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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Impact of Specific Epidermal Growth Factor Receptor (*EGFR*) Mutations and Clinical Characteristics on Outcomes After Treatment With EGFR Tyrosine Kinase Inhibitors Versus Chemotherapy in *EGFR*-Mutant Lung Cancer: A Meta-Analysis

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ABSTRACT

Purpose
We examined the impact of different epidermal growth factor receptor (*EGFR*) mutations and clinical characteristics on progression-free survival (PFS) in patients with advanced *EGFR*-mutated non–small-cell lung cancer treated with EGFR tyrosine kinase inhibitors (TKIs) as first-line therapy.

Patients and Methods
This meta-analysis included randomized trials comparing EGFR TKIs with chemotherapy. We calculated hazard ratios (HRs) and 95% CIs for PFS for the trial population and prespecified subgroups and calculated pooled estimates of treatment efficacy using the fixed-effects inverse-variance-weighted method. All statistical tests were two sided.

Results
In seven eligible trials (1,649 patients), EGFR TKIs, compared with chemotherapy, significantly prolonged PFS overall (HR, 0.37; 95% CI, 0.32 to 0.42) and in all subgroups. For tumors with exon 19 deletions, the benefit was 50% greater (HR, 0.24; 95% CI, 0.20 to 0.29) than for tumors with exon 21 L858R substitution (HR, 0.48; 95% CI, 0.39 to 0.58; $P_{interaction} < .001$). Never-smokers had a 36% greater benefit (HR, 0.32; 95% CI, 0.27 to 0.37) than current or former smokers (HR, 0.50; 95% CI, 0.40 to 0.63; $P_{interaction} < .001$). Women had a 27% greater benefit (HR, 0.33; 95% CI, 0.28 to 0.38) than men (HR, 0.45; 95% CI, 0.36 to 0.55; treatment-sex interaction $P = .02$). Performance status, age, ethnicity, and tumor histology did not significantly predict additional benefit from EGFR TKIs.

Conclusion
Although EGFR TKIs significantly prolonged PFS overall and in all subgroups, compared with chemotherapy, greater benefits were observed in those with exon 19 deletions, never-smokers, and women. These findings should enhance drug development and economic analyses, as well as the design and interpretation of clinical trials.

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INTRODUCTION

Advanced non–small-cell lung cancer (NSCLC) with activating mutations in the epidermal growth factor receptor (*EGFR*) gene is a distinct subtype of disease that is characterized by a high tumor response rate when treated with small-molecule EGFR tyrosine kinase inhibitors (TKIs). Randomized trials[1-8] and meta-analyses[9-11] have consistently demonstrated longer progression-free survival (PFS) with EGFR TKI therapy compared with chemotherapy.

Deletions in exon 19 and substitution of leucine for arginine (L858R) in exon 21 of the *EGFR* gene (so-called common mutations) constitute approximately 90% of all *EGFR* mutations that are detected in patients with advanced NSCLC who are enrolled onto randomized trials.[1,2,6,7] Common and uncommon mutation status is used as a stratification factor in many EGFR TKI trials. Although the two common mutations have been regarded as similar in predicting the benefit of EGFR TKIs, subgroup analyses of two studies[6,8] suggested that the benefit of EGFR TKIs is greater in exon 19 deletion

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than in exon 21 L858R substitution tumors. However, these findings have not been consistently observed in other trials.[2-5,7]

In the landmark NCIC Clinical Trials Group study BR.21,[12] Asian origin, adenocarcinoma histology, never smoking, and erlotinib were associated with improved overall survival (OS). Subsequent molecular analysis also showed that the benefit of erlotinib was strongly associated with *EGFR* mutation in this trial, and *EGFR* mutations were also more commonly detected in women, patients of Asian origin, patients with adenocarcinoma, and never-smokers.[13,14] Among patients with *EGFR* mutations, the influence of these clinical characteristics on the additional benefit of EGFR TKIs is unknown.

Individual randomized trials have not been designed nor adequately powered to demonstrate a treatment difference between subgroups of patients with these common mutations and other clinicopathologic characteristics. Identifying such factors may be important for future clinical trial design and development of newer generations of EGFR TKIs. To address these questions, this study was designed with the primary objective of testing the hypothesis that the relative effect on PFS of first-line therapy with EGFR TKIs versus chemotherapy is affected by mutation type. Secondary objectives were to test for interactions between clinical characteristics (age, sex, ethnicity, smoking status, performance status, tumor histology) that might be associated with EGFR TKI benefit in a population with *EGFR* mutations.

Ideally, a meta-analysis of randomized trials with OS as the primary end point will address these questions. However, in all of these trials, the effect of EGFR TKIs on OS has been diminished for two reasons: first, nearly all of the patients who were randomly assigned to chemotherapy crossed over to receive EGFR TKIs after disease progression, and second, EGFR TKIs are commercially available outside of clinical trial settings. Furthermore, unlike with EGFR TKIs, the benefit of chemotherapy diminished in second-line as compared with first-line settings. For these reasons, we performed this meta-analysis of PFS outcome using randomized trial data from patients undergoing first-line treatment with first-and second-generation EGFR TKIs.

PATIENTS AND METHODS

Study Eligibility and Identification

Eligible studies were identified from our previous broad systematic review that assessed the effectiveness of EGFR TKIs by *EGFR* mutation status.[9] The included studies were randomized trials that compared EGFR TKIs against platinum-based combination chemotherapy in adult patients with good performance status who did not receive any systemic therapy for their histologically or cytologically confirmed, newly diagnosed advanced NSCLC with sensitizing *EGFR* mutations. In brief, we updated our bibliographic search of MEDLINE, EMBASE, CANCERLIT, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases for articles published in English between January 1, 2004, and February 28, 2014, using the following search terms: lung neoplasms, non–small-cell lung cancer, gefitinib, erlotinib, afatinib, EGFR, meta-analysis, systematic review, randomized, and clinical trials. To identify unpublished studies, we also searched abstracts from conference proceedings of the American Society of Clinical Oncology, the European Society for Medical Oncology, and the World Lung Cancer Conference. Individual study sponsors and study investigators were contacted for conference presentation slides whenever slides were unavailable.

Data Extraction

For each included trial, we extracted the trial name, year of publication or conference presentation, clinicopathologic characteristics, type of chemotherapy, and type of EGFR TKIs. We also retrieved treatment estimates for these subgroups: age (< 65 *v* ≥ 65 years), sex (female *v* male), ethnicity (Asian *v* non-Asian), smoking status (never-smoker *v* current or former smoker), Eastern Cooperative Oncology Group (ECOG) performance status (0 and 1 *v* 2), tumor histology (adenocarcinoma *v* other), and *EGFR* mutation (exon 19 deletion *v* exon 21 L858R substitution) subtype. Data were extracted independently by two authors (P.N.D. and C.K.L.), and discrepancies were resolved by consensus that included a third author (S.J.L.). Risk of bias for PFS analysis in each trial was assessed by examining the methods used in random assignment, allocation concealment, outcome assessments, handling of patient attrition, use of intention-to-treat analysis, and handling of missing data for subgroup analyses.

Statistical Analyses

We extracted the hazard ratios (HRs) and 95% CIs for the overall cohort and subgroups. Data from independent assessment of PFS were used in preference to investigator assessment whenever both types of review were available. We used the fixed-effects inverse-variance-weighted method to pool the results from the studies and to estimate the size of the treatment benefit. Tests for interaction were used to assess differences in treatment effect across subgroups as defined by their baseline clinicopathologic characteristics.

Subgroups with statistically significant heterogeneity in treatment effect were examined further using individual patient data from four trials: NEJ002 (North East Japan 002),[2,15] OPTIMAL,[4] EURTAC (European Tarceva Versus Chemotherapy),[5] and WJTOG (West Japan Thoracic Oncology Group) trial 3405.[3,16] We re-estimated the HRs and 95% CIs in multivariable analyses for the treatment effect for each of these subgroups after adjusting for the other baseline characteristics. We repeated the tests for interaction on the basis of the adjusted HRs to assess differences in treatment effect.

Comparisons between *EGFR* mutations with exon 19 deletions versus exon 21 L858R substitution, with respect to baseline characteristics, involved data from the four trials.[2-5,15,16] The Kaplan-Meier approach was used to examine the difference in PFS between exon 19 deletion and exon 21 L858R substitution in patients who were randomly assigned to the chemotherapy and EGFR TKIs arms separately, and univariable Cox regressions were used to estimate the HRs and 95% CIs.

We performed three sensitivity analyses in which, first, studies were excluded if they reported highly significant subgroup differences in the treatment effect, given that such studies might skew the results if there was selective reporting of chance positive findings; second, the analysis was limited to first-generation EGFR TKIs (gefitinib and erlotinib) because we recognized that there might be differences in efficacy between first- and second-generation EGFR TKIs (afatinib); and third, studies were excluded if the median PFS of the chemotherapy arm differed substantially from that of other included trials because we recognized that there might be differences in efficacy between the different types of platinum combination chemotherapies.

Publication bias was evaluated using the approach of Gleser and Olkin,[17] with an examination of a funnel plot of the effect size for each subgroup of the trial against the reciprocal of its SE.

We used the χ^2 Cochran Q test to detect any heterogeneity across the different studies and between subgroups. The nominal level of significance was set at 5%. All 95% CIs were two sided.

RESULTS

We identified seven eligible studies[2-8,15,18] for inclusion in this meta-analysis (Fig 1). Trial data were obtained from published manuscripts and conference abstracts for three trials.[6-8] Updated individual patient data from the NEJ002[2,15] and OPTIMAL[4] trials were used for subgroup results. Individual patient data with longer follow-up than previously published for EURTAC[5] and WJTOG 3405[3,16] trials were used. Data that were based on independent reviews for PFS were used

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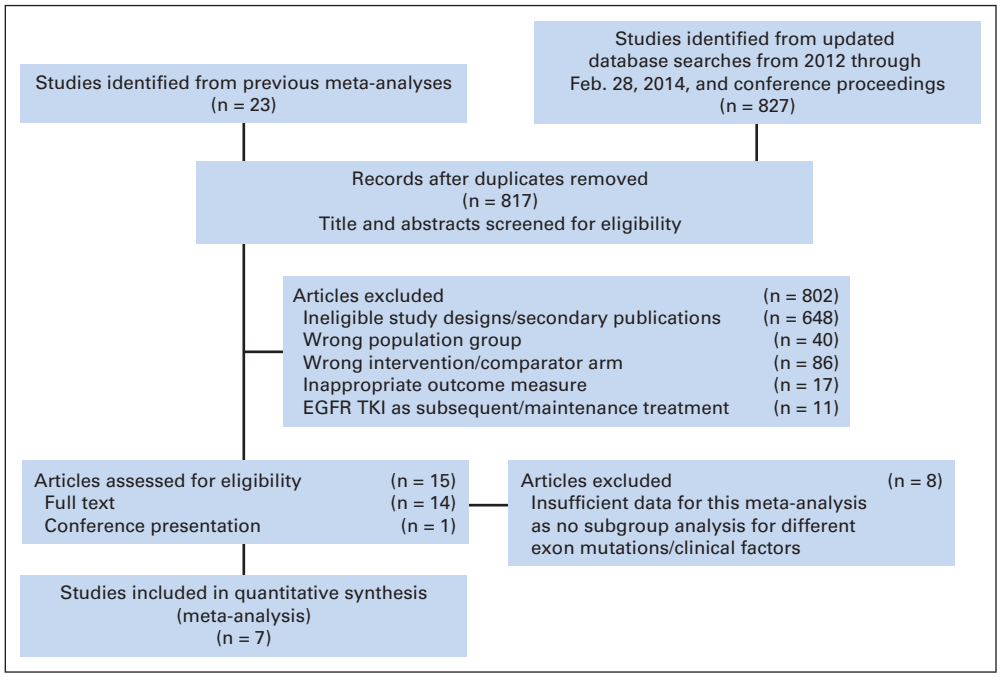

Fig 1. Flow diagram showing inclusion and exclusion of studies. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

for two studies.[6,7] Hoffmann-La Roche provided unpublished subgroup data for the ENSURE trial that was based on investigator assessment only.[8] All included trials were open label. Risk of bias was assessed as unclear in one unpublished trial,[8] and low for all other studies, although one trial[4] did not include independent review of disease progression.

A total of 1,649 patients participated in these trials. All trials except NEJ002,[2] LUX-Lung 3,[6] and LUX-Lung 6[7] recruited only patients with the two common *EGFR* mutations, exon 19 deletions and exon 21 L858R substitution. Other clinicopathologic characteristics of patients are summarized in Table 1.

Benefit of EGFR TKIs for PFS

Of the 1,649 patients, 950 (58%) had been randomly assigned to EGFR TKIs, and 699 (42%) patients had been randomly assigned to chemotherapy. Treatment with EGFR TKIs compared with chemotherapy was statistically significantly associated with a 63% reduction in the risk of disease progression or death (HR, 0.37; 95% CI, 0.32 to 0.42; $P < .001$).

Subgroup Analyses

Of the 1,558 patients with common mutations, 872 (56%) patients had exon 19 deletions and 686 (44%) had exon 21 L858R

Table 1. Characteristics of Patients in Constituent Trials

Study Name, Year	Treatment Comparison	Median PFS (months)	No. of Patients	Exon 19 Deletion (%)	Exon 21 L858R Substitution (%)	Age < 65 Years (%)	ECOG PS 0 and 1 (%)	Asian (%)	Women (%)	Never-Smoker (%)	Adenocarcinoma (%)
NEJ002, 2010, 2013[2,15*]	Gefitinib *v* CP	10.8 *v* 5.4	224†	51	43	49	99	100	63	62	93
WJTOG 3405, 2010, 2012[3,16]	Gefitinib *v* CisD	9.6 *v* 6.5	172	51	49	53	100	100	69	69	97
OPTIMAL, 2011, 2012[4,18]	Erlotinib *v* CG	13.1 *v* 4.6	154	53	47	75	94	100	59	71	87
EURTAC, 2012[5]	Erlotinib *v* platinum-G or platinum-D	9.7 *v* 5.2	173	66	34	49	86	0	73	69	92
LUX-Lung 3, 2013[6*]	Afatinib *v* CisPem	11.1 *v* 6.9	345	49	40	61	100	72	65	68	100
LUX-Lung 6, 2014[7*]	Afatinib *v* CisG	11.0 *v* 5.6	364	51	38	76	100	100	65	77	100
ENSURE, 2014[8‡]	Erlotinib *v* CisG	11.0 *v* 5.5	217	54	45	79	94	100	61	71	94

Abbreviations: CG, carboplatin-gemcitabine; CisD, cisplatin-docetaxel; CisG, cisplatin-gemcitabine; CisPem, cisplatin-pemetrexed; CP, carboplatin-paclitaxel; ECOG, Eastern Cooperative Oncology Group; EURTAC, European Tarceva Versus Chemotherapy; NEJ002, North East Japan 002; PFS, progression-free survival; PS, performance status; WJTOG, West Japan Thoracic Oncology Group.
*Includes patients with uncommon mutations of the *EGFR* gene.
†NEJ002 recruited a total of 228 patients; PFS outcome was only reported for 224 patients.
‡Reported in abstract only.

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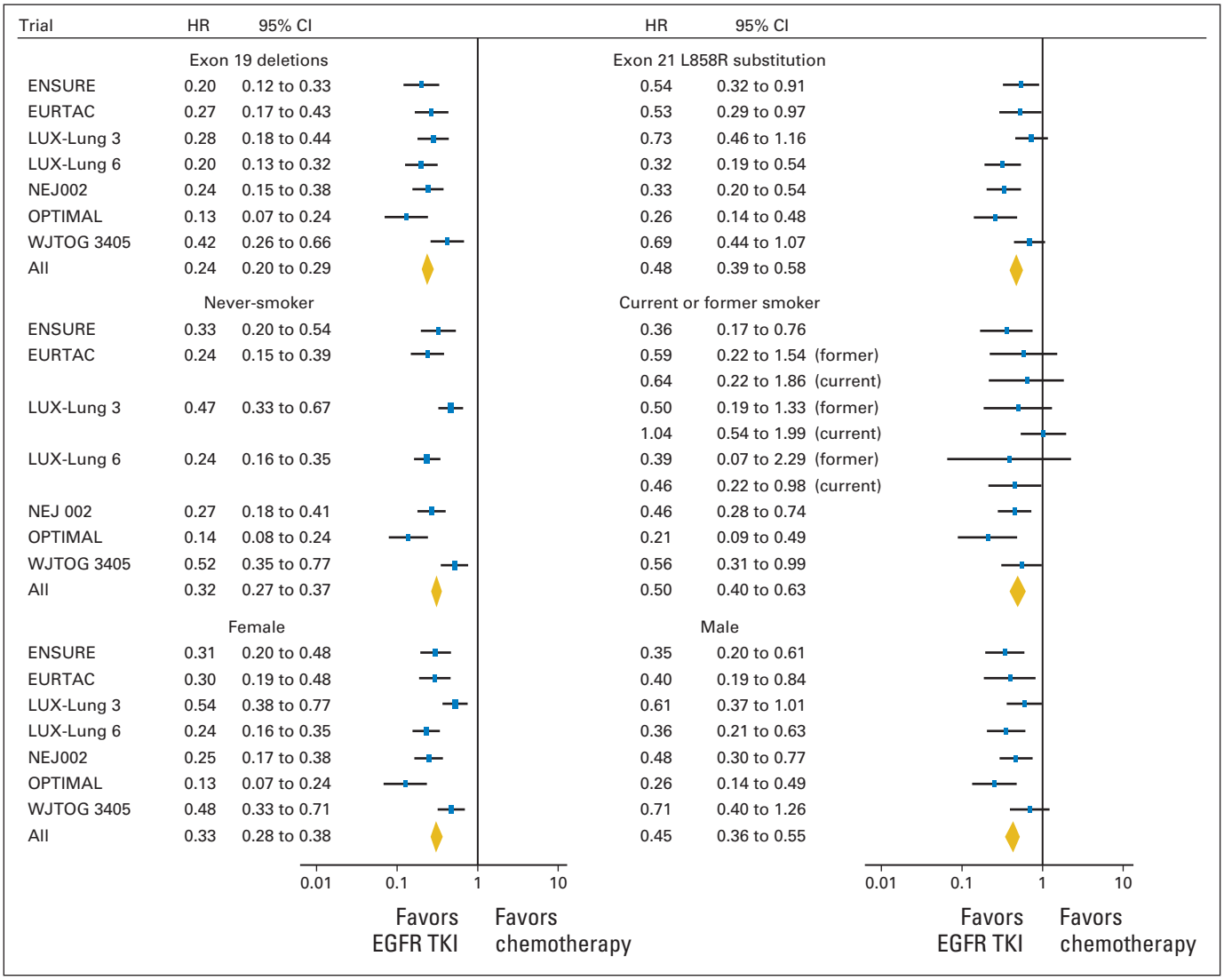

Fig 2. Forest plot of the effect of treatment on progression-free survival in subgroups of patients according to mutations of the epidermal growth factor receptor (*EGFR*) gene, smoking status, and sex. Hazard ratios (HRs) for each trial are represented by the squares, and the horizontal line crossing the square represents the 95% CI. The diamonds represent the estimated overall effect based on the meta-analysis fixed effect. All statistical tests were two sided. EURTAC, European Tarceva Versus Chemotherapy; NEJ002, North East Japan 002; TKI, tyrosine kinase inhibitor; WJTOG, West Japan Thoracic Oncology Group.

substitution. In the subgroup with exon 19 deletions, the pooled HR for PFS was 0.24 (95% CI, 0.20 to 0.29; $P < .001$). In the exon 21 L858R substitution subgroup, the pooled HR for PFS was 0.48 (95% CI, 0.39 to 0.58; $P < .001$). Compared with chemotherapy, treatment with EGFR TKIs demonstrated 50% greater benefit in exon 19 deletions than in exon 21 L858R substitution (interaction $P < .001$; Fig 2).

Of the 1,649 patients, most were never-smokers (n = 1,155; 70%) and 494 (30%) were current or former smokers. Among the never-smokers, the pooled HR for PFS was 0.32 (95% CI, 0.27 to 0.37; $P < .001$). Among the current or former smokers, the pooled HR for PFS was 0.50 (95% CI, 0.40 to 0.63; $P < .001$). Compared with chemotherapy, treatment with EGFR TKIs demonstrated a 36% greater benefit in never-smokers than current or former smokers (interaction $P = .002$; Fig 2).

Most patients (n = 1,073; 65%) were women; 576 (35%) were men. Among the women, the pooled HR for PFS was 0.33 (95% CI, 0.28 to 0.38; $P < .001$). Among the men, the pooled HR for PFS was 0.45 (95% CI, 0.36 to 0.55; $P < .001$). Compared with chemotherapy, EGFR TKI treatment demonstrated a 27% greater benefit in women than men (interaction $P = .02$; Fig 2).

In multivariable analysis using data from the four trials,[2-5,15,16] the pooled HRs for PFS were 0.26 and 0.44, adjusted for smoking status and sex, for exon 19 deletions and exon 21 L858R substitution subgroups, respectively (interaction $P = .004$). There was negligible difference in the result between unadjusted and adjusted HRs (exon 19 deletions: unadjusted pooled HR, 0.26; exon 21 L858R substitution: unadjusted pooled HR, 0.45; interaction $P = .004$). Table 2 compares the unadjusted and adjusted HRs of treatment effect to assess any potential inter-related impact of type of *EGFR* mutation, sex, and smoking on benefit with EGFR TKIs.

The improvement in PFS with EGFR TKI treatment compared with chemotherapy did not differ by ethnicity (interaction $P = .37$), age (interaction $P = .27$), tumor histologic subtype (interaction $P = .59$), or performance status (interaction $P = .85$; Fig 3).

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Table 2. Unadjusted and Adjusted Treatment Effect of EGFR TKIs Versus Chemotherapy in Four Clinical Trials

Subgroup	Unadjusted Analysis HR	Unadjusted Analysis 95% CI	Adjusted Analysis HR	Adjusted Analysis 95% CI
Exon 19 deletions				
EURTAC	0.27	0.17 to 0.43	0.25*	0.15 to 0.41
NEJ002	0.24	0.15 to 0.38	0.24*	0.15 to 0.38
OPTIMAL	0.13	0.07 to 0.25	0.12*	0.06 to 0.22
WJTOG 3405	0.42	0.26 to 0.68	0.46*	0.28 to 0.76
Pooled result	0.26	0.20 to 0.34	0.26	0.20 to 0.33
Exon 21 L858R substitution				
EURTAC	0.53	0.29 to 0.97	0.51*	0.28 to 0.94
NEJ002	0.33	0.20 to 0.54	0.33*	0.20 to 0.55
OPTIMAL	0.26	0.14 to 0.49	0.23*	0.12 to 0.45
WJTOG 3405	0.69	0.44 to 1.07	0.69*	0.44 to 1.08
Pooled result	0.45	0.34 to 0.58	0.44	0.34 to 0.58
Treatment-*EGFR* mutation interaction		$P = .004$		$P = .004$
Never-smoker				
EURTAC	0.24	0.15 to 0.39	0.23†	0.14 to 0.38
NEJ002	0.27	0.18 to 0.41	0.24†	0.16 to 0.37
OPTIMAL	0.14	0.08 to 0.25	0.14†	0.08 to 0.25
WJTOG 3405	0.52	0.35 to 0.77	0.52†	0.34 to 0.79
Pooled result	0.29	0.24 to 0.37	0.28	0.22 to 0.35
Current or former smoker				
EURTAC (former)	0.59	0.22 to 1.54	0.67†	0.25 to 1.78
EURTAC (current)	0.64	0.22 to 1.86	0.56†	0.19 to 1.71
NEJ002	0.46	0.28 to 0.74	0.45†	0.28 to 0.73
OPTIMAL	0.21	0.09 to 0.49	0.20†	0.08 to 0.47
WJTOG 3405	0.56	0.31 to 0.99	0.57†	0.32 to 1.02
Pooled result	0.46	0.34 to 0.62	0.46†	0.34 to 0.62
Treatment-smoking interaction		$P = .02$		$P = .01$
Women				
EURTAC	0.30	0.19 to 0.48	0.29‡	0.18 to 0.47
NEJ002	0.25	0.17 to 0.38	0.21‡	0.14 to 0.33
OPTIMAL	0.13	0.07 to 0.24	0.13‡	0.07 to 0.24
WJTOG 3405	0.48	0.33 to 0.71	0.50‡	0.33 to 0.76
Pooled result	0.30	0.24 to 0.38	0.28	0.22 to 0.36
Men				
EURTAC	0.40	0.19 to 0.84	0.37‡	0.17 to 0.81
NEJ002	0.48	0.30 to 0.77	0.45‡	0.28 to 0.74
OPTIMAL	0.26	0.14 to 0.50	0.23‡	0.12 to 0.45
WJTOG 3405	0.71	0.40 to 1.26	0.69‡	0.39 to 1.22
Pooled result	0.46	0.34 to 0.61	0.43	0.32 to 0.58
Treatment-sex interaction		$P = .02$		$P = .03$

Abbreviations: EGFR, epidermal growth factor receptor; EURTAC, European Tarceva Versus Chemotherapy; HR, hazard ratio; NEJ002, North East Japan 002; TKI, tyrosine kinase inhibitor; WJTOG, West Japan Thoracic Oncology Group.
*HR (EGFR TKI *v* chemotherapy) adjusted for smoking status and sex.
†HR (EGFR TKI *v* chemotherapy) adjusted for sex and type of *EGFR* mutation.
‡HR (EGFR TKI *v* chemotherapy) adjusted for smoking status and type of *EGFR* mutation.

Benefit of EGFR TKIs for OS

At the point of data cutoff for this analysis, several trials had reported preliminary OS data and had patients still in active follow-up. The data for OS remained immature for many of these studies. The OS data for the ENSURE trial was unavailable.[8] With the available preliminary OS data from the remaining six trials, treatment with EGFR TKIs compared with chemotherapy was not statistically significantly associated with reduction in the risk of death (HR, 1.01; 95% CI, 0.86 to 1.19; $P = .88$).

Association Between Mutations and Baseline Clinical Characteristics

In four trials,[2-5,15,16] there were no significant correlations between *EGFR* mutation type and age, performance status, sex, histology, or smoking status (Table 3).

Prognostic Outcomes for Patients With Common Mutations

Of the 348 patients in the four trials[2-5,15,16] who were randomly assigned to chemotherapy, those with exon 21 L858R substitution (n = 158) had a median PFS of 6.1 months, which was statistically significantly longer than those with exon 19 deletions (n = 190), who had a median PFS of 5.1 months (HR, 0.70; 95% CI, 0.56 to 0.89; $P = .003$). In comparison, of the 362 patients who were randomly assigned to EGFR TKIs in these trials, patients with exon 21 L858R substitution (n = 154) had a median PFS of 10.0 months, which was statistically significantly shorter than that of patients with exon 19 deletions (n = 208), who had a median PFS of 11.8 months (HR, 1.39; 95% CI, 1.10 to 1.76; $P = .006$).

Publication Bias

A funnel plot of the effect size for each subgroup category of the trial against the precision showed no asymmetry (not shown). A formal test[17] for potential publication bias yielded no potential unpublished studies.

Sensitivity Analyses

Two trials[6,8] individually demonstrated greater PFS benefit for EGFR TKIs versus chemotherapy in tumors with exon 19 deletions compared with those with exon 21 L858R substitution; therefore, we excluded these studies and observed consistent results (HR, 0.24 *v* 0.42; interaction $P < .001$; Appendix Fig A1, online only).

Restricting our analyses to trials of first-generation reversible EGFR TKIs, erlotinib[4,5,8,18] and gefitinib[2,3,15,16] (Appendix Fig A2, online only), we also found consistent results: greater benefit with EGFR TKIs for exon 19 deletions (interaction $P < .001$), never-smokers (interaction $P = .03$), and women (interaction $P = .03$).

Two trials[3,6] individually demonstrated median PFS greater than 6 months in the chemotherapy arm. Given that this was a longer PFS than reported in other studies (Table 1), we excluded these two studies and observed consistent results: greater benefit for EGFR TKIs for exon 19 deletions (interaction $P < .001$), never-smokers (interaction $P = .003$), and women (interaction $P = .01$; Appendix Fig A3, online only).

DISCUSSION

Treatment with EGFR TKIs compared with chemotherapy is associated with a 63% overall reduction in the risk of disease progression or death. Furthermore, the relative effect of EGFR TKIs compared with chemotherapy on PFS is 50% greater for patients with exon 19 deletions than for those with exon 21 L858R substitution. Other crucial findings include a 36% greater PFS benefit for never-smokers than

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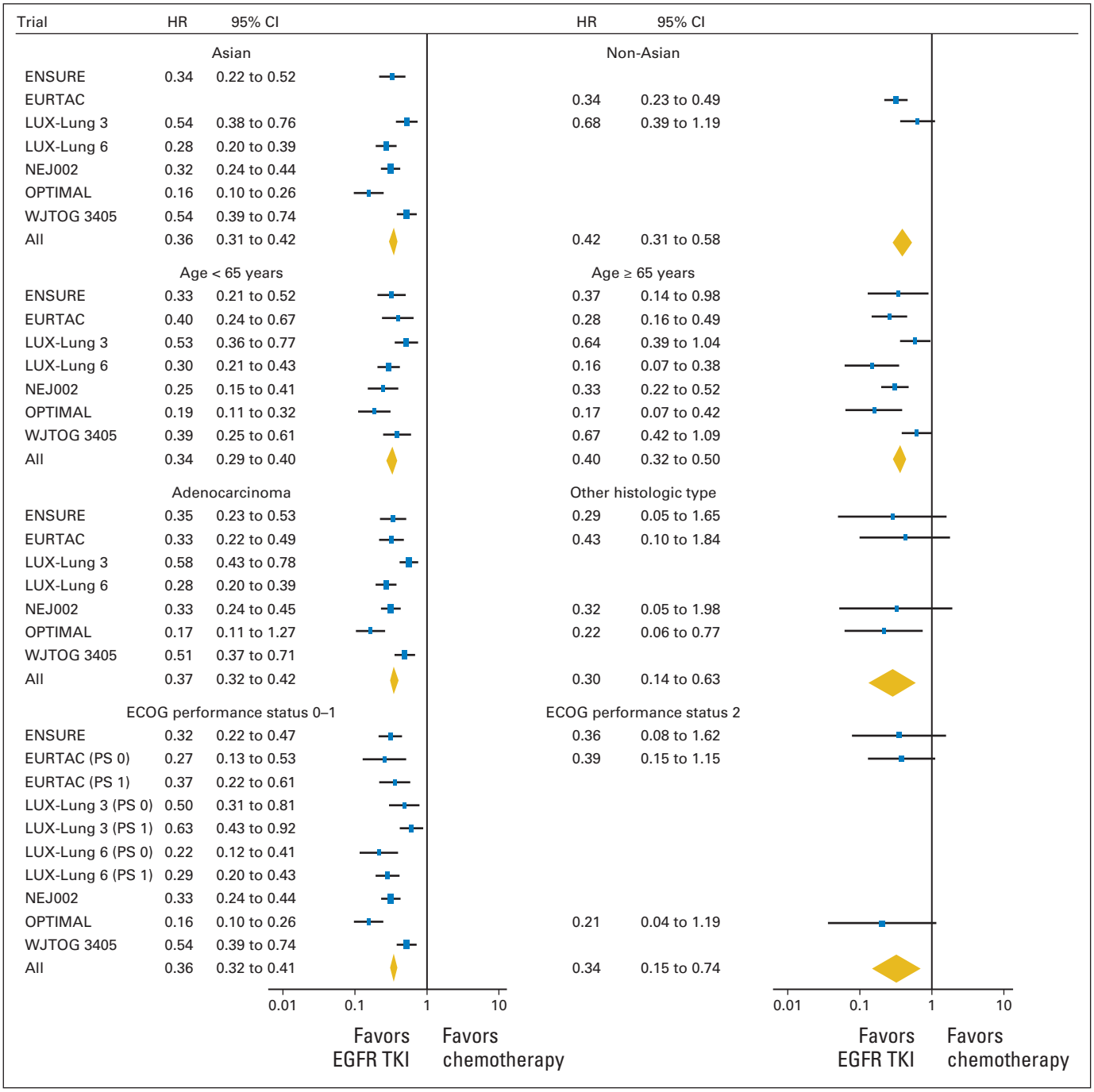

Fig 3. Forest plot of the effect of treatment on progression-free survival in subgroups of patients according to ethnicity, age, tumor histologic subtype, and performance status (PS). Hazard ratios (HRs) for each trial are represented by the squares, and the horizontal line crossing the square represents the 95% CI. The diamonds represent the estimated overall effect based on the meta-analysis fixed effect. All statistical tests were two sided. ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EURTAC, European Tarceva Versus Chemotherapy; NEJ002, North East Japan 002; TKI, tyrosine kinase inhibitor; WJTOG, West Japan Thoracic Oncology Group.

current or former smokers and a 27% greater PFS benefit for women than men with EGFR TKIs compared with chemotherapy.

Consistent with previous studies, patients with exon 19 deletions have a longer OS than those with exon 21 L858R substitution after gefitinib or erlotinib therapy.[19,20] In contrast, in patients who are not treated with EGFR TKIs, exon 21 L858R substitution, rather than exon 19 deletions, has been associated with longer OS.[14] Using data from four trials,[2-5,15,16] we found that patients randomly assigned to chemotherapy who had exon 21 L858R substitution had statistically significantly longer PFS than those with exon 19 deletions (median PFS, 6.1 *v* 5.1 months; $P = .003$). This indicates that patients who harbor exon 19 deletions and are not treated with EGFR TKIs have a poorer prognosis than those with exon 21 L858R substitution. Treatment with EGFR TKIs improves the prognosis more in those with exon 19 deletions than in those with exon 21 L858R substitution (median PFS, 11.8 *v* 10.0 months; $P = .006$).

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Table 3. Association Between Baseline Characteristics and Exon 19 Deletion or Exon 21 L858R Substitution: Pooled Data From Four Clinical Trials

Characteristic	Exon 19 Deletion (n = 401) No.	%	Exon 21 L858R Substitution (n = 313) No.	%	*P*
Age, years					.20
< 65	233	58	166	53	
≥ 65	168	42	147	47	
ECOG PS					.32
0	186	46	136	44	
1	191	48	164	52	
2	24	6	13	4	
Sex					.81
Female	268	67	206	66	
Male	133	33	107	34	
Smoking					.81
Never	268	67	212	68	
Ever	133	33	101	32	
Histologic subtype					.11
Adenocarcinoma	377	94	284	91	
Other	24	6	29	9	

Abbreviations: EGOG, Eastern Cooperative Oncology Group; PS, performance status.

The associations between different *EGFR* mutations and baseline clinicopathologic characteristics remain unclear. Several studies report that exon 21 L858R substitution is more frequently associated with female sex, never smoking, and having adenocarcinoma.[21-23] Use of the largest pooled individual patient data set of common mutations (n = 714) from four trials[2-5,15,16] failed to detect any association between the type of mutation and smoking status ($P = .81$), histology ($P = .11$), or sex ($P = .81$).

Our finding that smoking status modifies EGFR TKI benefit is also supported by existing studies. Smoking was found to be independently associated with poorer tumor response with gefitinib.[24] Smoking was also associated with significantly less drug exposure after ingestion of erlotinib.[25] A phase I study[26] of smokers reported a maximum tolerated erlotinib dose of 300 mg, which was much higher than the dose of 150 mg per day used in randomized trials.[4,5,8] Whether this metabolic difference is the true reason for the PFS difference or whether other factors are involved has yet to be determined, and further research is warranted.

Another interesting finding was that women had a 27% greater PFS benefit with EGFR TKIs than men. The benefit of EGFR TKIs in women has been previously attributed to the higher rate of *EGFR* mutations in women.[14] In this meta-analysis involving only trials conducted in populations with *EGFR* activating mutations, a difference in PFS benefit on the basis of sex was still detected. As a majority of the nonsmokers were also women in these trials, it is possible that smoking is confounding the interaction between sex and EGFR TKI efficacy. However, multivariable analysis performed using individual patient data from four trials[2-5,15,16] suggests that the predictive effect of sex is largely independent of smoking status and *EGFR* mutation type (Table 2). We acknowledge that there may be a difference between current and former smokers, but our analysis does not discriminate between these two cohorts of patients.

This meta-analysis has several strengths. We performed a comprehensive review, used the most up-to-date published data, and contacted individual investigators or trial sponsors to obtain relevant unpublished data. Another strength is that individual patient data from four trials[2-5,15,16] were available to investigate the relationships between different *EGFR* mutations and baseline clinical characteristics, for multivariable adjustment, and for prognostic analyses.

There are also limitations of this study. We have not reported the treatment effects within subgroups for OS because many of the trials have yet to report mature OS data. In a recently presented pooled analysis of two randomized trials, OS was longer with afatinib than chemotherapy, and a statistically significant prolongation of OS was reported in tumors with exon 19 deletions but not exon 21 L858R substitution.[27] It remains unknown whether there would be a similar finding in first-generation EGFR TKI trials. We restricted our study to common *EGFR* mutations, and the predictive value of uncommon mutations remains unknown. We are currently planning an individual patient data meta-analysis using all randomized trials with mature OS data to address the limitations of our current work.

Our results have several important clinical and research implications. Our findings will be useful for counseling patients. Our meta-analysis demonstrates that exon 19 deletion and exon 21 L858R substitution mutations have different prognostic and predictive roles and are hence important as a stratification factor in future clinical trials. Further drug development of EGFR TKIs to enhance antitumor activity, particularly for tumors with exon 21 L858R substitution, remains important.

Another potential use of these findings is in economic analyses. With differences in PFS benefits for various subgroups, there will be differences in the costs required to achieve these benefits. In addition, economic factors related to patient screening may also identify greater cost-benefit for different identifiable subgroups.

In conclusion, EGFR TKIs significantly prolong PFS in all patients with advanced NSCLC with *EGFR* mutations compared with chemotherapy. The relative benefits of EGFR TKIs compared with chemotherapy were greatest in patients with exon 19 deletions. Greater PFS benefit with EGFR TKIs compared with chemotherapy was also seen in never-smokers and women. These findings have important implications for clinical trial design and interpretation, economic analyses, and future drug development for *EGFR*-mutated, advanced NSCLC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Impact of Specific Epidermal Growth Factor Receptor (*EGFR*) Mutations and Clinical Characteristics on Outcomes After Treatment With EGFR Tyrosine Kinase Inhibitors Versus Chemotherapy in *EGFR*-Mutant Lung Cancer: A Meta-Analysis

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Appendix

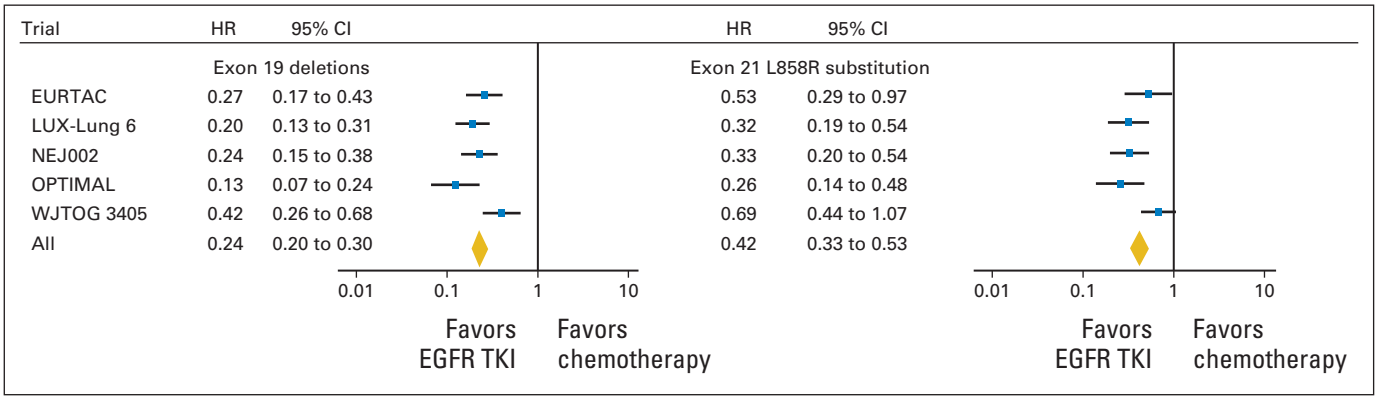

Fig A1. Forest plot of effect of treatment on progression-free survival in subgroups of patients according to different mutations of the epidermal growth factor receptor (*EGFR*), with exclusion of the LUX-Lung 3 and ENSURE trials. Hazard ratios (HRs) for each trial are represented by the squares, and the horizontal line crossing the square represents the 95% CI. The diamonds represent the estimated overall effect based on the meta-analysis fixed effect (all $P < .001$). All statistical tests were two sided. EURTAC, European Tarceva Versus Chemotherapy; NEJ002, North East Japan 002; TKI, tyrosine kinase inhibitor; WJTOG, West Japan Thoracic Oncology Group.

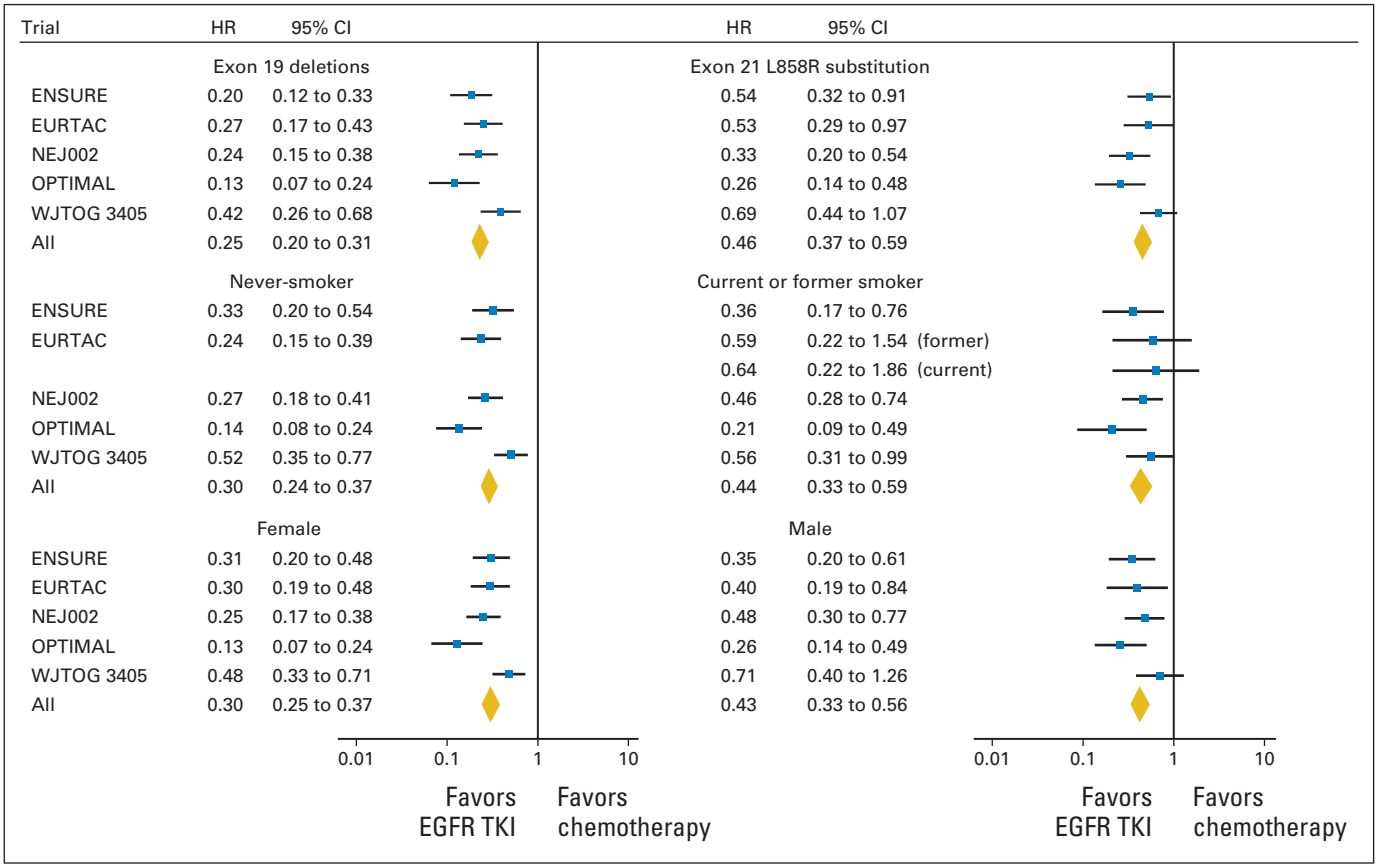

Fig A2. Forest plot of effect of treatment on progression-free survival in subgroups of patients according to mutations of the epidermal growth factor receptor (*EGFR*) gene, smoking status, and sex in gefitinib and erlotinib trials only. Hazard ratios (HRs) for each trial are represented by the squares, and the horizontal line crossing the square represents the 95% CI. The diamonds represent the estimated overall effect based on the meta-analysis of fixed effect (all $P < .001$). All statistical tests were two sided. EURTAC, European Tarceva Versus Chemotherapy; NEJ002, North East Japan 002; TKI, tyrosine kinase inhibitor; WJTOG, West Japan Thoracic Oncology Group.

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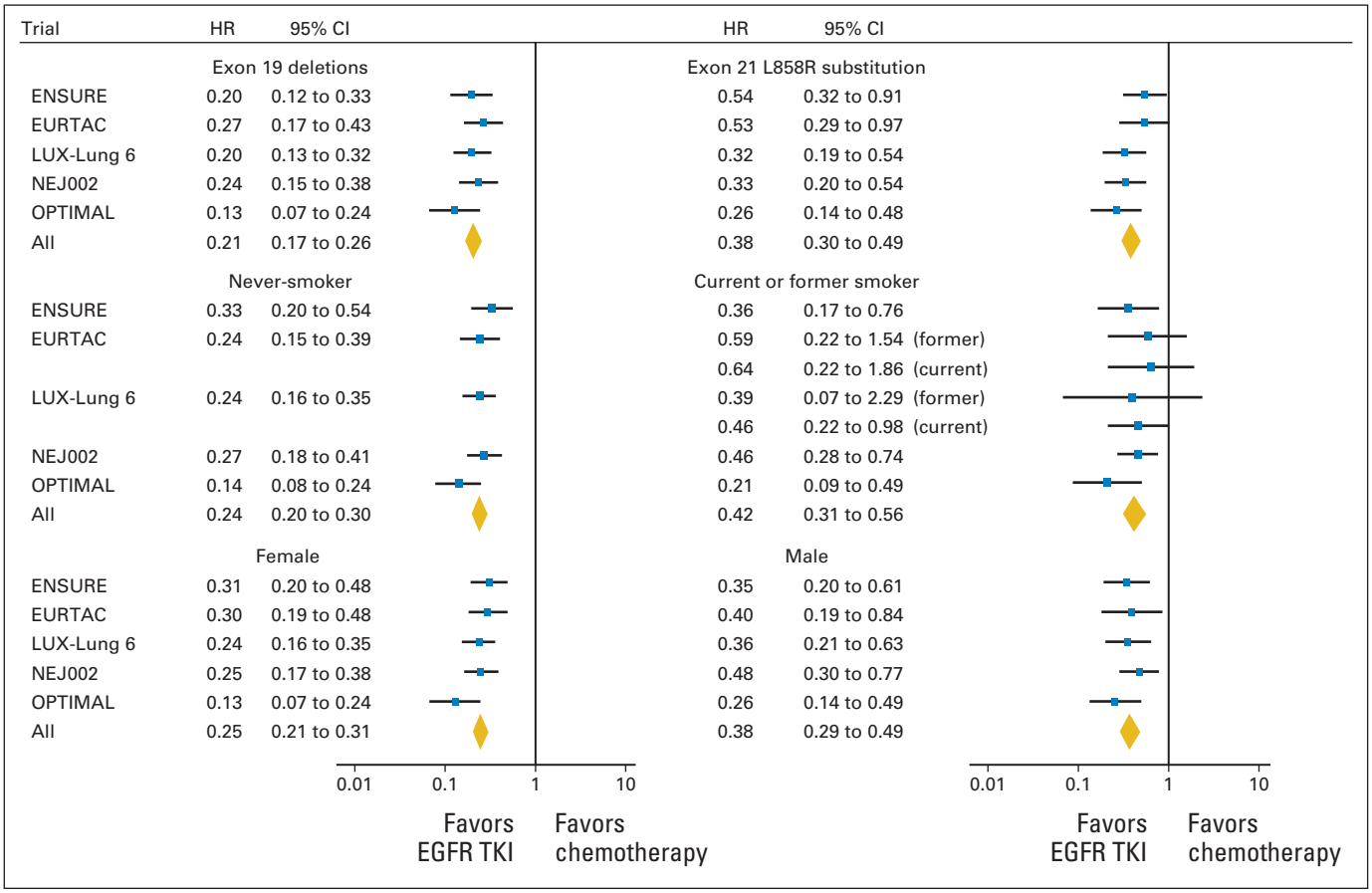

Fig A3. Forest plot of effect of treatment on progression-free survival in subgroups of patients according to different mutations of the epidermal growth factor receptor (*EGFR*), with exclusion of the LUX-Lung 3 and WJTOG 3405 (West Japan Thoracic Oncology Group 3405) trials. HR, hazard ratio; NEJ002, North East Japan 002; TKI, tyrosine kinase inhibitor.

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