Table 4
Grade 3 or worse toxicity.

	UP arm (n = 35)				NP arm (n = 31)				P
	Grade		≥Grade 3		Grade		≥Grade 3		
	3	4	No.	(%)	3	4	No.	(%)	
Hematologic									
Leucopenia	7	1	8	22.9	14	5	19	61.3	0.0024
Neutropenia	3	4	7	20.0	8	10	18	58.1	0.0022
Anemia	2	0	2	5.7	2	0	2	6.5	1.000
Thrombocytopenia	1	0	1	2.9	1	0	1	3.2	1.000
Febrile neutropenia	0	0	0	0	4	0	4	12.9	0.0437
Non-hematologic									
Anorexia	5	0	5	14.3	3	0	3	9.7	0.7132
Nausea/vomiting	4	0	4	11.4	2	0	2	6.5	0.6762
Diarrhea	2	0	2	5.7	0	0	0	0	0.4942
Infection	0	0	0	0	2	0	2	6.5	0.2168
Pneumonitis	2	0	2	5.7	0	2[a]	2	6.5	1.000

[a] Both patients died of radiation pneumonitis.

might rise to a less toxic new standard regimen in comparison with the third-generation regimen for locally advanced NSCLC.

S-1 is a novel oral fluoropyrimidine agent designed for enhancing anticancer activity and reducing gastrointestinal toxicity. Indeed, it showed potent activity not only as a single agent but also in combination with CDDP for metastatic NSCLC [24,25]. In addition S-1 plus CDDP with concurrent TRT in a phase II study yielded high response rates, good survival data, and only mild toxicities [26,27]. Therefore oral fluoropyrimidines such as UFT and S-1 hereafter may play an important role in terms of concurrent chemoradiotherapy for locally advanced NSCLC.

As a limitation of this study, the radiation technique was old-fashioned. At the start of this multi-institutional study, 3D treatment planning system using CT was not available at all institutions. Therefore, both 2D and 3D treatment planning systems were allowed in the protocol. Because 3D dose constraints for both planning target volume and normal-risk organs were not determined by modern radiation technologies, the quality of radiotherapy in this study might have be rather lowered.

In conclusion, combined with concurrent TRT, UP achieved more favorable efficacy and safety than NP, suggesting it to be a promising candidate as a standard regimen with concurrent TRT for locally advanced NSCLC. Further evaluation of this regimen is warranted in a phase III setting in comparison with platinum-based third-generation chemotherapy with concurrent TRT.

Conflict of interest statement

None declared.

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REVIEW

Impact of EGFR Inhibitor in Non–Small Cell Lung Cancer on Progression-Free and Overall Survival: A Meta-Analysis

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Background The epidermal growth factor receptor (EGFR) signaling pathway is crucial for regulating tumorigenesis and cell survival and may be important in the development and progression of non–small cell lung cancer (NSCLC). We examined the impact of EGFR–tyrosine kinase inhibitors (TKIs) on progression-free survival (PFS) and overall survival (OS) in advanced NSCLC patients with and without EGFR mutations.

Methods Randomized trials that compared EGFR-TKIs monotherapy or combination EGFR-TKIs-chemotherapy with chemotherapy or placebo were included. We used published hazard ratios (HRs), if available, or derived treatment estimates from other survival data. Pooled estimates of treatment efficacy of EGFR-TKIs for the EGFR mutation–positive ($EGFRmut^+$) and EGFR mutation–negative ($EGFRmut^-$) subgroups were calculated with the fixed-effects inverse variance weighted method. All statistical tests were two-sided.

Results We included 23 eligible trials (13 front-line, 7 second-line, 3 maintenance; n = 14570). EGFR mutation status was known in 31% of patients. EGFR-TKIs treatment prolonged PFS in $EGFRmut^+$ patients, and EGFR mutation was predictive of PFS in all settings: The front-line hazard ratio for $EGFRmut^+$ was 0.43 (95% confidence interval [CI] = 0.38 to 0.49; $P < .001$), and the front-line hazard ratio for $EGFRmut^-$ was 1.06 (95% CI = 0.94 to 1.19; $P = .35$; $P_{interaction} < .001$). The second-line hazard ratio for $EGFRmut^+$ was 0.34 (95% CI = 0.20 to 0.60; $P < .001$), and the second-line hazard ratio for $EGFRmut^-$ was 1.23 (95% CI = 1.05 to 1.46; $P = .01$; $P_{interaction} < .001$). The maintenance hazard ratio for $EGFRmut^+$ was 0.15 (95% CI = 0.08 to 0.27; $P < .001$), and the maintenance hazard ratio for $EGFRmut^-$ was 0.81 (95% CI = 0.68 to 0.97; $P = .02$; $P_{interaction} < .001$). EGFR-TKIs treatment had no impact on OS for $EGFRmut^+$ and $EGFRmut^-$ patients.

Conclusions EGFR-TKIs therapy statistically significantly delays disease progression in $EGFRmut^+$ patients but has no demonstrable impact on OS. EGFR mutation is a predictive biomarker of PFS benefit with EGFR-TKIs treatment in all settings. These findings support EGFR mutation assessment before initiation of treatment. EGFR-TKIs should be considered as front-line therapy in $EGFRmut^+$ advanced NSCLC patients.

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The greatest changes in the treatment of advanced non–small cell lung cancer (NSCLC) have been novel molecular-targeted agents and the concomitant ability to personalize treatment. Controversy continues in many areas related to the incorporation of these changes into clinical medicine. How should such therapy be selected for individual patients? Is molecular testing required or is the use of demographic factors (such as histologic NSCLC type, sex, smoking history) sufficient for personalizing therapy? Questions remain concerning whether therapy with chemotherapy or with agents affecting the epidermal growth factor receptor (EGFR) influence progression-free survival (PFS) and/or overall survival (OS) in patients who do or do not harbor known mutations associated with EGFR. Is PFS a good surrogate for OS, or is PFS a useful endpoint on its own? Data directed at answering these controversies can guide oncologists in interpreting trials and in making more appropriate diagnostic and therapeutic choices for hundreds of thousands of patients each year.

The objective of this meta-analysis is to estimate better the treatment effect of EGFR–tyrosine kinase inhibitors (TKIs) on PFS and OS while examining for heterogeneity of treatment effects between groups of patients with and without EGFR mutations. The EGFR signaling pathway is crucial for regulating tumorigenesis and cell survival and may be overexpressed in the development and progression of NSCLC (1–3). Patients with activating somatic mutations in the region of the EGFR gene that encodes the tyrosine kinase domain are highly responsive to EGFR-TKIs (4–6). Previously published meta-analyses have been limited by studying the minority of patients with NSCLC—that is, the influence of EGFR-TKIs only in the population of patients harboring EGFR

mutations and predominantly in the front-line treatment setting (7–9). These meta-analyses have not demonstrated an OS advantage for patients with EGFR mutation treated with EGFR-TKIs. This analysis uses all trial data available to date and examines the effect of EGFR-TKIs treatment in major clinical settings—front-line, maintenance, and second-line or subsequent therapies. Additionally, the impact of EGFR-TKIs-chemotherapy combinations compared with EGFR-TKIs monotherapy is also explored. It is now recognized that as with EGFR mutations, other genetic alterations [such as EML-ALK abnormalities (10) and ROS-1 mutations (11)] are also more common in nonsmokers with adenocarcinoma, but these latter groups do not benefit from EGFR-TKIs–directed therapy. Such findings highlight the need for more specific molecular testing of patients and the need to include the most recent data from meta-analyses to understand better the treatment effects.

Individual trials and meta-analyses have clearly indicated that PFS and response rates are improved in patients with EGFR mutation who are treated with EGFR-TKIs, when compared with chemotherapy (7–9). The impact on OS is less clear, especially in patients treated beyond first-line therapy. Two separate trials have indicated that erlotinib is effective as second-line (12) and maintenance (13) therapy, with no statistically significant difference in treatment effect between those with EGFR mutation and wild-type tumors. However, a recent trial reported that chemotherapy was superior over erlotinib as second-line treatment for patients without EGFR mutations in exon 19 or 21 (14). Clearly, newer and larger meta-analyses are required to resolve these differences. Definitive analyses can provide stronger rationales for the choice of a specific therapy and can result in better utilization of health-care resources with these costly agents. For these reasons, we conducted this meta-analysis, which included the largest number of studies and patients to date with known EGFR mutation status and tested both PFS and OS as outcomes.

Methods

Study Eligibility and Identification

All randomized trials of EGFR-TKIs monotherapy vs any chemotherapy, EGFR-TKIs and chemotherapy vs the same chemotherapy alone, and EGFR-TKIs monotherapy vs placebo or best supportive care were eligible for inclusion.

Trials were identified from previous meta-analyses (7–9), and a search of Medline, Embase, CancerLit, and the Cochrane Central Register of Controlled Trials (CENTRAL) using the following terms: lung neoplasms, non-small cell lung cancer, gefitinib, erlotinib, EGFR, meta-analysis, systemic review, randomized, and clinical trials. Database searches were restricted to articles published in the English language between January 1, 2004, and June 6, 2012. Trials that enrolled patients with prior EGFR-TKIs treatment were excluded. Abstracts from conference proceedings of the American Society of Clinical Oncology, the European Society for Medical Oncology, and the World Lung Cancer Conference were searched to identify unpublished studies. Individual study sponsors (Hoffmann-La Roche and AstraZeneca) were contacted for relevant presentation slides and posters from these conferences when they were inaccessible from the websites. Individual investigators were also contacted if essential information relevant to this meta-analysis was unavailable from these sources.

Data Extraction

Information recorded from each trial included study name, year of publication or conference presentation, study design, line of treatment, and clinicopathological and demographic data. Mutational analysis data were also extracted, and the different methods of EGFR mutation assessment were recorded. We classified patients as EGFR mutation–positive ($EGFRmut^+$) based on the presence of a mutation as detected using molecular assessment tools such as Sanger sequencing, polymerase chain reaction clamp, and amplification refractory mutation system. Patients were classified as EGFR mutation–negative ($EGFRmut^-$) if no mutation was detected. We did not classify patients' EGFR mutation status based on immunohistochemistry and fluorescent in situ hybridization for EGFR gene copy numbers. Most trials analyzed exons 19 and 21 for EGFR mutations, and some trials also included exons 18 and 20.

Data were extracted independently by three authors (J. C.-H. Yang, C. K. Lee, and C. Brown), and discrepancies were resolved by consensus including a fourth author (V. Gebski).

Statistical Analyses

We extracted the hazard ratios (HRs) and the associated 95% confidence intervals (CIs) for PFS and OS outcomes to assess treatment efficacy within the $EGFRmut^+$ and $EGFRmut^-$ subgroups. Where available, we included the most updated OS data. If hazard ratios and confidence intervals were not reported, these were estimated where possible using the methods of Parmar (15).

Pooled estimates of the treatment efficacy of EGFR-TKIs for the $EGFRmut^+$ and $EGFRmut^-$ subgroups were calculated by using the fixed-effects inverse variance weighted method. We performed indirect comparisons to quantify the benefits of adding chemotherapy to EGFR-TKIs over EGFR-TKIs alone in both subgroups.

A sensitivity analysis was also conducted to examine the impact of the overall results from this study by limiting the analyses on front-line trials that were known to have determined EGFR mutation based on exons 19 and 21 only.

We used the $\chi 2$ Cochran Q test to detect for heterogeneity across the different studies and between subgroups defined by EGFR mutation status, study setting, and study design. The nominal level of significance was set at 5%. All 95% confidence intervals were two-sided.

Cochrane Review Manager (version 5, Cochrane Collaboration, Copenhagen, Denmark, http://ims.cochrane.org/home) was used for all analyses.

Results

The search strategy identified 40 studies, of which 23 (12–14,16–44) were eligible for inclusion in this meta-analysis (Figure 1). Trial data were obtained from published manuscripts and conference abstracts for 19 trials, and additional data on treatment efficacy by $EGFRmut^+$ and $EGFRmut^-$ subgroups were obtained directly from study investigators for four studies [ISEL (41), V-15-32 (31), TOPICAL (43), and IFCT-GFPC 0502 (32, 44)]. Treatment estimates for the TALENT study (37) were calculated on the basis of data extracted from presented survival curves. The hazard ratios for OS for ISEL (41), IFCT-GFPC 0502 (32,44), and V-15–32 (31) were estimated on the basis of the observed number of deaths. In all other studies, hazard ratios and associated variances were obtained directly from trial reports.

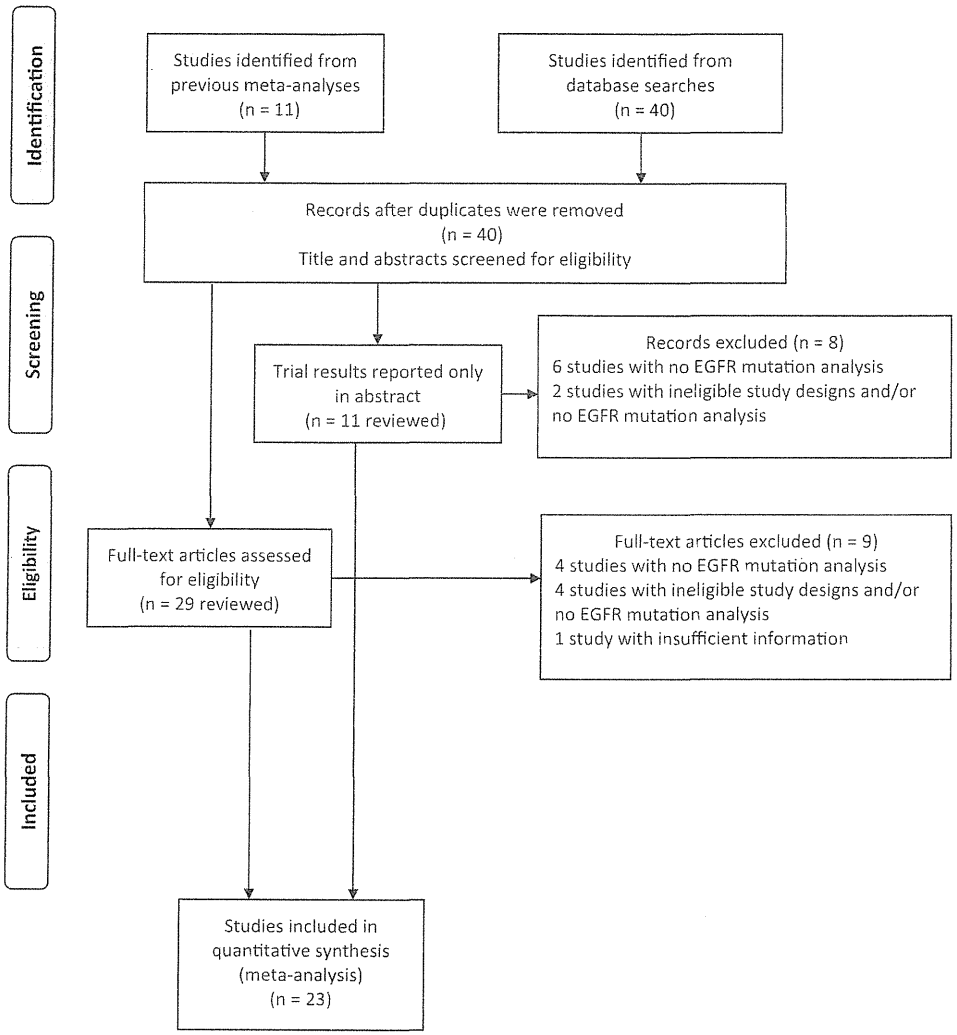

Figure 1. Flow diagram showing inclusion and exclusion of studies. EGFR = epidermal growth factor receptor.

A total of 14570 patients participated in these 23 trials. EGFR mutation status, as determined by mutation analysis only, was known for at least 31% (n = 4473) of trial patients. [In the TALENT study (37), the treatment comparisons for the subgroups were reported, but the number of patients in each subgroup was unknown.] Clinicopathological and demographic characteristics of patients enrolled in these studies are summarized in Table 1.

Trials investigated EGFR-TKIs for front-line therapy in treatment-naive patients (n = 13 trials), second-line or subsequent treatment after failure of chemotherapy (n = 7 trials), and maintenance treatment in patients with nonprogressive disease after front-line chemotherapy (n = 3 trials). Among the 13 front-line studies, eight compared EGFR-TKIs as monotherapy vs chemotherapy (16–21,23,27,33–35,38), four compared EGFR-TKIs with chemotherapy vs chemotherapy alone (22,24–26,37,45), and one was a placebo-controlled trial (36,43). Among the seven second-line and subsequent treatment trials, five compared EGFR-TKIs as monotherapy vs chemotherapy (12,14,28,29,31,42), and two were placebo-controlled studies (39–41). All three maintenance studies had a placebo arm (13,30,32,44).

Benefit of EGFR-TKIs on PFS in Different Settings

Data on PFS were available from 21 trials except ISEL (41) and BR21 (39). The treatment effect of EGFR-TKIs in different settings is shown in Figure 2. The test of interaction between treatment and EGFR mutation status was statistically significant (front-line setting: $P < .001$; second-line or subsequent treatment: $P < .001$).

In EGFRmut$^+$ patients, EGFR-TKIs treatment was associated with a lower risk of disease progression in the front-line setting (HR = 0.43; 95% CI = 0.38 to 0.49; $P < .001$) and second-line or subsequent treatment (HR = 0.34; 95% CI = 0.20 to 0.60; $P < .001$).

In EGFRmut$^-$ patients, EGFR-TKIs did not show a treatment advantage in the front-line setting or beyond. There was no statistically significant difference between EGFR-TKIs and chemotherapy in reducing the risk of disease progression in front-line therapy (HR = 1.06; 95% CI = 0.94 to 1.19; $P = .35$). EGFR-TKIs treatment was statistically significantly inferior to chemotherapy in second-line or subsequent therapy (HR = 1.23; 95% CI = 1.05 to 1.46; $P = .01$).

Maintenance therapy with EGFR-TKIs compared with placebo was effective in reducing the risk of disease progression in EGFRmut$^+$

Table 1. Demographic characteristics of patients*

Study name (year) (reference)	Treatment comparison	EGFR mutation assessment method	No. of EGFR+ patients (%)	No. of EGFR- patients (%)	No. of EGFR unknown patients (%)	Age, y, median	Asian, %	Males, %	Present/ former smokers, %	Adeno-carcinoma, %
Front-line treatment										
INTACT 1 (2004) (24,43)	Gefitinib + CisG vs CisG	Direct sequencing	32 (2)	280 (13)	1818 (85)	60	6	74	NK	46
INTACT 2 (2004) (25,43)	Gefitnib + CP vs CP					62	NK	60	NK	55
TRIBUTE (2005) (22)	Erlotinib + CP vs CP	Direct sequencing	29 (3)	198 (18)	851 (79)	63	3	61	89	61
TALENT (2007) (26,37)	Erlotinib + CisG vs CisG	NK	NK	NK	NK	61	4	77	NK	38
IPASS (2009) (19,20)	Gefitinib vs CP	ARMS	261 (21)	176 (15)	780 (64)	57	100	21	6	96
NEJ002 (2010) (17,38)	Gefitinib vs CP	PCR clamp	228 (100)	0	0	63‡	100	36	38	94
GTOWG† (2010) (27)	Erlotinib vs CV	Direct sequencing	10 (4)	75 (26)	199 (70)	76	NK	68	83	50
TOPICAL (2010) (36,43)	Erlotinib vs placebo	SequenomOncoCarta Panel	28 (4)	362 (54)	280 (42)	77	2	61	95	38
WJTOG3405* (2010) (21,33)	Gefitinib vs CisD	Direct sequencing, PCR clamp	172 (100)	0	0	64	100	31	31	97
OPTIMAL* (2011) (16,35)	Erlotinib vs CG	Direct sequencing	154 (100)	0	0	58	100	41	29	87
First-SIGNAL (2012) (23)	Gefitinib vs CisG	Direct sequencing	43 (14)	54 (17)	212 (69)	57	100	11	NK	NK
EURTAC* (2012) (18)	Erlotinib vs platinum-G or platinum-D	Direct sequencing	173 (100)	0	0	65	0	27	31	92
LUX Lung 3† (2012) (34)	Afatinib vs CisPem	TheraScreen EGFR29	345 (100)	0	0	61	72	35	32	100
Maintenance therapy										
IFCT-GFPC 0502* (2010) (32)	Erlotinib or G vs placebo	NK	8 (3)	106 (34)	196 (63)	58	0	73	90	65
SATURN (2010) (13)	Erlotinib vs placebo	Direct sequencing	49 (6)	388 (44)	452 (50)	60	15	74	83	45
INFORM (2011) (30)	Gefitinib vs placebo	NK	30 (10)	49 (17)	217 (73)	55	100	59	46	71
Second-line/subsequent treatment										
ISEL (2005) (41)	Gefitinib vs placebo	Direct sequencing, ARMS	26 (2)	189 (11)	1477 (87)	62	20	67	78	45
BR21 (2005) (39,40)	Erlotinib vs placebo	Direct sequencing, ARMS	34 (5)	170 (23)	527 (72)	61	13	65	75	50
INTEREST (2008) (28,29)	Gefitinib vs D	Direct sequencing	44 (3)	253 (17)	1169 (80)	61	22	65	80	54
V-15–32 (2008) (31)	Gefitinib vs D	Direct sequencing	31 (6)	26 (6)	432 (88)	NK	100	62	68	78
TITAN (2012) (12)	Erlotinib vs pemetrexed or D	Direct sequencing	11 (3)	149 (35)	264 (62)	59	13	76	83	50
TAILOR† (2012) (14)	Erlotinib vs D	Direct sequencing	0	219 (100)	0	67	0	68	77	69
KCSG-LU08-01 (2012) (42)	Gefitinib vs Pem	Direct sequencing	33 (24)	38 (28)	64 (48)	61	100	15	0	100

* ARMS = amplifcation refractory mutation system; CG = carboplatin-gemcitabine; CisD = cisplatin-docetaxel; CisG = cisplatin-gemcitabine; CisPem = cisplatin-pemetrexed; CP = carboplatin-paclitaxel; CV = carboplatin-venorelbine; D = docetaxel; EGFR+ = presence of epidermal growth factor receptor mutation; EGFR- = absence of epidermal growth factor receptor mutation; G = gemcitabine; NK = not known; PCR = polymerase chain reaction; PEM = pemetrexed.

* EGFR mutation based on exon 19 and exon 21 only.

† Trials reported in abstract format.

‡ Median age not available; mean age calculated instead.

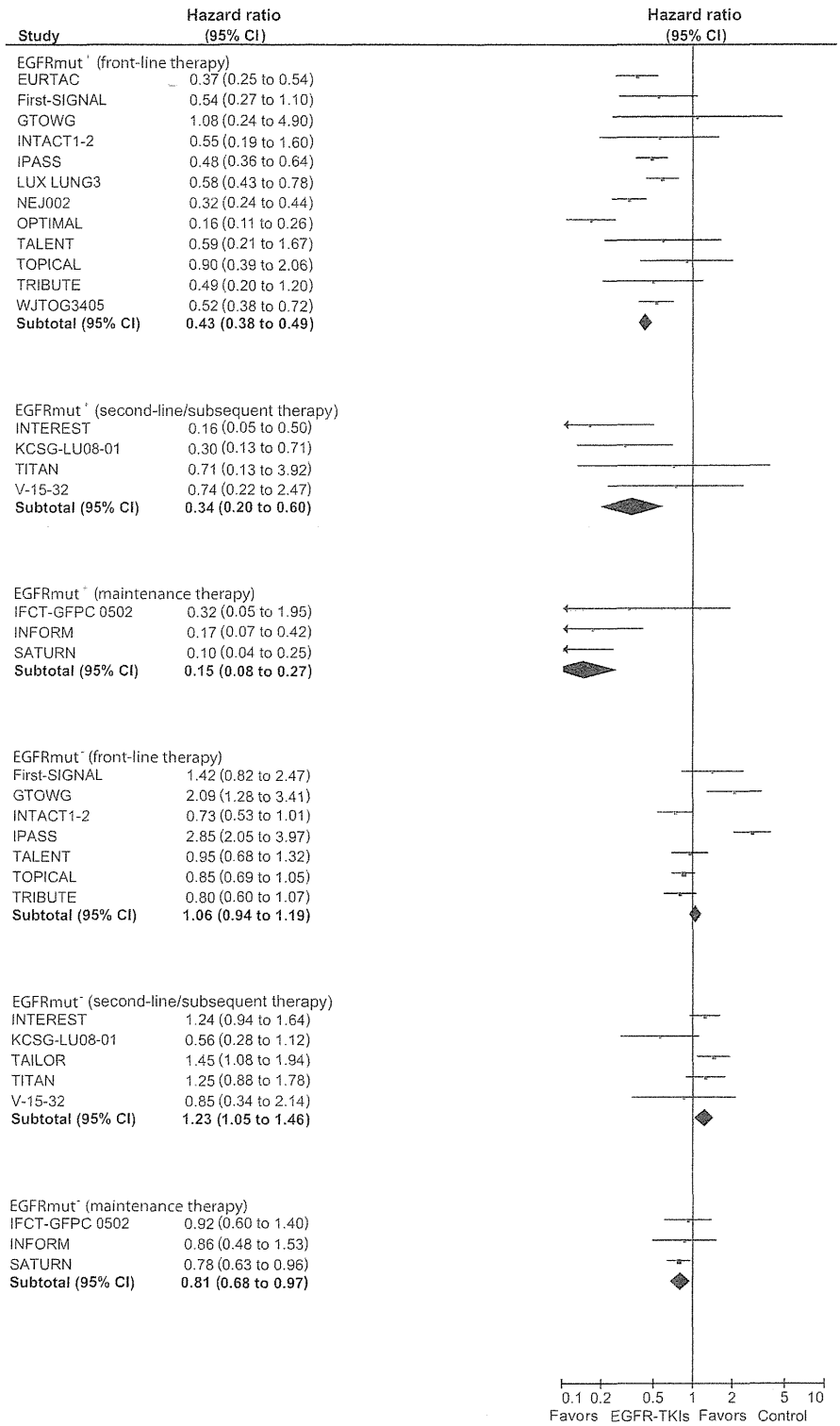

Figure 2. Forest plot of hazard ratios comparing progression-free survival in subgroups of epidermal growth factor receptor (EGFR) mutation–positive (EGFRmut+) and EGFR mutation–negative (EGFRmut-) patients who received EGFR–tyrosine kinase inhibitors (TKIs) vs control. Hazard ratios for each trial are represented by the **squares**, and the **horizontal line** crossing the square represents the 95% confidence interval (CI). The **diamonds** represent the estimated overall effect based on the meta-analysis fixed effect of the trials. All statistical tests were two-sided.

and EGFRmut⁻ subgroups (EGFRmut⁺: HR = 0.15, 95% CI = 0.08 to 0.27, $P < .001$; EGFRmut⁻: HR = 0.81, 95% CI = 0.68 to 0.97, $P = .02$). The test of interaction between treatment and EGFR mutation status was statistically significant ($P < .001$).

Effect of EGFR-TKIs Combined With Chemotherapy on PFS

Data were available for four trials [INTACT 1 and 2 (45), TRIBUTE (22) and TALENT (37)] that combined EGFR-TKIs with chemotherapy. Combination EGFR-TKIs and chemotherapy compared with chemotherapy alone was effective in reducing the risk of disease progression in both subgroups (EGFRmut⁺: HR = 0.54, 95% CI = 0.30 to 0.95, $P = .04$; EGFRmut⁻: HR = 0.82, 95% CI = 0.68 to 0.98, $P = .03$; treatment-by-EGFR mutation status interaction: $P = .17$) (Figure 3). When EGFR-TKIs monotherapy was compared with chemotherapy, EGFR-TKIs treatment was associated with a reduced risk of disease progression in the EGFRmut⁺ subgroup (HR = 0.42; 95% CI = 0.37 to 0.48; $P < .001$) but an increased risk in the EGFRmut⁻ subgroup (HR = 1.56; 95% CI = 1.36 to 1.80; $P < .001$).

Within the EGFRmut⁺ subgroup, an indirect comparison of data available from these trials indicates EGFR-TKIs treatment in combination with chemotherapy was not more effective than EGFR-TKIs alone in reducing the risk of disease progression (HR = 1.42; 95% CI = 0.80 to 2.53; $P = .23$). By contrast, within the EGFRmut⁻ subgroup, EGFR-TKIs treatment in combination with chemotherapy was more effective in reducing the risk of disease progression than EGFR-TKIs alone (HR = 0.51; 95% CI = 0.43 to 0.62; $P < .001$).

Effect of EGFR-TKIs on OS in Different Settings

Data on OS were available from 19 trials except Lux Lung 3 (34), TAILOR (14), KCSG-LU08-01 (42), and INFORM (30). Subgroup analyses by treatment setting are summarized in Figure 4. The test interaction for treatment and EGFR mutation status was not statistically significant (front-line setting: $P = .91$; second-line or subsequent therapy: $P = .37$). For EGFRmut⁺ patients, there was no treatment advantage of EGFR-TKIs in the front-line setting (HR = 1.01; 95% CI = 0.87 to 1.18; $P = .86$) or for second-line or subsequent therapy (HR = 0.74; 95% CI = 0.45 to 1.19; $P = .21$) in the risk of death. Similar results were observed in EGFRmut⁻ patients.

Only two studies [SATURN (13) and IFCT-GFPC 0502 (32,44)] reported OS in the maintenance setting. There was no clear benefit of treatment with EGFR-TKIs over placebo in either EGFRmut⁺ patients (HR = 0.78; 95% CI = 0.33 to 1.84; $P = .57$) or EGFRmut⁻ patients (HR = 0.84; 95% CI = 0.69 to 1.04; $P = .10$). The test for interaction between treatment and EGFR mutation status was not statistically significant ($P = .87$).

Publication Bias

In this meta-analysis, the overall treatment effect was not statistically significant for the OS outcome. Any potential publication bias through the exclusion of non–statistically significant studies would therefore not have influenced these results.

Sensitivity Analysis

EGFR mutation, based on exons 19 and 21 only, was known to have been examined in three trials in a front-line setting (Table 1). One trial (34) provided the treatment estimate for PFS limited to patients with exons 19 and 21 only. In the front-line setting, similar qualitative results were obtained when the analyses were limited to only these four trials on PFS and OS outcomes for the EGFRmut⁺ subgroup (Supplementary Figures 1 and 2, available online).

Discussion

This study extends the analysis beyond prior publications of the most clinically important molecular factor relevant to the treatment

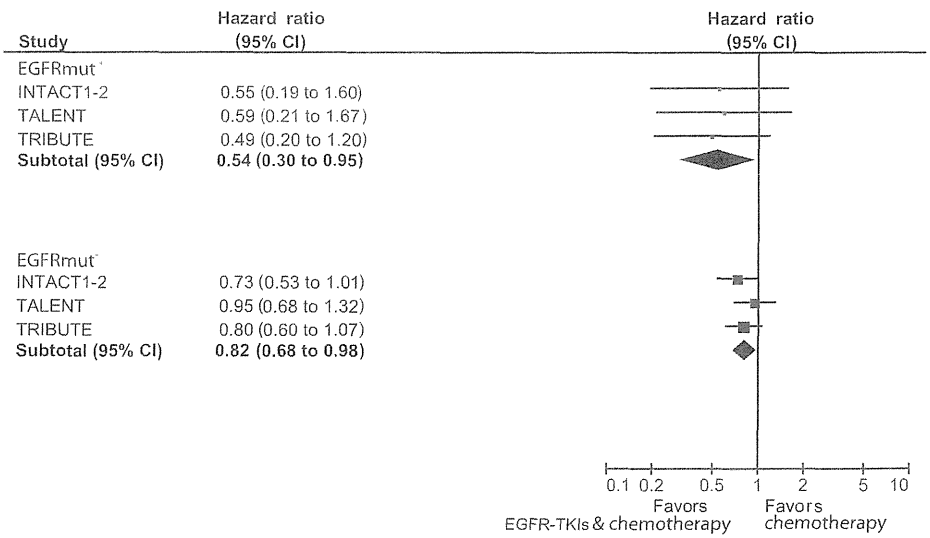

Figure 3. Forest plot of hazard ratios comparing progression-free survival in subgroups of epidermal growth factor receptor (EGFR) mutation–positive (EGFRmut⁺) and EGFR mutation–negative (EGFRmut⁻) patients who received EGFR–tyrosine kinase inhibitors (TKIs) and chemotherapy vs chemotherapy. Hazard ratios for each trial are represented by the **squares**, and the **horizontal line** crossing the square represents the 95% confidence interval (CI). The **diamonds** represent the estimated overall effect based on the meta-analysis fixed effect of the trials. All statistical tests were two-sided.

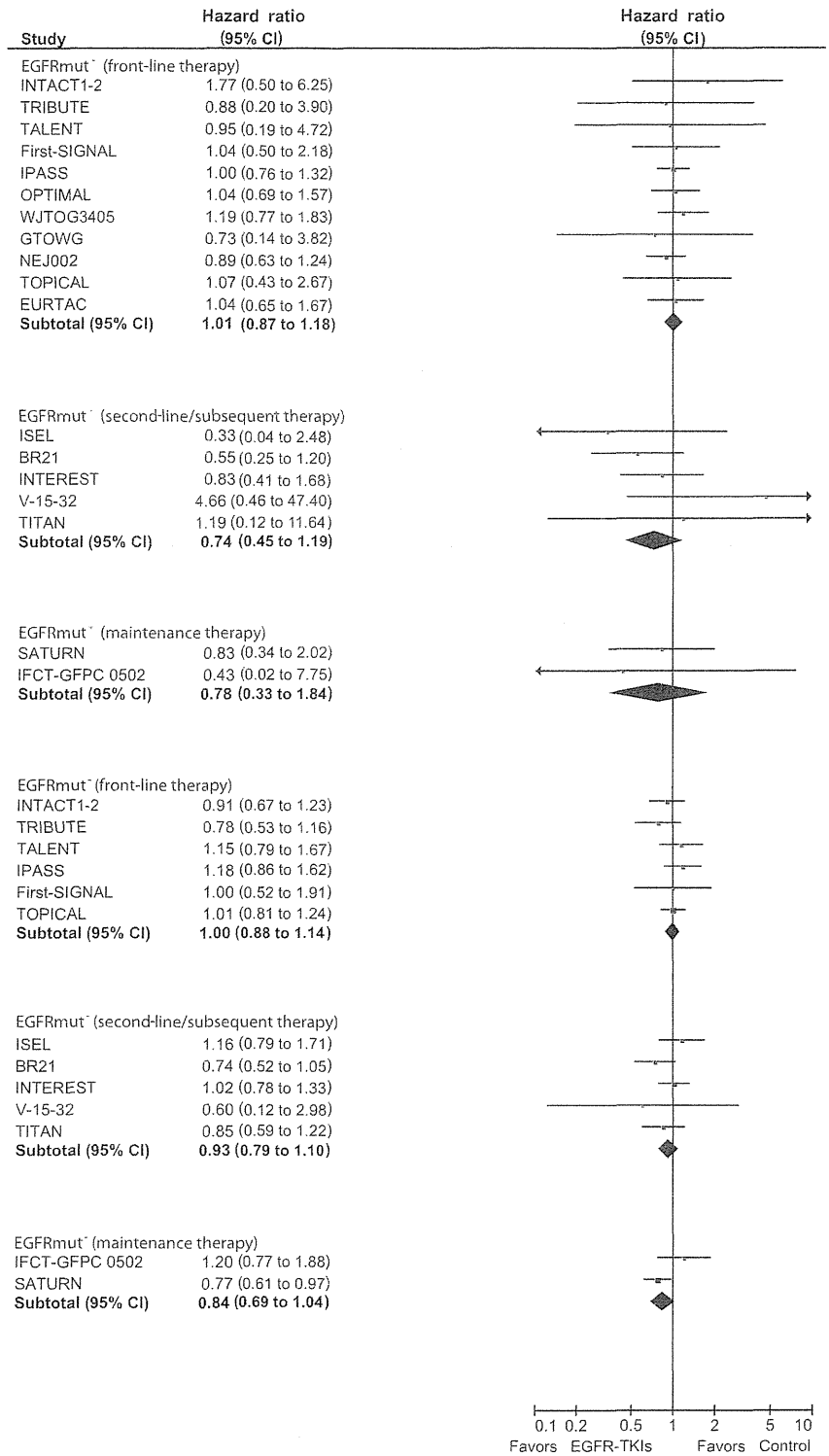

Figure 4. Forest plot of hazard ratios comparing overall survival in subgroups of epidermal growth factor receptor (EGFR) mutation–positive (EGFRmut$^+$) and EGFR mutation–negative (EGFRmut$^-$) patients who received EGFR–tyrosine kinase inhibitors (TKIs) vs control. Hazard ratios for each trial are represented by the **squares**, and the **horizontal line** crossing the square represents the 95% confidence interval (CI). The **diamonds** represent the estimated overall effect based on the meta-analysis fixed effect of the trials. All statistical tests were two-sided.

of NSCLC. Increased confidence in the findings is evident through the incorporation of results from 23 trials in nearly 15 000 patients with more than 4000 having molecular analysis. Additionally, this study approached issues not addressed in prior meta-analyses. As such, results from this study have implications for treatment and for study interpretation and design.

This meta-analysis summarizes the best available evidence to guide the use of EGFR-TKIs in patients with advanced NSCLC. EGFR-TKIs treatment is associated with 57% and 66% reduction in the risk of disease progression in EGFRmut$^+$ patients in front-line and second-line settings, respectively, but with no benefit in EGFRmut$^-$ patients (Figure 2). This study also demonstrates that EGFR mutation is an important predictive biomarker of TKIs treatment benefit in terms of PFS for all settings: front-line, maintenance, and second-line or subsequent therapy. This study demonstrates for the first time that the magnitude of effect on PFS for EGFRmut$^+$ patients is similar in patients receiving EGFR-TKIs in either the first- or second-line setting (HR = 0.43 and 0.34, respectively).

Even with mutational analyses in more than 4000 patients and with a large PFS benefit, this meta-analysis does not demonstrate OS advantage with EGFR-TKIs. Regardless of EGFR mutation status, the overall treatment effects on OS were similar. The frequently suggested reason for this lack of OS effect is the confounding effect of postprogression therapy between the randomization arms. None of the front-line trials prohibited patients from crossing over to the other treatment arm, and crossover was increasingly frequent over the decade during which these trials were conducted. For example, the NEJ002 trial randomly assigned patients to receive either gefitinib or chemotherapy. Not only did most patients receive subsequent treatment, but 94.6% of patients in the chemotherapy arm were reported to have received second-line gefitinib on disease progression (17). A recent systematic review of chemotherapy trials also indicated that PFS advantage is unlikely to be associated with an OS advantage with increasing impact of salvage therapy and that the prolongation of survival postprogression might limit the role of OS for assessing true efficacy derived from front-line therapy (46). Moreover, analysis of a recent trial indicated that compared with EGFRmut$^-$ patients, twice as many EGFRmut$^+$ patients responded to chemotherapy (28). Crossover effects, lack of blinding in experimental arms, and other factors that have been previously discussed can make PFS a difficult surrogate for OS (47–49). Ongoing work is still required to demonstrate the impact of other clinically meaningful benefits of EGFR-TKIs beyond survival and PFS for these patients.

Controversy continues regarding the role of the addition of EGFR-TKIs in patients receiving chemotherapy. For this reason, we analyzed this issue in four large, published, prospective, randomized trials in front-line treatment [INTACT 1 and 2 (45), TALENT (37), and TRIBUTE (22)]. Pooled results from these four front-line trials showed that combining EGFR-TKIs with chemotherapy over chemotherapy alone statistically significantly delayed disease progression in both the EGFRmut$^+$ and EGFRmut$^-$ subgroups. Preclinical studies (50,51) have demonstrated a synergistic effect of combining EGFR-TKIs with chemotherapy. However, indirect comparison of trial arms suggests that combined EGFR-TKIs treatment and chemotherapy is not more effective than EGFR-TKIs alone in reducing the risk of disease progression in EGFRmut$^+$ patients (HR = 1.42; 95% CI = 0.80 to 2.53; P = .23). A lack of additional benefit was confirmed in a prospective phase II trial (52) in which erlotinib monotherapy was compared with erlotinib chemotherapy combination in the EGFRmut$^+$ subgroup (median PFS 14.1 vs 17.2 months).

This meta-analysis provides information to define better the relative effectiveness of EGFR-TKIs for EGFRmut$^-$ patients. In front-line therapy, there was a non–statistically significant difference between EGFR-TKIs and control in reducing the risk of disease progression (pooled HR = 1.06; P = .35). This finding is consistent with previous in vitro studies that demonstrated a lack of sensitivity of wild-type EGFRmut$^-$ receptor lung tumor to EGFR-TKIs treatment (4–6). Although a small benefit of EGFR-TKIs over placebo in the EGFRmut$^-$ subgroup has been demonstrated in three maintenance studies [SATURN (13), INFORM (30), and IFCT-GFPC 0502 (32,44)] (pooled HR = 0.81; 95% CI = 0.68 to 0.97; P = .02), it must be realized that this benefit is markedly and both clinically and statistically significantly greater in EGFRmut$^+$ subgroups (pooled HR = 0.15; 95% CI = 0.08 to 0.27; P < .001), and the test of interaction between EGFR mutation status and treatment is highly statistically significant (P < .001).

This meta-analysis also examined the role of EGFR mutation in selecting patients for second-line or subsequent treatment. A 2012 editorial has illustrated the debate in this area (53). Although trials have differed in their results, one study (TAILOR) reported that chemotherapy was statistically significantly superior over erlotinib in terms of tumor response and PFS (OS results are not yet available) in patients without EGFR mutations in exon 19 or 21 undergoing second-line treatment, but the data remain premature and only available as a conference presentation (14). In the current meta-analysis, pooled results from trials of second-line and subsequent therapies demonstrated that treatment with EGFR-TKIs treatment, compared with chemotherapy, was associated with a 66% reduction in the risk of disease progression in the EGFRmut$^+$ subgroup (Figure 2). In contrast, EGFR-TKIs treatment, compared with chemotherapy, was 23% inferior (Figure 2) in delaying disease progression (but not OS) in EGFRmut$^-$ patients with good performance status who were suitable to receive chemotherapy. The test of interaction between EGFR mutation status and second-line or subsequent treatment was statistically significant (P < .001), suggesting that EGFR mutation is still an important treatment effect modifier and should be used to guide treatment decisions in this setting. Interestingly, updated results from the TOPICAL trial demonstrated that rash during the first cycle predicted PFS benefits with erlotinib in the EGFRmut$^-$ subgroup (43).

This meta-analysis has several strengths. We performed a comprehensive review, reported the most up-to-date published data, and contacted individual investigators to obtain relevant unpublished data. By examining both the EGFRmut$^+$ and EGFRmut$^-$ subgroups, the value of EGFR mutation status as a treatment effect modifier can be adequately assessed. This meta-analysis also overcomes the problem of inadequate power of individual studies to compare subgroups. For example, only six studies (16,18,19,21,34,38) included in this review had EGFRmut$^+$ results for more than 50 patients. Reliable interpretation of independent treatment effects in most of the individual studies in this review is not possible because of small sample sizes. Altogether, more than 4000 patients with mutational

analysis were included in this study. A major strength of this current meta-analysis is that the pooled results allow examination of second-line and maintenance treatment as well as elucidation of the effect of adding EGFR-TKIs to chemotherapy.

There are also limitations that should be noted from this analysis. Firstly, we assumed that all EGFR-TKIs, including gefitinib, erlotinib, and afatinib, have equivalent therapeutic efficacy for both the EGFRmut$^+$ and EGFRmut$^-$ subgroups. Secondly, EGFR mutation status was only assessed in 31% of patients enrolled in eligible trials, with treatment efficacy estimated from small numbers of EGFRmut$^+$ patients identified in many of these trials (Table 1). The potential influence on the results of restricting our analyses to this subset of patients is unknown. We further obtained efficacy data in the subgroups with known EGFR mutation status through personal communication with investigators of four trials (31,32,41,43). Although these subgroup data have not been published, the primary trial outcomes of these studies have been peer reviewed. Although nearly 15 000 patients were included in the analysis, the fact that only a minority had reported mutational analysis limits the ability to address several issues. Sequencing was the most commonly used method to detect EGFR mutation, and it has poor sensitivity in detecting EGFR mutant alleles in DNA samples extracted from tumors (54). These DNA samples may contain both malignant and nonmalignant (from adjacent normal or tumor stroma) cells and hence may impact the outcome of this meta-analysis through misclassification of patients' EGFR mutation status. Moreover, mutation of EGFR exons 19 and 21 are sensitizing mutations predictive of PFS benefit with EGFR-TKIs, whereas de novo mutations in exon 20 might reduce the effectiveness of EGFR-TKIs (55–57). In this meta-analysis, patients classified as EGFRmut$^+$ in some trials included those with mutations in exon 20. However, when we restricted our analysis to studies that classified patients as EGFRmut$^+$ based on presence of EGFR exon 19 and exon 21 mutations, we observed similar quantitative results. In front-line therapy, information on crossover and postprogression therapies was often not available, so adjustments could not be made to account for the lack of OS benefit in EGFRmut$^+$ patients treated with EGFR-TKIs.

Many reports have confirmed that EGFR mutations are more commonly found in patients with adenocarcinoma and in patients with low- and never-smoking histories. These factors have led to the debate as to whether knowledge of such demographic factors, rather than use of molecular studies, would be sufficient for treatment. The current meta-analysis, which examines multiple treatment settings, demonstrates that EGFR mutation status should guide personalization of treatment. Additionally, recent findings have reported that these same demographic features are more common in other genetic differences [such as those associated with EML-ALK translocations (10) and ROS 1 mutations (11)] that are not beneficially affected by EGFR-TKIs and for which specific therapy is available. Determining mutational status can avoid side effects of either EGFR-TKIs or chemotherapy and can lead to rational decision making. In that only the minority of all patients with NSCLC will have EGFR or other treatment-altering mutations, and because nearly all lung cancer therapy is costly, molecular analysis is increasingly important from clinical, scientific, and economic perspectives.

In conclusion, based on this meta-analysis, treatment with EGFR-TKIs statistically significantly delays disease progression in EGFRmut$^+$ patients but has no demonstrable impact on OS. EGFR mutation is a predictive biomarker of benefit with EGFR-TKIs treatment in delaying disease progression in front-line, second-line, and subsequent therapy and in maintenance settings. These findings support assessment of EGFR mutation status before initiation of EGFR-TKIs treatment and indicate that EGFR-TKIs should be considered as front-line therapy in EGFRmut$^+$ patients with advanced NSCLC.

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Interstitial Lung Disease Associated with Gefitinib in Japanese Patients with *EGFR*-mutated Non-small-cell Lung Cancer: Combined Analysis of Two Phase III Trials (NEJ 002 and WJTOG 3405)

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Objective: Interstitial lung disease associated with gefitinib is a critical adverse reaction. When geftinib was administered to *EGFR*-unknown patients, the interstitial lung disease incidence rate was approximately 3–4% in Japan, and usually occurs during the first 4 weeks of treatment. However, it has not been fully investigated in *EGFR*-mutated patients.
Methods: We collected clinical records of participants of two Phase III trials (WJTOG 3405 and NEJ 002), which compared gefitinib with platinum doublet chemotherapy. All patients were *EGFR* mutated, chemo-naïve and had good performance status.
Results: A total of 402 patients were enrolled in this study. In the gefitinib arm, 10 (5.0%) of 201 patients developed interstitial lung disease, of whom five (2.5%) were Grade 3 or greater, with two deaths (1.0%). In contrast, only one patient developed interstitial lung disease (Grade 1) in the chemotherapy arm. With regard to gefitinib, smoking history was significantly associated with developing interstitial lung disease (odds ratio 0.18; 95% confidence interval: 0.05–0.74; $P = 0.01$). The cumulative incidence rate of interstitial lung disease was similar in the 0–4, 5–8 and 9–12 week time periods. However, between smokers and never-smokers, cumulative incidence rates in the first 4 weeks were significantly different (4.7% versus 0%, $P = 0.03$). Three of 10 patients developed interstitial lung disease after 8 weeks of gefitinib administration (days 135, 171 and 190, respectively).
Conclusions: Among *EGFR*-mutated patients, the incidence of interstitial lung disease associated with gefitinib was not different from that in previous reports. Smoking history was associated with developing interstitial lung disease, and smokers had a higher incidence rate of interstitial lung disease in the first 4 weeks.

Key words: epidermal growth factor receptor mutation – gefitinib – epidermal growth factor receptor-tyrosine kinase inhibitor – interstitial lung disease – Japanese

INTRODUCTION

The recent introduction of targeted agents has dramatically changed the treatment of non-small-cell lung cancer (NSCLC). Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) is a prototype of such therapy which targets NSCLC harboring the *EGFR* mutation (1,2). EGFR-TKIs have demonstrated a higher response rate and longer progression-free survival than platinum doublet chemotherapy (3–6). Common adverse events associated with EGFR-TKIs include skin rash, diarrhea and hepatotoxicity. Interstitial lung disease (ILD) is a rare but potentially fatal adverse event (7). The incidence of ILD has been reported to be higher in Japanese than in Caucasians. Two large, multi-institutional studies in Japan (8–10) reported that its incidence is 3.5–4.0%, compared with just 0.3% in the USA (11). They also suggested that male gender, history of smoking, poor performance status, pre-existing lung disorder and prior history of chemotherapy were predictive risk factors (8–10).

Today, clinical guidelines recommend that administration of EGFR-TKIs should be limited to *EGFR*-mutated patients, reflecting the high efficacy of this drug in this patient population (12). Since it is known that *EGFR* mutation is relatively rare in males or smokers, which are known risk factors of ILD, ILD incidence might be lower in patients with *EGFR* mutation. However, a detailed investigation of ILD associated with EGFR-TKIs among *EGFR*-mutated patients has not been done. Therefore, we conducted a combined analysis of two Phase III trials that compared gefitinib with platinum doublet chemotherapy in Japanese NSCLC patients with *EGFR* mutation.

PATIENTS AND METHODS

Patient Selection and Treatment Methods

We collected the clinical records of participants of two Phase III trials (WJTOG 3405 (3) and NEJ 002 (4)). These trials compared gefitinib with platinum doublet chemotherapy in Japanese NSCLC patients with *EGFR* mutation. *EGFR* mutation was screened by PCR-based methods as previously described (13,14). All of the participants were required to be chemo-naïve, with Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1 and aged between 20 and 75 years, with adequate organ function. Patients with active infectious disease or severe heart disease were excluded. All patients were confirmed not to have pulmonary fibrosis by chest computed tomography (CT) within 1 month prior to registration. Both studies were approved by the institutional review board at each participating site.

Eligible patients were randomly assigned to receive either gefitinib (250 mg daily) or standard chemotherapy. The latter consisted of paclitaxel 200 mg/m^2 plus carboplatin (area under the curve of six) in NEJ 002 or docetaxel 60 mg/m^2 plus cisplatin 80 mg/m^2 in WJOG 3405, every 3 weeks. All participants who had received at least one dose of a study drug were included in the safety analysis.

Baseline data were collected for each patient, including information on sex, age, history of smoking, ECOG PS, tumor histology, clinical stage and type of *EGFR* mutation.

Evaluation of ILD and Statistical Analysis

All patients were assessed by chest CT for their response to treatment every 2 months. The diagnosis of ILD was based on clinical manifestations (worsening dry cough or dyspnea within days to weeks), accompanied by interstitial pulmonary infiltrates on a chest X-ray and a chest CT (15). Close investigation, such as blood and bacterial examination, was required in the protocols to exclude other ILDs. Bronchoalveolar lavage was also recommended, if possible. ILD was assessed according to the National Cancer Institute

Table 1. Baseline characteristics of the patients in the gefitinib arm

	Total (n = 201)	Non-ILD (n = 191)	ILD (n = 10)	P value
Age (years)				
Mean	64	64	63	0.67
Range	34–75	34–75	56–75	
Sex (no.)				
Male	71	65	6	0.17
Female	130	126	4	
Smoking status (no.)				
Never	137	134	3	0.01
Previous/current	64	57	7	
ECOG performance status (no.)				0.35
0	111	107	4	(PS 0 versus 1)
1	89	83	6	
2	1	1	0	
Histology (no.)				
Ad	187	180	7	1.0
Other	14	14	0	
Clinical stage (no.)				
IIIB	25	25	0	0.52
IV	129	122	7	
Post-operative relapse	47	44	3	
Type of *EGFR* mutation				
Exon 19 del	108	104	4	0.42
L858R	85	80	5	
Other	8	7	1	

ILD, interstitial lung disease; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor.

Common Terminology Criteria (NCI-CTC, version 3.0). All events were assessed by investigators at first; then severe cases were confirmed by independent committees based on medical, pathological and radiological findings.

Differences between covariates in patients with or without ILD were analyzed using Fisher's exact tests or Pearson's tests. The Kaplan–Meier method was used to estimate the cumulative incidence rate of ILD, and differences according to the smoking status were analyzed by the log-rank test. All the analyses were performed using JMP version 7 (SAS Institute Inc., USA).

RESULTS

In WJOG 3405, 177 patients were randomized and 175 were included in the safety analysis. In NEJ 002, 230 patients were randomized and 227 were included in the safety analysis. In our study a total of 402 patients were enrolled, half of them in the gefitinib arm.

Baseline characteristics of the patients were well balanced between the treatment groups. As previously reported (3,4), about two-thirds of patients were female, the median age was 64 years, 65% were never-smokers, 55% had an ECOG PS of 0 and 95% had adenocarcinoma.

At the time of data cut-off, the median duration of gefitinib treatment was 165 days (WJTOG 3405) and 308 days (NEJ 002); the median number of chemotherapy cycles was four. In the gefitinib arm, 10 (5.0%) of 201 patients developed ILD, of whom five (2.5%) were Grade 3 or greater, with two deaths (1.0%). In contrast, only one patient developed ILD (Grade 1) in the chemotherapy arm.

The background and clinical course of the patients in the gefitinib arm are summarized in Tables 1 and 2. The clinical background of patients who developed ILD and those who did not showed no difference other than smoking status. Univariate analysis showed that smoking history was significantly associated with developing ILD (odds ratio 0.18; 95% confidence interval (CI): 0.05–0.74; $P = 0.01$). This accounted for 10.9% (95% CI: 5.4–20.9%) of the incidence rate of ILD among smokers, versus 2.2% (95% CI: 0.8–6.3%) among never-smokers.

Figure 1 shows a Kaplan–Meier curve of the cumulative incidence rate of ILD. Among the overall population, the cumulative incidence rate in the first 4 weeks, 5th–8th weeks and 9th–12th weeks was 1.5% (95% CI: 0.5–4.3%), 1.5% (95% CI: 0.5–4.4%) and 0.5% (95% CI: 0.1–2.9%), respectively. Smoking status was associated with the timing of the onset of ILD . Between smokers and never-smokers, the cumulative incidence rate of ILD in the first 4 weeks was significantly different (4.7 versus 0%, $P = 0.03$), whereas that in the other periods (5th–8th weeks and 9th–12th weeks) was similar (Fig. 1). Three of 10 patients developed ILD after 8 weeks of gefitinib administration (days 135, 171 and 190, respectively).

Most of the patients who developed severe ILD (Gr $\geq$ 3) were given steroid therapy. One patient was treated with an immunosuppressive agent (cyclosporine). Non-invasive positive pressure ventilation was used in one patient (No. 10) but unfortunately this patient died.

DISCUSSION

Three large studies of ILD associated with EGFR-TKI have been conducted in Japan (Table 3). Ando et al. (8) performed a retrospective study including 1976 NSCLC patients treated with gefitinib and found an incidence rate of 3.5% and mortality rate of 1.6%. In a prospective cohort and nested-case control study by Kudoh et al. (9), cumulative incidence rates during 12 weeks of treatment were 4.0%. They also mentioned that the risk of developing ILD was higher

Table 2. Clinical characteristics of 10 patients who developed ILD in the gefitinib arm

No.	Age	Sex	Smoking index (BI)	PS	Stage	Site of *EGFR* mutation	Onset day from EGFR-TKI	ILD (CTCAE grade)	Outcome
1	69	M	800	0	r	Exon 19	48	1	Improved
2	57	F	0	1	4	Exon 19	70	1	Improved
3	60	M	860	1	4	Exon 21	15	1	Improved
4	56	F	370	1	4	Exon 19	14	1	Improved
5	71	F	0	1	4	Exon 21	171	2	Improved
6	57	M	740	0	r	Exon 19	25	3	Improved
7	68	M	1075	0	4	Exon 21	190	3	Improved
8	75	M	525	1	4	Exon 21	53	3	Improved
9	65	M	1320	0	r	Exon 19	135	5	Died
10	60	F	0	1	4	Exon 21	32	5	Died

BI, Brinkman Index; PS, Eastern Cooperative Oncology Group performance status; EGFR-TKI, EGFR-tyrosine kinase inhibitor; CTCAE, Common Terminology Criteria for Adverse Events; M, male; F, female.

with gefitinib than with chemotherapy (the odds ratio was 3.2). With regard to erlotinib, Nakagawa et al. (10) conducted a post-marketing survey in Japan and reported that 158 of 3488 patients were confirmed to have ILD (any grade, 4.5%), with a mortality rate of 1.6%. These studies suggested that male gender, smoking history, poor PS, pre-existing lung disorder and prior history of chemotherapy were risk factors of ILD. However, none of the three studies mentioned *EGFR* mutation status.

To our knowledge, ours is the first study to describe the clinical characteristics of ILD associated with gefitinib limited to *EGFR*-mutated patients. Similar to Kudoh's report, ILD was relatively more common in the gefitinib arm than in the chemotherapy arm. The incidence rate of ILD associated with gefitinib was as high as 5% with a mortality rate of 2.5%, even though our analysis contained a high proportion of patients from low-risk groups (female, non-smokers with good PS).

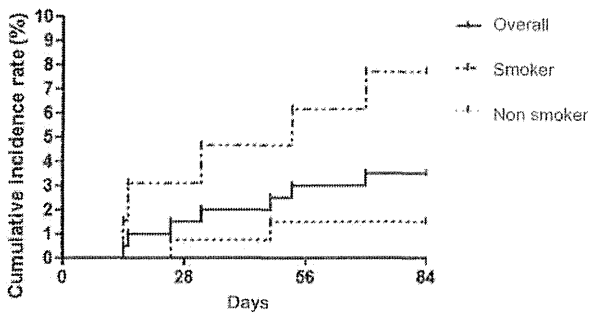

Figure 1. Cumulative incidence rate of interstitial lung disease associated with gefitinib. Kaplan–Meier-estimated cumulative incidence rate of interstitial lung disease in patients who were allocated to the gefitinib arm in WJTOG 3405 and NEJ 002 trial (overall population ($n = 201$), bold line; smoker ($n = 64$), dashed line; non-smoker ($n = 137$), dotted line).

Similarly to the previous studies, our analysis showed that smoking history was highly associated with developing ILD associated with gefitinib (odds ratio 0.18). Smoking induces airway epithelial damage, and lung injury could be prolonged and worsened by gefitinib in a preclinical model (16). Most of the other risk factors were excluded at the time of registration, because enrolled patients were required to be chemo-naïve, with a PS of 0–1, and confirmed not to have pulmonary fibrosis. Therefore, we should pay more attention to smoking status even if the patient has *EGFR* mutation. In terms of the timing of the onset of ILD, smoking history seemed to be an important factor. Between smokers and never-smokers, the cumulative incidence rate of ILD in the first 4 weeks was significantly different (4.7 versus 0%, $P = 0.03$). Previous studies stated that ILD occurred most commonly in the first 4 weeks (median: 23–31 days) and 60% of participants were smokers. So, despite the small subset analysis in the present study, the higher incidence rate observed in the first 4 weeks among smokers is noteworthy.

Another point is that three of 10 patients developed ILD after several months of gefitinib treatment. With erlotinib, it was reported that ILD occurred at the rate of 0.11 per 100 patient-weeks after 8 weeks of treatment. It is not clear whether the mechanism of ILD varies over time from its onset; further investigation on late-onset ILD is needed.

Our analysis has several limitations. First, this was an investigator-dependent analysis. Most of the ILD cases were diagnosed by clinical manifestations and a chest CT. Bronchoalveolar lavage was recommended in the protocols, but actually done in only one case. As acute exacerbation of ILD after bronchoscopy has been reported (15), this may be acceptable. In our analysis, all patients were assessed by chest CT every 2 months, and severe cases were confirmed by independent, multidisciplinary committees. Secondly, this analysis was done with a small sample size due to the population and rarity of incidence.

Table 3. ILD associated with EGFR-TKI in Japanese patients: pivotal studies and ours

	Ando et al. (8)	Kudoh et al. (9)	Nakagawa et al. (10)	Present data
Study design	Retrospective	Prospective	Retrospective	Retrospective
No. of patients	1976	1482	3488	201
Type of EGFR-TKI	Gefitinib	Gefitinib	Erlotinib	Gefitinib
Patient selection by *EGFR* mutation status	No	No	No	Yes
ILD (any Grade; %)	70 (3.5)	59 (4.0)	158 (4.5)	10 (5.0)
ILD (Grade 5; %)	31 (1.6)	25 (1.7)	55 (1.6)	2 (1.0)
Risk factors of ILD	Smoking Pre-existing lung disorder Male	Smoking Pre-existing lung disorder Poor PS Elderly Cardiac disease	Smoking Pre-existing lung disorder Poor PS Lung infection	Smoking

In conclusion, the incidence of ILD associated with gefitinib among *EGFR*-mutated patients was not different from that in previous reports. Smoking history was highly associated with developing ILD. In addition, a substantial number of patients developed ILD after several months of gefitinib treatment.

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Conflict of interest statement

A.I., K.N. and N.Y. have received honoraria from Astra Zeneca. T.M. has received honoraria from Astra Zeneca and Chugai. T.N. has received honoraria from Chugai. Y.N. has received honoraria and research grants from Chugai. All other authors declare no conflicts of interest.

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INTERNAL MEDICINE

□ CASE REPORT □

Bilateral Peripheral Infiltrates Refractory to Immunosuppressants were Diagnosed as Autoimmune Pulmonary Alveolar Proteinosis and Improved by Inhalation of Granulocyte/Macrophage-Colony Stimulating Factor

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Abstract

A 55-year-old non-smoking woman was admitted to our hospital for re-evaluation of unimproved peripheral ground-glass opacities despite prednisolone and cyclosporine treatment. She was diagnosed with autoimmune pulmonary alveolar proteinosis (PAP) based on transbronchial lung biopsy and granulocyte/macrophage colony-stimulating factor (GM-CSF) antibody testing. GM-CSF inhalation therapy markedly improved the opacities. Bilateral, centrally located lung opacities are typical in PAP, however 10 PAP cases with peripheral infiltration were reported in Japan recently, of which GM-CSF antibody was positive in six. To avoid inappropriate immunosuppressant treatment, PAP should be considered in the differential diagnosis of such peripheral opacities. GM-CSF antibody might be useful for diagnosis.

Key words: pulmonary alveolar proteinosis, subpleural infiltration, GM-CSF inhalation, GM-CSF antibody, steroid therapy

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Introduction

Pulmonary alveolar proteinosis (PAP), first described in 1958 (1) as a rare and severe lung disease characterized by the intra-alveolar accumulation of surfactant lipids and proteins, impairs gas exchange and results in progressive respiratory insufficiency. Currently, PAP is classifiable into four classes: congenital PAP, autoimmune (idiopathic) PAP, secondary PAP, and unclassified PAP. More than 90% of cases are diagnosed as autoimmune PAP (2). Patients with autoimmune PAP present high levels of autoantibodies against the granulocyte/macrophage colony-stimulating factor (GM-CSF) in the serum as well as in bronchoalveolar lavage fluid (2-6).

Findings from computed tomography (CT) studies of PAP include air space ground-glass interlobular and intralobular opacities and consolidation, which are distributed in a geographic or patchy pattern from the central to peripheral zones (7, 8). Usually, the distribution of PAP shadows is predominantly central: it is rarely peripheral. Furthermore, previous reports show that the peripheral shadows in PAP patients disappear without treatment (9, 10). Here, we describe a patient with autoimmune PAP showing peripheral ground-glass appearance that worsened during steroid and cyclosporine therapy, however it was improved with GM-CSF inhalation therapy.

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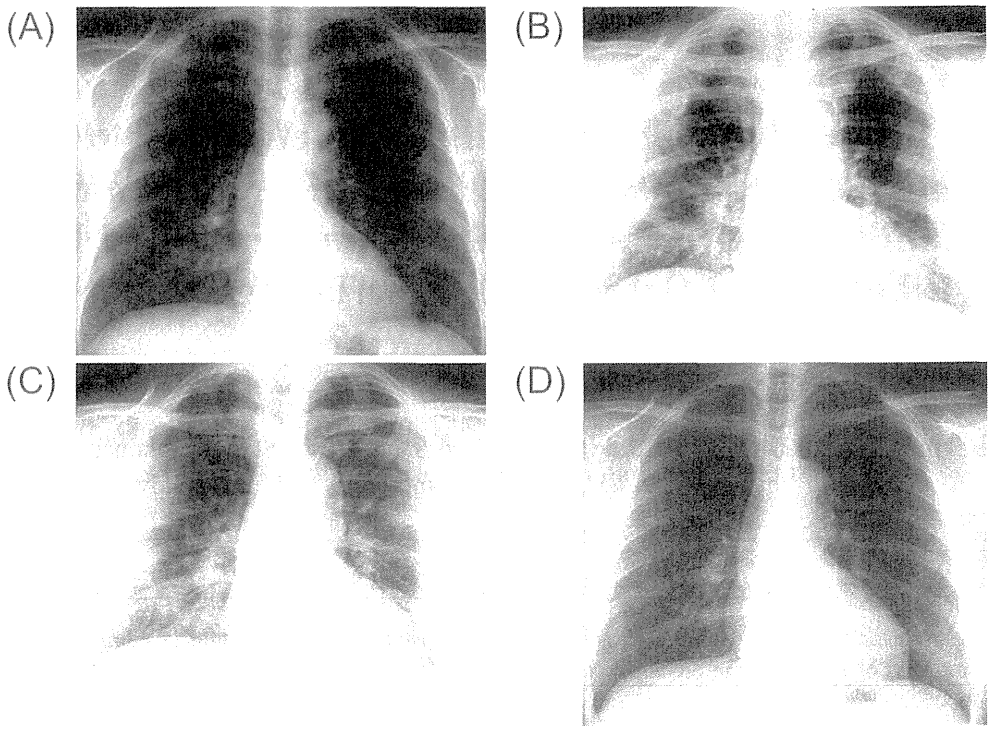

Figure 1. Chest radiograph from an annual check-up showing an abnormal shadow, predominantly in the bilateral peripheral lung field (A). The shadow worsened after prednisolone treatment (B) and worsened further after adding cyclosporine treatment (C). The shadow improved markedly after 6-month granulocyte/macrophage colony-stimulating factor (GM-CSF) inhalation therapy (D).

Case Report

A previously healthy 55-year-old non-smoking woman who had a normal chest radiograph at an annual health check-up 1 year previously was referred to our affiliated hospital because of the appearance of bilateral peripheral shadows on a chest radiograph in September 2004 (Fig. 1A). The patient was a homemaker without a remarkable family history. She had shortness of breath on exertion (Grade 1 of MRC Breathlessness Scale). A chest CT image revealed subpleural heterogeneous ground-glass opacities (GGOs) partially including consolidation and without definite interlobular thickening (Fig. 2A). Examination of the bronchoalveolar lavage fluid (BALF) revealed lymphocytosis (macrophages, 75.5% of total cells; lymphocytes, 23.5%; neutrophils, 1%) with no turbidity, no foamy macrophages, and no amorphous materials. Transbronchial lung biopsy (TBLB) yielded no specific or diagnostically helpful finding. A serum level of KL-6, a mucin-like glycoprotein, was 611 U/mL. Based on these findings, she was provisionally diagnosed with cryptogenic organizing pneumonia. Because the symptom did not improve during the initial observation, she was treated with oral prednisolone (0.5 mg/kg) for three months, but showed no clinical improvement. She was referred to our hospital in December 2004. The patient did not agree to undergo further examination and therefore was treated with prednisolone for 1 year. However, peripheral shadows on the chest radiograph worsened (Fig. 1B). Later, cyclosporine was added to her treatment for three months. The chest radiograph and CT findings worsened with time (Fig. 1C, 2B). She was admitted to our hospital for re-evaluation in December 2005.

Laboratory studies showed an elevated white blood cell count (11,600/μL), probably because of steroid therapy (Table 1). Serum levels of total bilirubin were elevated by an unknown cause. Levels of surfactant protein D (SP-D) (151.2 ng/mL) and KL-6 (1,176 U/mL) were increased significantly. Arterial blood gas analysis in room air revealed mild hypoxemia (partial pressure of oxygen (PaO_2), 67.6 Torr), indicating a significantly expanded alveolar-arterial oxygen gradient (A-aDO_2). Pulmonary function tests indicated normal respiratory functions. Electrocardiography indicated slight sinus tachycardia at 116 beats/min, perhaps associated with hypoxemia. A repeat of bronchoscopy revealed milky lavage fluid containing large foamy macrophages (macrophages, 84%; lymphocytes, 15%; neutrophils, 1%; Fig. 3A). The TBLB specimens showed that the alveoli with preserved lung architecture were filled with periodic acid-Schiff (PAS)-positive eosinophilic amorphous materials (Fig. 4). The serum was positive for GM-CSF antibody (41.3 μg/mL). Autoimmune PAP was diagnosed based on the detection of GM-CSF antibody in the serum.

Although prednisolone and cyclosporine were discontin-