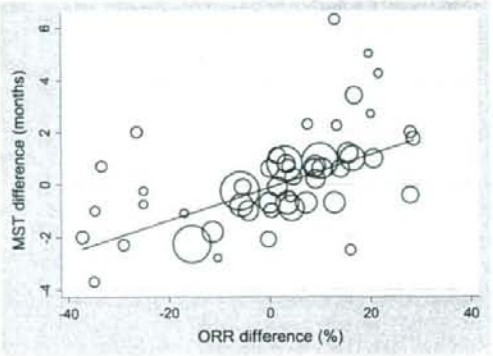

Figure 2. Correlations between the median survival time (MST) difference between the investigational and reference arms and differences in the objective response rate (ORR) in the eligible trial pairs weighted by the number of randomised patients ($R^2 = 0.3314$). The R^2 scores suggest that the ORR difference between the investigational and reference arms could explain 33.1% of the variance in the MST difference between the arms. Each trial is represented by a circle; the size of each circle is proportional to the number of randomised patients.

except the ORR difference. This turned out to be a significant factor affecting the MST difference ($P = 0.003$); however, only 31.6% of the variance in the MST ratio was accounted for even by this model ($R^2 = 0.3156$).

association between the MST and ORR differences in several subgroups

To investigate whether the trial setting could affect the relationship between the MST and ORR differences, eligible

Table 2. Degree of association between the ORR and MST differences in various clinical settings in the simple regression analysis

	No. of trials	Regression coefficient	R^2
Overall	52	0.063	0.3314
Various subgroups			
Trials including PCI for those with an objective response to the initial therapy			
Yes	20	0.083	0.6279
No	32	0.053	0.2254
CAV regimen			
Yes	24	0.062	0.3302
No	28	0.063	0.3264
PE regimen			
Yes	32	0.062	0.3376
No	20	0.064	0.3185
Trial design of additional thoracic irradiation			
Yes	14	0.061	0.4954
No	38	0.063	0.2937
Published year			
1996 or before	26	0.037	0.2346
1997 or later	26	0.094	0.4671
% of good PS patients			
≥80[a]	12	0.061	0.3351
<80[a]	13	0.092	0.4505

All analyses were weighted by trial size.
[a]Median percent of patients with good PS.
ORR, objective response rate; MST, median survival time; R^2, the proportion of variation; PCI, prophylactic cranial irradiation; CAV, cyclophosphamide, doxorubicin and vincristine; PE, cisplatin and etoposide; PS, performance status.

trial pairs were divided into several subgroups (Table 2). We found a stronger association between the two parameters for those trials in which all the patients with an OR to the initial chemotherapy were given PCI ($R^2 = 0.6279$; Figure 3A), whereas a weaker association was found in those trials without that type of design ($R^2 = 0.2254$; Figure 3B). None of the other characteristics assessed seemed to affect the association (Table 2).

predicted MST difference based on the fitted model for those trials with the PCI setting

We next constructed a fitted formula for predicting the MST difference using the actual ORR difference for those trials that included PCI as part of their design in which a high R^2 value was obtained:

> Predicted MST difference between the investigational and reference arms = 0.083 × (actual ORR difference) − 0.125.

The predicted MST differences are listed in Table 3 according to the various ORR differences. For example, when the investigational regimen was expected to yield a 10% increase in the ORR as compared with the state-of-the-art regimen, the MST was predicted to increase only by 0.7 months (21.2 days) in the investigational arm.

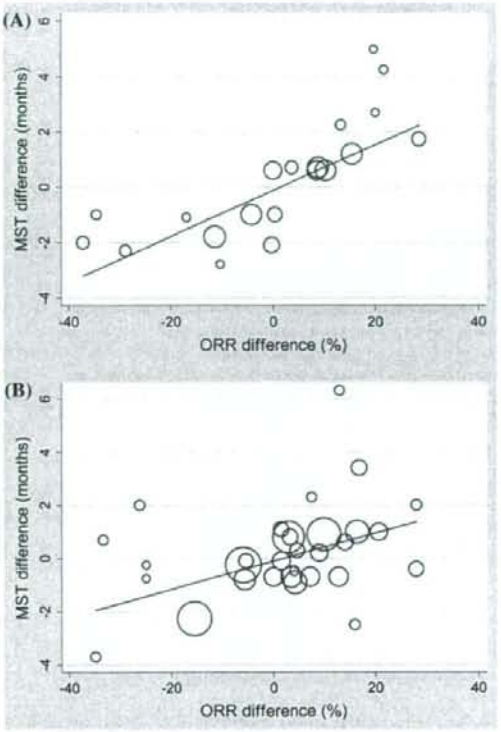

Figure 3. Correlations between the median survival time (MST) difference and objective response rate (ORR) difference between the investigational and reference arms in trials (**A**) designed to administer prophylactic cranial irradiation (PCI) to those with an objective response to the inductive therapy ($R^2 = 0.6279$) or (**B**) not ($R^2 = 0.2254$). The analysis was weighted by the number of randomised patients. The R^2 scores suggest that the ORR difference between the investigational and reference arms could explain as much as 62.8% of the variance in the MST difference between the arms in trials including PCI, while in the trials without PCI, the MST difference was less exactly accounted for by the ORR difference (22.5%). Each trial is represented by a circle; the size of each circle is proportional to the number of randomised patients.

discussion

In this study, we found a modest association between the ORR and MST differences in the complete trial ($R^2 = 0.3314$; Figure 2). In contrast, the design of PCI setting for all responders to the initial chemotherapy favourably affected the relationship ($R^2 = 0.6279$; Figure 3A). In this setting, large differences in ORR were needed to predict a survival benefit (1.2-day survival advantage per 2% increase in ORR).

Note that the relationship was stronger only for those trials in which PCI was assigned to all patients with an OR to the initial treatment ($R^2 = 0.6279$; Figure 3A). One would postulate that this result is related to the ability of anticancer agents to penetrate the blood–brain barrier (BBB). Apart from clinically

Table 3. Predicted MST difference according to the ORR difference

ORR difference[a] (%)	Predicted MST difference[a], months (days)
2.5	0.1 (2.5)
5.0	0.3 (8.7)
7.5	0.5 (14.9)
10.0	0.7 (21.2)
12.5	0.9 (27.4)
15.0	1.2 (33.6)
17.5	1.4 (39.8)
20.0	1.6 (46.1)

[a]Difference between the investigational and reference arms. For example, when an investigational regimen was expected to yield a 10% increase in the ORR as compared with the standard regimen, the MST was predicted to increase by 0.7 months (21.2 days) in the investigational arm.
ORR, objective response rate; MST, median survival time.

obvious cranial metastases, which would be sensitive to systemic chemotherapy because of an impaired BBB [9], radiologically undetected micrometastases in the brain, which are common in patients with ED-SCLC, are generally considered to be insensitive to chemotherapy because they are able to hide behind the still-intact BBB [9]. Thus, even if systemic chemotherapy was effective against detectable extracranial diseases, such small undetectable cranial diseases could continue to grow without the use of PCI, possibly resulting in a poor outcome. That could explain why a tight association was not observed between the radiological response and survival data. However, with the PCI setting for responders to the initial chemotherapy, such a difference in the response pattern between extracranial and intracranial diseases would theoretically be minimised. This may be why a stronger association between the radiological response and survival was observed when only those trials that included PCI as part of their design were assessed in the analysis (Figure 3A). This hypothesis requires further study. Other clinical factors including PS examined did not seem to influence the relationship between ORR and MST (Table 2), while a number of studies have shown that PS has impacts on outcome [10–12]. This would simply reflect that good PS patients can respond well to chemotherapies and survive longer and that poor PS patients hardly respond to them, resulting in the poor outcome.

In addition, knowing how much of a difference in ORR is needed to predict an obvious survival difference in ED-SCLC is also clinically necessary. In their abstracted database study, Johnson et al. [13] investigated the role of ORR as a surrogate marker in the treatment of advanced non-small-cell lung cancer (NSCLC) by comparing incremental differences in MST between the arms with those in ORR. The formula they used to predict the MST difference was nearly identical to ours, except for the difference in cancer type: MST difference = 0.090 × (the ORR difference) − 0.048. Using this formula for patients with NSCLC, if the investigational regimen was expected to yield a 10% increase in the ORR as compared with the standard regimen, the MST was predicted to increase by only 0.9 months (25.6 days) in the investigational arm. Given either formula, one could intuitively predict the survival benefit of a new therapy by comparing the OR data from their early clinical trials with the ORR for the state-of-the-art therapy. At any rate, both sets of results indicate that, irrespective of the small- or non-small-cell subtype, the survival advantage would be small even if a relatively large ORR difference was obtained.

Few randomised trials of metastatic lung cancer have reported hazard ratios, and predictions based on this measure would not be representative and could be biased. Additionally, differences in follow-up duration between trials could affect the calculated hazard ratios. For these reasons, the MST was used in this study to ensure that all trials were long enough to capture the relevant end points in at least half of the patients. The reason for this pragmatic approach is that the value of a treatment of metastatic disease is usually measured in terms of incremental survival gains rather than the proportional or absolute risk of death [13].

Trial-level surrogacy as described here is not necessarily linked to individual-level surrogacy; thus, our data cannot be used to predict an individual's chance of survival on the basis of their response to treatment. Analyses based on data derived from both sources have strengths and weaknesses [14]. Although the use of individual patient data (IPD) restricts the analysis to a limited number of trials and the analysis is not easily replicated by independent researchers, it allows better characterisation of important covariates that affect survival. Future investigations using IPD could show a more precise relationship between survival and the response to treatment. In addition, as a point to be discussed, assessment of response rate would be variable and unreliable. It is well documented that response rates have dropped in recent years as more rigorous criteria are used. This is borne out by the fact that the correlation dropped in studies with clearly defined response criteria. Using differences in response rates rather than absolute values would help address this.

In conclusion, in this study, we found a favourable relationship between the ORR and MST differences for trials in which those who responded to the initial chemotherapy subsequently received PCI. Given the recent finding of a survival advantage from PCI even in patients with ED-SCLC [15], the frequency at which PCI is used for responders to the initial treatment will likely increase. Considering such circumstances, ORR data may be useful for predicting how much improvement in OS can be obtained. In contrast, large differences in ORR are needed to predict a survival benefit, strongly suggesting the need for the development of new chemotherapeutic agents in ED-SCLC.

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