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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.

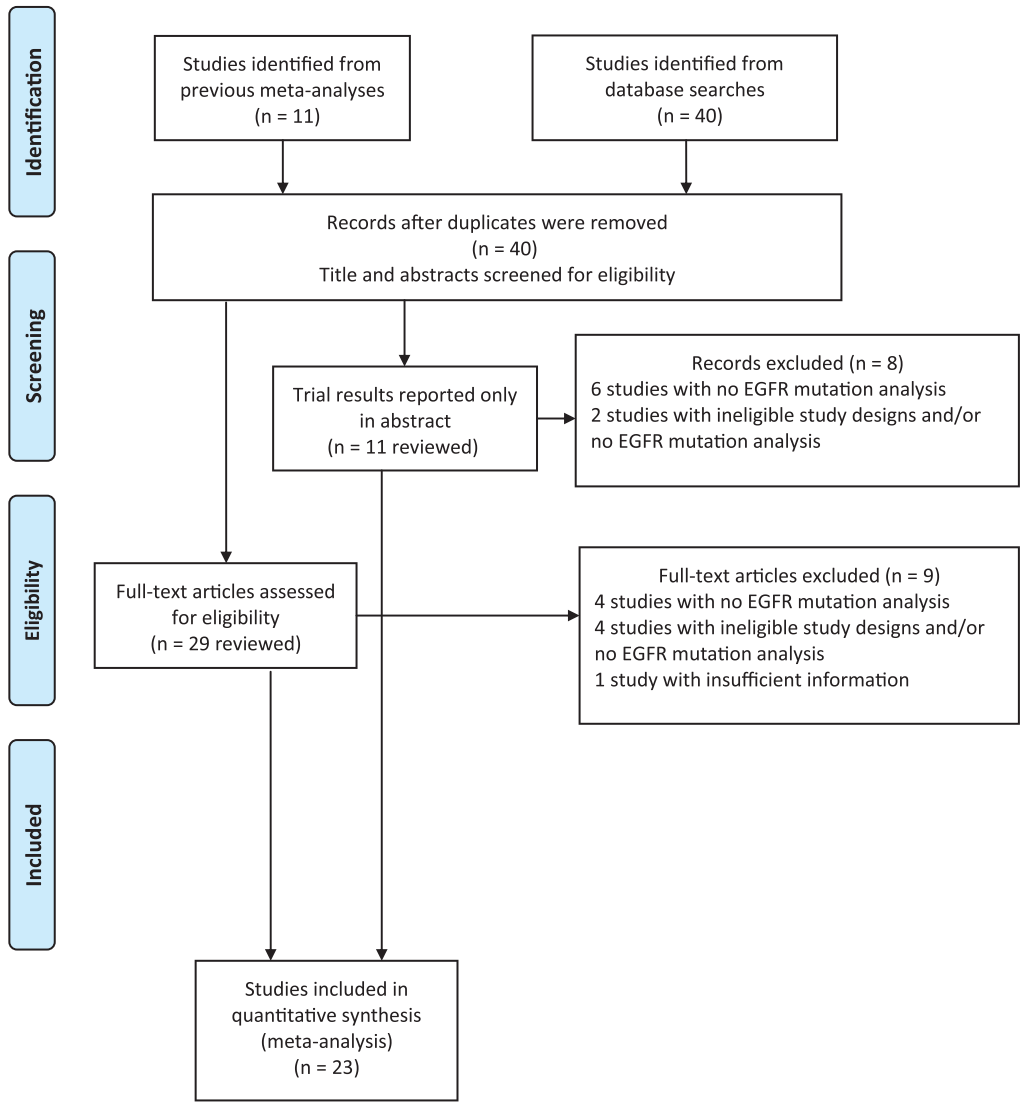

Figure 1. Flow diagram showing inclusion and exclusion of studies. EGFR = epidermal growth factor receptor.

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.

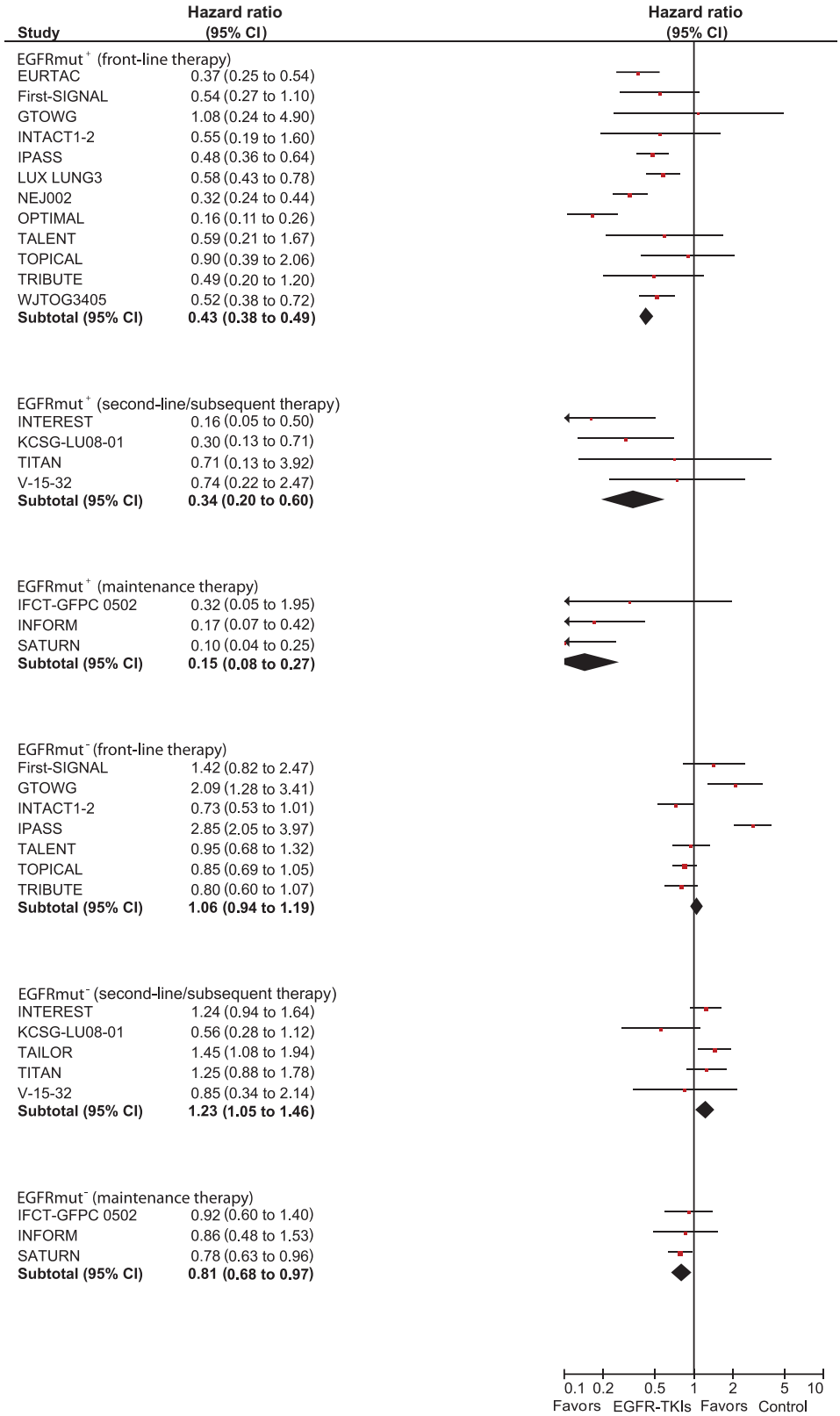

Figure 2. Forest plot of hazard ratios comparing progression-free survival in subgroups of epidermal growth factor receptor (EGFR) mutation–positive (EGFRmut$^+$) and EGFR mutation–negative (EGFRmut$^-$) patients who received EGFR–tyrosine kinase inhibitors (TKIs) vs control. Hazard ratios for each trial 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

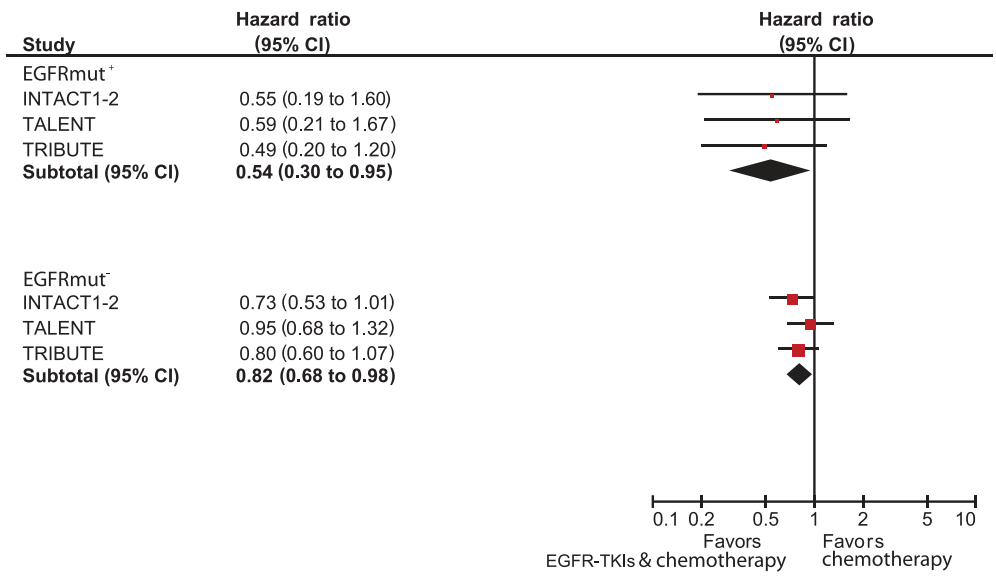

Figure 3. Forest plot of hazard ratios comparing progression-free survival in subgroups of epidermal growth factor receptor (EGFR) mutation–positive (EGFRmut⁺) and EGFR mutation–negative (EGFRmut⁻) patients who received EGFR–tyrosine kinase inhibitors (TKIs) and chemotherapy vs chemotherapy. Hazard ratios 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.

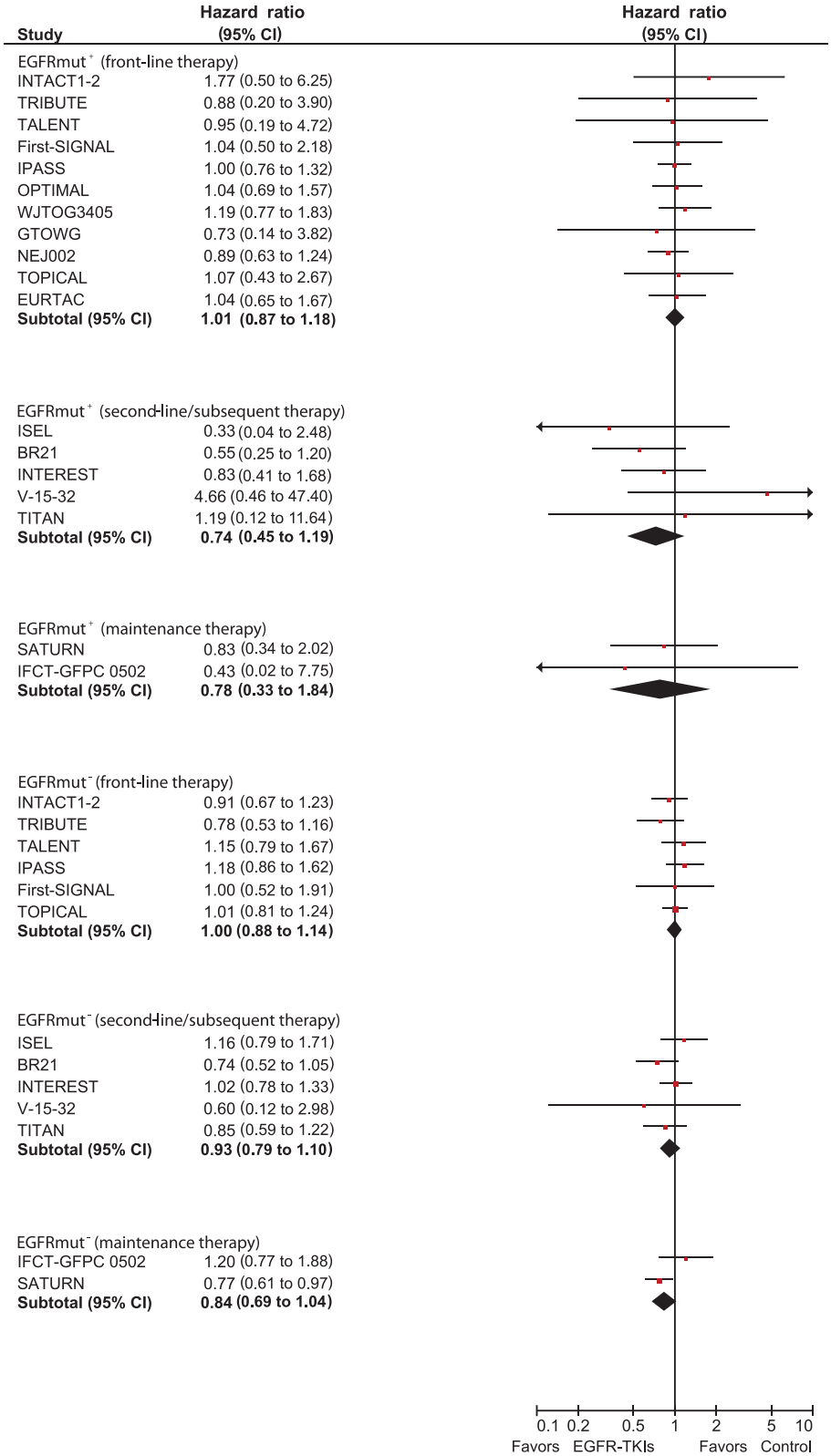

Figure 4. Forest plot of hazard ratios comparing overall survival in subgroups of epidermal growth factor receptor (EGFR) mutation–positive (EGFRmut+) and EGFR mutation–negative (EGFRmut−) patients who received EGFR–tyrosine kinase inhibitors (TKIs) vs control. Hazard ratios for each trial are represented 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.

References

1. Sato M, Shames DS, Gazdar AF, Minna JD. A translational view of the molecular pathogenesis of lung cancer. *J Thorac Oncol*. 2007;2(4):327–343.
2. Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers—a different disease. *Nat Rev Cancer*. 2007;7(10):778–790.
3. Tang X, Shigematsu H, Bekele BN, et al. EGFR tyrosine kinase domain mutations are detected in histologically normal respiratory epithelium in lung cancer patients. *Cancer Res*. 2005;65(17):7568–7572.
4. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non–small-cell lung cancer to gefitinib. *N Engl J Med*. 2004;350(21):2129–2139.
5. Paez JG, Jänne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*. 2004;304(5676):1497–1500.
6. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci U S A*. 2004;101(36):13306–13311.
7. Bria E, Milella M, Cuppone F, et al. Outcome of advanced NSCLC patients harboring sensitizing EGFR mutations randomized to EGFR tyrosine kinase inhibitors or chemotherapy as first-line treatment: a meta-analysis. *Ann Oncol*. 2011;22(10):2277–2285.
8. Petrelli F, Borgonovo K, Cabiddu M, Barni S. Efficacy of EGFR tyrosine kinase inhibitors in patients with EGFR-mutated non–small-cell lung cancer: a meta-analysis of 13 randomized trials. *Clin Lung Cancer*. 2012;13(2):107–114.
9. Gao G, Ren S, Li A, et al. Epidermal growth factor receptor-tyrosine kinase inhibitor therapy is effective as first-line treatment of advanced non-small-cell lung cancer with mutated EGFR: a meta-analysis from six phase III randomized controlled trials. *Int J Cancer*. 2012:131(5):E822–829.
10. Kwak EL, Bang Y-J, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non–small-cell lung cancer. *N Engl J Med*. 2010;363(18):1693–1703.
11. Shaw AT, Camidge DR, Engelman JA, et al. Clinical activity of crizotinib in advanced non-small cell lung cancer (NSCLC) harboring ROS1 gene rearrangement. *J Clin Oncol*. 2012;30(15 suppl):7508.
12. Ciuleanu T, Stelmakh L, Cicenas S, et al. Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. *Lancet Oncol*. 2012;13(3):300–308.
13. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol*. 2010;11(6):521–529.
14. Garassino MC, Martelli O, Bettini A, et al. TAILOR: phase III trial comparing erlotinib with docetaxel in the second-line treatment of NSCLC patients with wild-type (wt) EGFR. *J Clin Oncol*. 2012;30(15 suppl):LBA7501.
15. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med*. 1998;17(24):2815–2834.
16. Zhou C, Wu Y-L, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol*. 2011;12(8):735–742.
17. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non–small-cell lung cancer with mutated EGFR. *N Engl J Med*. 2010;362(25):2380–2388.

18. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012;13(3):239–246.
19. Mok TS, Wu Y-L, Thongprasert S, et al. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361(10):947–957.
20. Fukuoka M, Wu Y-L, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non–small-cell lung cancer in Asia (IPASS). *J Clin Oncol*. 2011;29(21):2866–2874.
21. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol*. 2010;11(2):121–128.
22. Herbst RS, Prager D, Hermann R, et al. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non–small-cell lung cancer. *J Clin Oncol*. 2005;23(25):5892–5899.
23. Han J-Y, Park K, Kim S-W, et al. First-SIGNAL: First-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. *J Clin Oncol*. 2012;30(10):1122–1128.
24. Giaccone G, Herbst RS, Manegold C, et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non–small-cell lung cancer: a phase III trial—INTACT 1. *J Clin Oncol*. 2004;22(5):777–784.
25. Herbst RS, Giaccone G, Schiller JH, et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non–small-cell lung cancer: a phase III trial—INTACT 2. *J Clin Oncol.* 2004;22(5):785–794.
26. Gatzemeier U, Pluzanska A, Szczesna A, et al. Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non–small-cell lung cancer: the Tarceva Lung Cancer Investigation Trial. *J Clin Oncol.* 2007;25(12):1545–1552.
27. Reck M, Von Pawel J, Fischer JR, et al. Erlotinib versus carboplatin/vinorelbine in elderly patients (age 70 or older) with advanced non-small cell lung carcinoma (NSCLC): a randomized phase II study of the German Thoracic Oncology Working Group. *J Clin Oncol*. 2010;28(15 suppl):7565.
28. Douillard J-Y, Shepherd FA, Hirsh V, et al. Molecular predictors of outcome with gefitinib and docetaxel in previously treated non–small-cell lung cancer: data from the randomized phase III INTEREST trial. *J Clin Oncol.* 2010;28(5):744–752.
29. Kim ES, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. *Lancet.* 2008;372(9652):1809–1818.
30. Zhang L, Ma S, Song X, et al. Gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804): a multicentre, double-blind randomised phase 3 trial. *Lancet Oncol*. 2011;13(5):466–475.
31. Maruyama R, Nishiwaki Y, Tamura T, et al. Phase III study, V-15–32, of gefitinib versus docetaxel in previously treated Japanese patients with non–small-cell lung cancer. *J Clin Oncol.* 2008;26(26):4244–4252.
32. Perol M, Chouaid C, Milleron BJ, et al. Maintenance with either gemcitabine or erlotinib versus observation with predefined second-line treatment after cisplatin-gemcitabine induction chemotherapy in advanced NSCLC: IFCT-GFPC 0502 phase III study. *J Clin Oncol.* 2010;28(15 suppl):7507.
33. Mitsudomi T, Morita S, Yatabe Y, et al. Updated overall survival results of WJTOG 3405, a randomized phase III trial comparing gefitinib (G) with cisplatin plus docetaxel (CD) as the first-line treatment for patients with non-small cell lung cancer harboring mutations of the epidermal growth factor receptor (EGFR). *J Clin Oncol*. 2012;30(15 suppl):7521.
34. Yang JC-H, Schuler MH, Yamamoto N, et al. LUX-Lung 3: a randomized, open-label, phase III study of afatinib versus pemetrexed and cisplatin as first-line treatment for patients with advanced adenocarcinoma of the lung harboring EGFR-activating mutations.*J Clin Oncol.* 2012;30(15 suppl):LBA7500.
35. Zhou C, Wu YL, Liu X, et al. Overall survival (OS) results from OPTIMAL (CTONG0802), a phase III trial of erlotinib (E) versus carboplatin plus gemcitabine (GC) as first-line treatment for Chinese patients with EGFR mutation-positive advanced non-small cell lung cancer (NSCLC). *J Clin Oncol.* 2012;30(15 suppl):7520.
36. Lee S, Rudd R, Khan I, et al. TOPICAL: Randomized phase III trial of erlotinib compared with placebo in chemotherapy-naive patients with advanced non-small cell lung cancer (NSCLC) and unsuitable for first-line chemotherapy. *J Clin Oncol*. 2010;28(15 suppl):7504.
37. Gatzemeier U, Heller A, Foernzler D, et al. Exploratory analyses EGFR, kRAS mutations and other molecular markers in tumors of NSCLC patients (pts) treated with chemotherapy +/– erlotinib (TALENT). *J Clin Oncol.* 2005;23(16 suppl):7028.
38. Inoue A, Kobayashi K, Maemondo M, et al. Final overall survival results of NEJ002, a phase III trial comparing gefitinib to carboplatin (CBDCA) plus paclitaxel (TXL) as the first-line treatment for advanced non-small cell lung cancer (NSCLC) with EGFR mutations. *J Clin Oncol*. 2011;29(15 suppl):7519.
39. Zhu C-Q, da Cunha Santos G, Ding K, et al. Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21. *J Clin Oncol.* 2008;26(26):4268–4675.
40. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non–small-cell lung cancer. *N Engl J Med.* 2005;353(2):123–132.
41. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet.* 2005;366(9496):1527–1537.
42. Sun JM, Lee KH, Kim SW, et al. Gefitinib versus pemetrexed as second-line treatment in patients with nonsmall cell lung cancer previously treated with platinum-based chemotherapy (KCSG-LU08-01) [published online ahead of print June 6, 2012]. *Cancer*. 2012. doi:10.1002/cncr.27630.
43. Lee SM, Khan I, Upadhyay S, et al. First-line erlotinib in patients with advanced non-small-cell lung cancer unsuitable for chemotherapy (TOPICAL): a double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2012;13(11):1161–1170.
44. Pérol M, Chouaid C, Pérol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non–small-cell lung cancer. *J Clin Oncol*. 2012;30(28):3516–3524.
45. Bell DW, Lynch TJ, Haserlat SM, et al. Epidermal growth factor receptor mutations and gene amplification in non–small-cell lung cancer: molecular analysis of the IDEAL/INTACT gefitinib trials. *J Clin Oncol*. 2005;23(31):8081–8092.
46. Hotta K, Kiura K, Fujiwara Y, et al. Role of survival post-progression in phase III trials of systemic chemotherapy in advanced non-small-cell lung cancer: a systematic review. *PLoS One*. 2011;6(11):e26646.
47. Fleming TR. Standard versus adaptive monitoring procedures: a commentary. *Stat Med.* 2006;25(19):3305–3312.
48. Fleming TR, Rothmann MD, Lu HL. Issues in using progression-free survival when evaluating oncology products. *J Clin Oncol*. 2009;27(17):2874–2880.
49. Dodd LE, Korn EL, Freidlin B, et al. Blinded independent central review of progression-free survival in phase III clinical trials: important design element or unnecessary expense? *J Clin Oncol.* 2008;26(22):3791–3796.
50. Ciardiello F, Caputo R, Bianco R, et al. Antitumor effect and potentiation of cytotoxic drugs activity in human cancer cells by ZD-1839 (Iressa), an epidermal growth factor receptor-selective tyrosine kinase inhibitor. *Clin Cancer Res*. 2000;6(5):2053–2063.
51. Sirotnak FM, Zakowski MF, Miller VA, Scher HI, Kris MG. Efficacy of cytotoxic agents against human tumor xenografts is markedly enhanced by coadministration of ZD1839 (Iressa), an inhibitor of EGFR tyrosine kinase. *Clin Cancer Res*. 2000;6(12):4885–4892.
52. Jänne PA, Wang X, Socinski MA, et al. Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who were never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 trial. *J Clin Oncol.* 2012;30(17):2063–2069.
53. Luis P-A. Beyond first-line NSCLC therapy: chemotherapy or erlotinib? *Lancet Oncol.* 2012;13(3):225–227.

54. Tsiatis AC, Norris-Kirby A, Rich RG, et al. Comparison of Sanger sequencing, pyrosequencing, and melting curve analysis for the detection of KRAS mutations: diagnostic and clinical implications. *J Mol Diagn*. 2010;12(4):425–432.
55. Maheswaran S, Sequist LV, Nagrath S, et al. Detection of mutations in EGFR in circulating lung-cancer cells. *N Engl J Med*. 2008;359(4):366–377.
56. Rosell R, Molina MA, Costa C, et al. Pretreatment EGFR T790M mutation and BRCA1 mRNA expression in erlotinib-treated advanced non–small-cell lung cancer patients with EGFR mutations. *Clin Cancer Res*. 2011;17(5):1160–1168.
57. Su K-Y, Chen H-Y, Li K-C, et al. Pretreatment epidermal growth factor receptor (EGFR) T790M mutation predicts shorter egfr tyrosine kinase inhibitor response duration in patients with non–small-cell lung cancer. *J Clin Oncol*. 2012;30(4):433–440.

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