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Article

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Gefitinib or Erlotinib vs Chemotherapy for *EGFR* Mutation-Positive Lung Cancer: Individual Patient Data Meta-Analysis of Overall Survival

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Abstract

Background: We performed an individual patient data meta-analysis to examine the impact of first-generation epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitor (TKI) therapy on overall survival (OS) in advanced non–small cell lung cancer (NSCLC).

Methods: Data from trials comparing EGFR-TKI against chemotherapy in exon 19 deletion (del19) or exon 21 L858R (L858R) *EGFR* mutations patients were used. We performed Cox regression to obtain hazard ratios (HRs) and 95% confidence intervals (CIs). Impact of postprogression therapies was examined in exploratory analyses. All statistical tests were two-sided.

Results: Six eligible trials (gefitinib = 3, erlotinib = 3) included 1231 patients; 632 received EGFR-TKI and 599 received chemotherapy. At a median 35.0 months follow-up, there were 780 deaths and 1004 progressions. There was no difference in OS between EGFR-TKI and chemotherapy (HR = 1.01, 95% CI = 0.88 to 1.17, $P = .84$). There was also no difference in OS for Del19 (n = 682, HR = 0.96, 95% CI = 0.79 to 1.16, $P = .68$) and L858R (n = 540, HR = 1.06, 95% CI = 0.86 to 1.32, $P = .59$) subgroups ($P_{interaction} = .47$), or according to smoking status, sex, performance status, age, ethnicity, or histology. However, EGFR-TKI statistically significantly prolonged progression-free survival (PFS) overall (HR = 0.37, 95% CI = 0.32 to 0.42, $P < .001$) and in all subgroups. Following progression, 73.8% from the chemotherapy arm received EGFR-TKI, and 65.9% from the EGFR-TKI arm received chemotherapy. Nine percent from the EGFR-TKI arm received no further treatment vs 0.6% from the chemotherapy arm. Following disease progression, patients randomly assigned to EGFR-TKI had shorter OS than those randomly assigned to chemotherapy (12.8 months, 95% CI = 11.4 to 14.3, vs 19.8 months, 95% CI = 17.6 to 21.7).

Conclusions: Despite statistically significant PFS benefit, there is no relative OS advantage with frontline gefitinib or erlotinib vs chemotherapy in *EGFR*-mutated NSCLC. This finding is likely due to the high rate of crossover at progression.

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In advanced non–small cell lung cancer (NSCLC) with activating mutations of the epidermal growth factor receptor (*EGFR*) gene, EGFR tyrosine kinase inhibitor (EGFR-TKI) is the standard of care treatment. Multiple randomized controlled trials (RCTs) have demonstrated improvement in progression-free survival (PFS) when comparing EGFR-TKI against platinum-based chemotherapy in this genetically distinct subset of NSCLC (1–8).

In all firstline RCTs comparing EGFR-TKI against chemotherapy in patients with known activating *EGFR* mutations, overall survival (OS) was a key secondary end point. Despite statistically significant PFS benefit, no trials have reported a statistically significant OS difference between the randomized groups (1,2,9–13). These conflicting findings are perplexing, and the reason has been widely speculated to be due to salvage treatment effect with EGFR-TKI and chemotherapy in patients randomly assigned to chemotherapy and EGFR-TKI, respectively (14).

In addition, there has also been interest in the influence of different *EGFR* mutation types on EGFR-TKI treatment efficacy. When treated with afatinib, a second-generation EGFR-TKI, there were 46% and 36% reductions in risk of death over chemotherapy in LUX-Lung 3 and LUX-Lung 6 trials, respectively (13). In contrast, there was no difference in OS benefit for those with exon 21 substitution of leucine for arginine (L858R). In RCTs of the first-generation EGFR-TKIs, the question of OS benefit for different *EGFR* mutation types remains unresolved. Individual trials have not been designed or adequately powered to demonstrate a treatment difference between subgroups of patients with different *EGFR* mutation types or clinical characteristics, thus a meta-analysis is necessary to address these questions.

In this study, the primary objective was to determine the pooled overall treatment effect on OS of firstline therapy with gefitinib or erlotinib as first-generation EGFR-TKI vs chemotherapy in patients with newly diagnosed *EGFR*-mutated advanced NSCLC using individual patient data from RCTs with updated survival outcomes. Secondary objectives were to test for interactions between different *EGFR* mutation types and other baseline characteristics that might be associated with EGFR-TKI benefit. An exploratory analysis was also performed to assess the potential impact of postprogression therapies on OS following progression of firstline randomized treatments.

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Methods

Eligible RCTs were identified from our prior systematic review, which assessed the effectiveness of EGFR-TKI on PFS (15). In brief, we searched MEDLINE, EMBASE, CANCERLIT, and the Cochrane Central Register of Controlled Trials 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, 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.

RCTs that compared firstline therapy with gefitinib or erlotinib against platinum-based combination chemotherapy were eligible for analysis. Other RCT inclusion criteria were: patients had advanced incurable disease; *EGFR* mutation status was known in 100 or more patients (to minimize nonrandom distribution of subgroups with different predictive or prognostic factors); both PFS and OS were reported as outcomes.

The principal investigators and/or the sponsors of eligible RCTs were contacted for individual patient data (IPD). For eligible studies, selective baseline characteristics and survival outcomes–anonymized data were transferred electronically by all principal investigators and trial sponsors via secured websites to the University of Sydney for analysis. To check data retrieval accuracy, all results reported in prior RCT publications were replicated. Patients were excluded from further analysis if they had uncommon *EGFR* mutations, *EGFR* wild-type, or *EGFR* mutation status unknown.

Statistical Analyses

The study cohort consisted of only patients with common *EGFR* mutations (deletions in exon 19 and L858R in exon 21 of the *EGFR* gene). For each RCT, we compared OS and PFS between treatment groups (EGFR-TKI vs chemotherapy) using a log-rank test, and we estimated the hazard ratios (HRs) and 95% confidence intervals (CIs) from the Cox proportional hazard models of the overall cohort and subgroups. The subgroups examined were age (<65 vs ≥ 65 years), sex (female vs male), ethnicity (Asian vs non-Asian), smoking status (never smoker vs current or former smoker), performance status (PS; 0 and 1 vs 2), tumor histology (adenocarcinoma vs other), and *EGFR* mutation (exon 19 deletion vs exon 21 L858R) subtype. We used the fixed effects inverse variance–weighted method to pool the results from these studies to estimate the size of the overall treatment benefit. Tests for interaction were used to assess differences in treatment effect across subgroups. We further examined for the prognostic impact of baseline clinicopathologic variables in univariate and multivariable Cox regression analyses stratified by treatment and trial. The proportional hazards assumption of all multivariable Cox models was confirmed using the Harrell and Lee modification of the Schoenfeld goodness of fit test (16).

To explore the impact of cancer treatments after progression, we grouped patients according to their postprogression therapies as: 1) "none" if no systemic therapy, 2) "EGFR-TKI" if this was one of the postprogression therapies received for patients randomly assigned to chemotherapy, 3) "EGFR-TKI" if this was the only class of therapy received for patients randomly assigned to EGFR-TKI, 4) "chemotherapy" if this was one of the postprogression therapies received for patients randomly assigned to EGFR-TKI, 5) "chemotherapy" if this was the only class of therapy received for patients randomly assigned to chemotherapy, 6) "other" nonchemotherapy or non-EGFR-TKI, and 7) "unknown." We then compared the rates and types of postprogression therapies received between randomly assigned groups. We further compared the difference in time from progression to death (or censored) between these different postprogression therapies. These analyses are hypothesis generating, and the methods could not adequately minimize the possibility of selection bias, including survivor bias, as addressed in greater detail in the "Discussion" section.

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 standard error. We used the χ^2 Cochran Q test to detect any heterogeneity across the different studies and between subgroups. In all of these analyses, we did not adjust for multiple testing. All *P* values were two-sided.

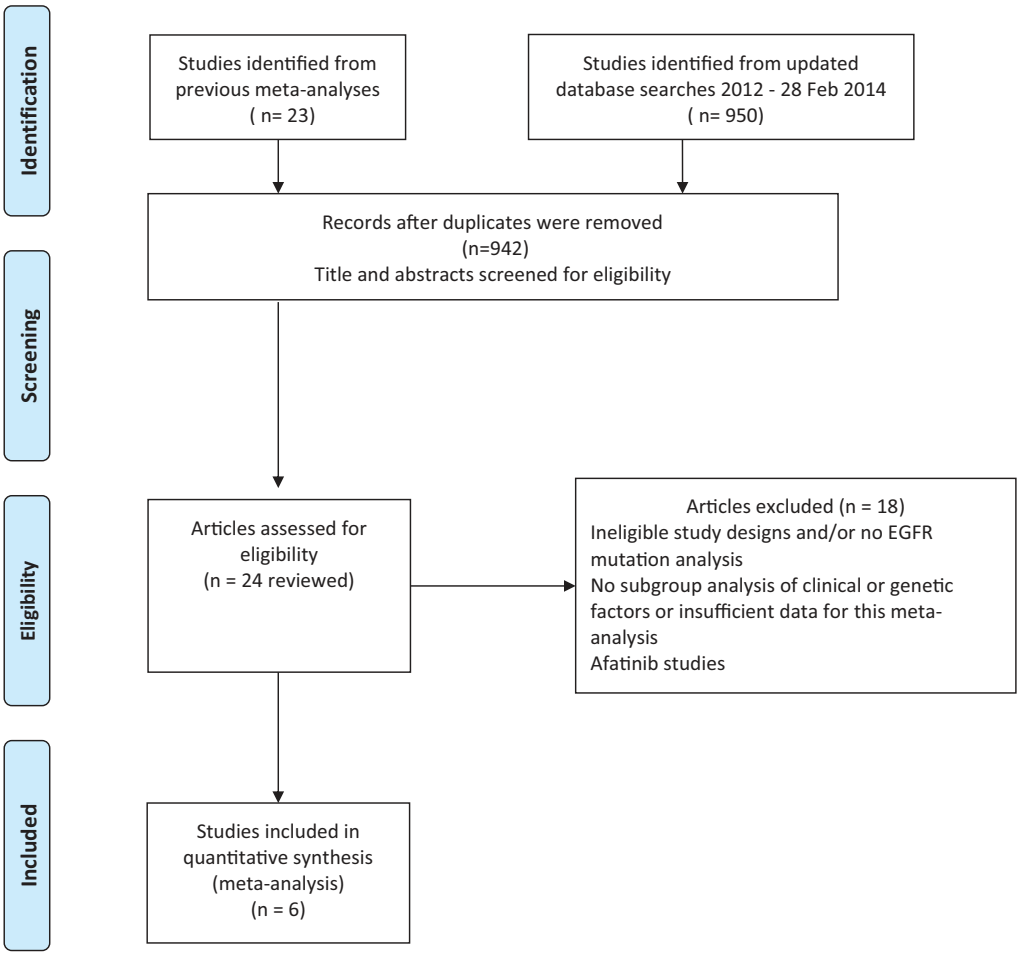

Figure 1. Flow diagram showing inclusion and exclusion of studies. EGFR = epidermal growth factor receptor.

Results

We identified six eligible RCTs for inclusion (Figure 1) that provided IPD from 1231 patients with common *EGFR* mutations (exon 19 deletion: n = 682; exon 21 L858R: n = 540; exons 19 deletion and 21 L858R: n = 9). Each RCT was an open-label, phase III trial conducted in Japan (4,6,10,12), China (5,11), Europe (5,11), or East Asia (1,3,9). Patients were between age 24 to 82 years and had previously untreated stage IIIB (12.6%), IV (80.3%), or postoperative recurrence (6.9%) NSCLC. All except one RCT included PS 2 patients (6,12). In all except one RCT (3,9), tumor tissue had to be *EGFR* mutation positive at screening based on central laboratory analysis before random assignment. Four RCTs (1,2,5,6,11,12) recruited only patients with *EGFR* mutations with exon 19 deletions and/or exon 21 L858R. Three RCTs compared gefitinib (250 mg per day orally) with chemotherapy (3,4,6,9,10,12), and three RCTs compared erlotinib (150 mg per day orally) with chemotherapy (1,2,5,11). In total, 632 (51.3%) patients received gefitinib or erlotinib, and 599 (48.7%) received chemotherapy. EGFR-TKI was administered until disease progression, development of intolerable toxic effects, or withdrawal of consent. The maximum number of chemotherapy cycles in each RCT varied from three to six; patients were treated with the maximum number of chemotherapy cycles unless intolerable toxic effects or disease progression occurred. In all RCTs, the primary end point was PFS, and OS was a secondary end point. Risk of bias was assessed as low for all RCTs, although two (3,5) did not include independent review of disease progression at the time of this publication.

The median duration of follow-up was 35.0 months (interquartile range = 15 to 32). Of 1231 patients, 780 (63.4%) died (EGFR-TKI: 65.4%; chemotherapy: 61.3%). The number of deaths increased from 595 in the previous publications to 780 deaths in the current study. OS from random assignment did not statistically significantly differ between treatment groups (EGFR-TKI: median OS = 25.8 months, 95% CI = 23.8 to 27.5 months; vs chemotherapy: median OS = 26.0 months, 95% CI = 23.6 to 28.9 months; HR = 1.01, 95% CI = 0.88 to 1.17 months, $P = .84$) (Figure 2). OS also did not statistically significantly differ between treatment groups for the subgroup of patients with exon 19 deletions (EGFR-TKI: median = 27.4 months, 95% CI = 25.1 to 29.3 months; vs chemotherapy: median OS = 25.9 months, 95% CI = 23.2 to 29.5 months; HR = 0.96, 95% CI = 0.79 to 1.16 months, $P = .68$; or exon 21 L8585R, EGFR-TKI: median OS = 24.1 months, 95% CI = 21.6 to 26.8 months; vs chemotherapy: median OS = 25.9, 95% CI = 22.5 to 29.6 months; HR = 1.06, 95% CI = 0.86 to 1.32 months, $P = .59$; $P_{interaction} = .47$) (Figure 3). There was also no heterogeneity in treatment effects in all of the other examined subgroups (Supplementary Figure 1, available online).

PFS data were only available for 1227 patients as four patients from NEJ002 (4) randomly assigned to chemotherapy did not have a date for disease progression recorded. A total of 1004 (81.8%) patients had progressed (EGFR-TKI: 78.0%; chemotherapy: 85.7%). EGFR-TKI was associated with statistically

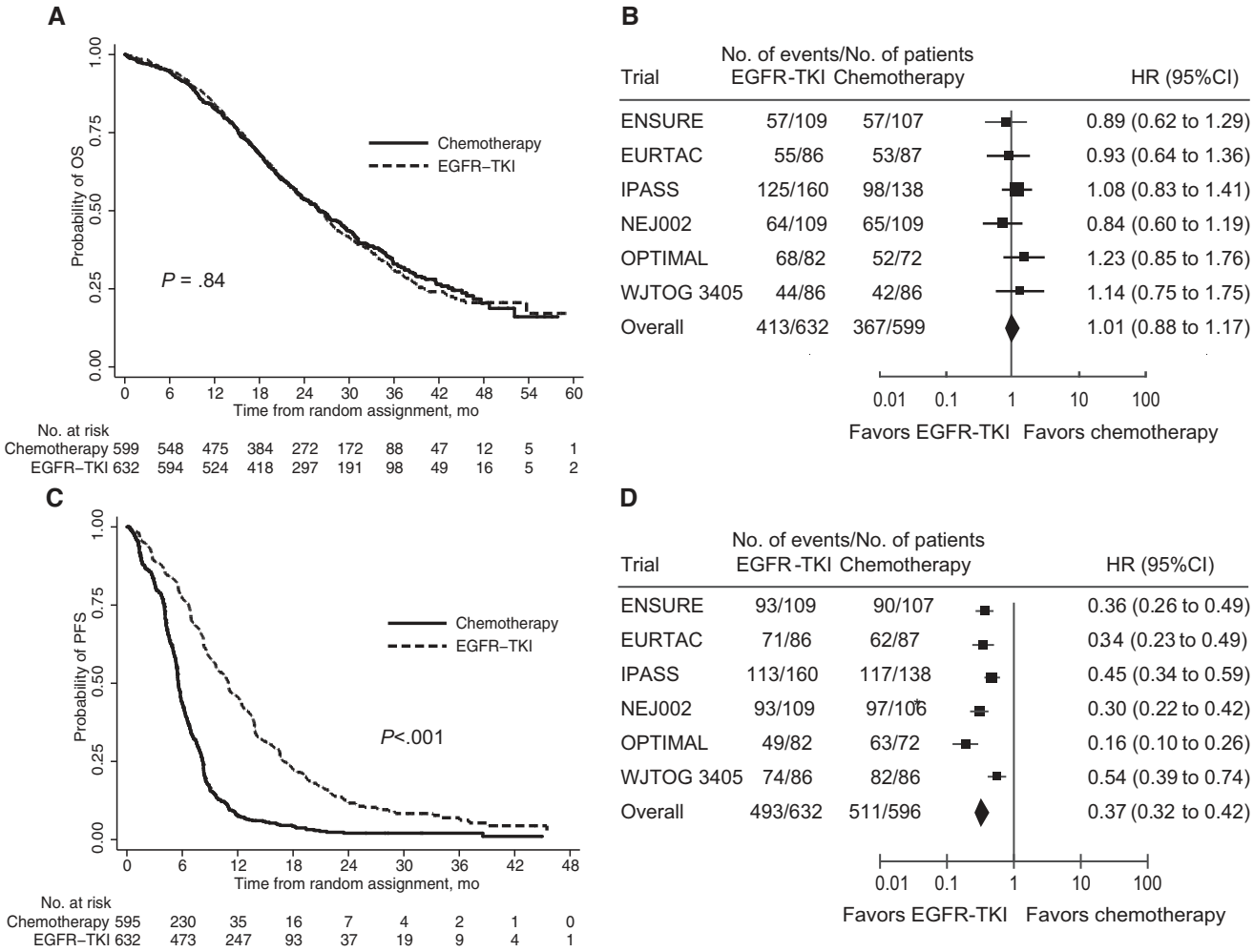

Figure 2. Randomized treatment effect on overall survival and progression-free survival. **A)** Kaplan-Meier curve comparing overall survival from random assignment between epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) and chemotherapy. **B)** Forest plot of the effect of treatment on overall survival. Hazard ratios for each trial are represented by the squares, and the horizontal line crossing the square represents the 95% confidence interval. The diamonds represent the estimated overall treatment effect using the fixed effects method. All statistical tests were two-sided. **C)** Kaplan-Meier curve comparing progression-free survival from random assignment between EGFR-TKI and chemotherapy. **D)** Forest plot of the effect of treatment on progression-free survival. Hazard ratios for each trial are represented by the squares, and the horizontal line crossing the square represents the 95% confidence interval. The diamonds represent the estimated overall treatment effect using the fixed effects method. All statistical tests were two-sided. CI = confidence interval; EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor; HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

significantly longer PFS than chemotherapy (EGFR-TKI: median PFS = 11.0 months, 95% CI = 9.9 to 11.8 months; vs chemotherapy: median PFS = 5.6 months, 95% CI = 5.4 to 5.8 months; HR = 0.37, 95% CI = 0.32 to 0.42 months, $P < .001$) (Figure 2, C and D). In the exon 19 deletion subgroup, the hazard ratio for PFS was 0.28 (95% CI = 0.23 to 0.34 months, $P < .001$). In the exon 21 L858R subgroup, the hazard ratio for PFS was 0.49 (95% CI = 0.40 to 0.60 months, $P < .001$). Compared with chemotherapy, EGFR-TKI demonstrated 42.9% greater benefit with exon 19 deletions than exon 21 L858R ($P_{interaction} < .001$). There was no heterogeneity in treatment effects in all of the other examined subgroups (Supplementary Figure 2, available online).

Among those with documented disease progression (n = 1004), 73.8% (n = 377) in the chemotherapy arm received EGFR-TKI as salvage therapy, as compared with 65.9% (n = 325) in the EGFR-TKI arm who received chemotherapy as salvage treatment (Table 2). For the exon 19 deletion subgroup, the crossover rate from the chemotherapy arm to EGFR-TKI was 71.1% (n = 207), and from the EGFR TKI arm to chemotherapy it was 64.0% (n = 165). For the exon 21 L858R subgroup, the crossover rate from the chemotherapy arm to EGFR-TKI was 77.2% (n = 166), and from the EGFR TKI arm to chemotherapy it was 67.7% (n = 157). There were more patients in the EGFR-TKI arm who received no systemic treatment at disease progression than those in the chemotherapy arm (9.1% vs 0.6%).

Following disease progression, patients from the EGFR-TKI arm had shorter OS than patients in the chemotherapy arm (OS = 12.8 months, 95% CI = 11.4 to 14.3 months; vs OS = 19.8 months, 95% CI = 17.6 to 21.7 months) (Figure 4A). Assessment of OS from the time of disease progression according to postprogression treatment showed patients who progressed and received EGFR-TKI as a second or subsequent line of therapy had longer OS (median = 21.5 months, 95% CI = 19.1 to 24.9 months) than those who received chemotherapy (median = 15.9 months, 95% CI = 14.2 to 17.5 months), no treatment (median = 4.1 months, 95% CI = 3.0 to 5.9 months) or other/unknown therapies (median = 4.9 months, 95% CI = 3.5 to 5.8 months) (Figure 4B). There were another 77 patients (chemotherapy arm: n = 26;

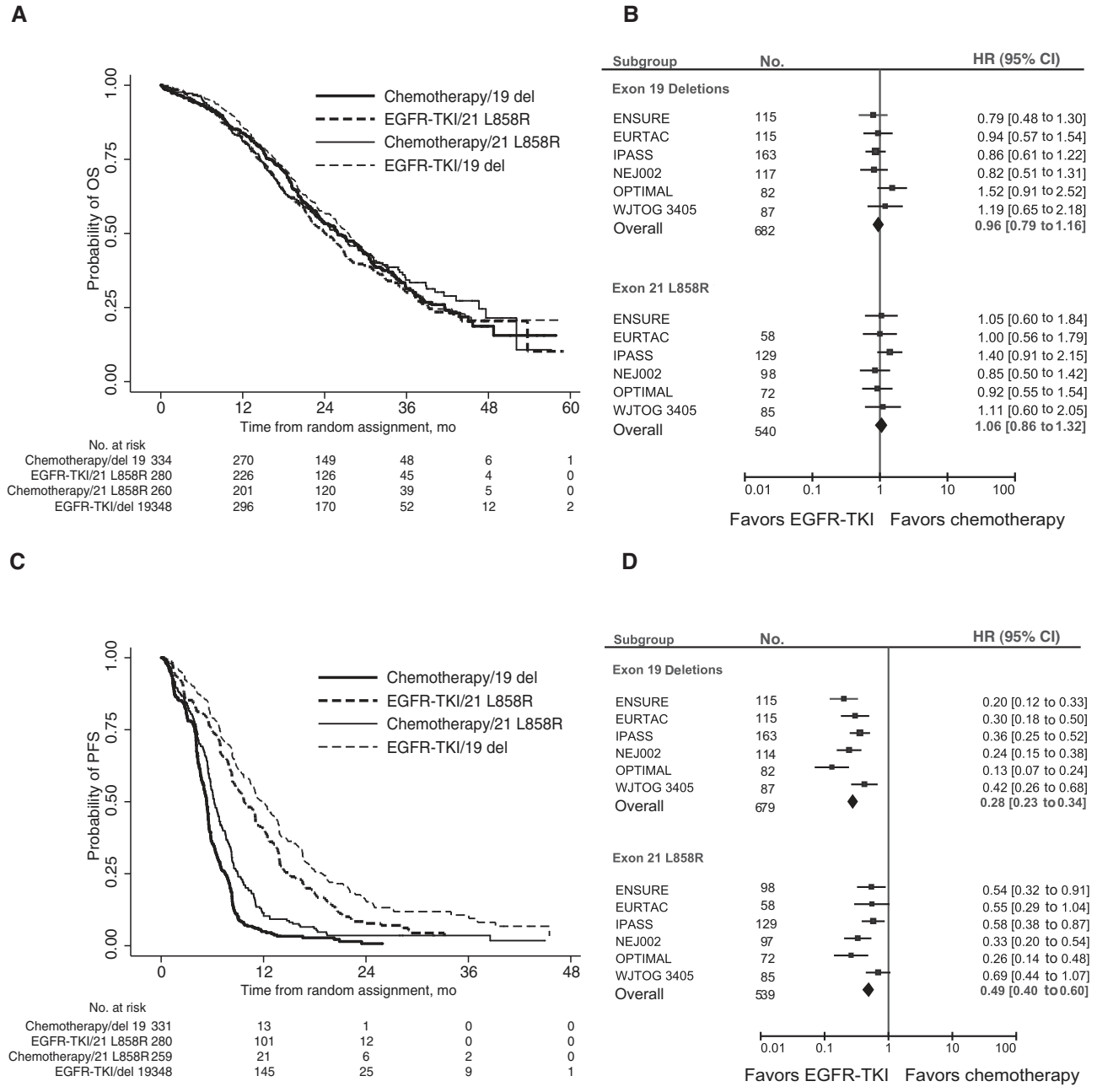

Figure 3. Randomized treatment effect on overall survival and progression-free survival for the different *EGFR* mutations. **A)** Kaplan-Meier curve comparing overall survival from random assignment between epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) and chemotherapy in subgroups of patients with different *EGFR* mutations. **B)** Forest plot of the effect of treatment on overall survival according to mutations of the epidermal growth factor receptor gene. Hazard ratios for each trial are represented by the **squares**, and the **horizontal line crossing the square** represents the 95% confidence interval. The **diamonds** represent the estimated overall treatment effect using the fixed effects method. All statistical tests were two-sided. **C)** Kaplan-Meier curve comparing progression-free survival from random assignment between EGFR-TKI and chemotherapy in subgroups of patients with different *EGFR* mutations. **D)** Forest plot of the effect of treatment on progression-free survival according to mutations of the epidermal growth factor receptor gene. Hazard ratios for each trial are represented by the **squares**, and the **horizontal line crossing the square** represents the 95% confidence interval. The **diamonds** represent the estimated overall treatment effect using the fixed effects method. All statistical tests were two-sided. EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor.

EGFR-TKI arm: n = 51) with no documented disease progression at data cutoff who crossed over to receive EGFR-TKI and chemotherapy, respectively.

Poor performance status and stage IV cancer at baseline were statistically significantly associated with shorter OS and PFS in both univariate and multivariable analyses (Table 3). Older patients (age ≥ 65 years) had a 23.0% reduction in risk of disease progression in multivariable analyses, but age did not impact OS outcome statistically significantly.

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

Table 1. Characteristics of patients in constituent trials

Study name (reference)	Treatment comparison	Median OS* (95% CI)	No.	Exon 19 deletion, %	Exon 21 L858R substitution, %	Age < 65 y, %	ECOG 0 & 1, %	Asian, %	Women, %	Never smoker, %	Adeno-carcinoma, %
NEJ002† (4,11)	Gefitinib vs CP	28.9 (25.1 to 34.2) vs 27.6 (23.1 to 34.9)	218	53.7	45.0	49.1	98.6	100	64.7	62.4	93.6
WJTOG3405 (6,13)	Gefitinib vs CisD	35.5 (26.1 to 45.5) vs 38.0 (31.2 to 47.6)	172	50.6	49.4	53.5	100	100	69.2	68.6	96.5
OPTIMAL (5,12)	Erlotinib vs CG	22.8 (20.0 to 28.3) vs 27.1 (20.1 to 31.4)	154	53.2	46.8	75.3	93.5	100	59.1	70.8	87.0
EURTAC (2)	Erlotinib vs platinum-G or platinum-D	22.9 (16.1 to 26.8) vs 20.9 (16.5 to 28.4)	173	66.5	33.5	49.1	86.1	0	72.8	69.4	92.5
IPASS† (3,10)	Gefitinib vs CP	21.6 (19.8 to 26.3) vs 21.9 (18.8 to 27.4)	298	54.7	43.3	71.5	91.6	100	79.9	95.0	100
ENSURE (1)	Erlotinib vs CisG	26.3 (22.2 to 33.7) vs 25.5 (21.6 to 28.3)	216	54.6	45.4	79.2	93.5	100	61.1	70.4	95.4

*Overall survival in months only for patients with common mutation of the epidermal growth factor receptor gene. CI = confidence interval; CisD = cisplatin-docetaxel; CisG = cisplatin-gemcitabine; CisPem = cisplatin-pemetrexed; CG = carboplatin-gemcitabine; CP = carboplatin-paclitaxel; EGOG = Eastern Cooperative Oncology Group; OS = overall survival.
†Three patients from NEJ002 and six patients from IPASS had concurrent exon 19 deletion and exon 21 L858R mutations.

In sensitivity analysis, we excluded two RCTs (OPTIMAL, WJTOG) (5,6,11,12) that reported a hazard ratio for OS in a different direction to the hazard ratio for PFS. Both RCTs (5,6,11,12) demonstrated consistent PFS findings with other studies in that there was greater EGFR-TKI benefit compared with chemotherapy in the overall population. In the subgroup with exon 19 deletions, there was greater PFS than those with exon 21 L858R. Although not statistically significant, there was an OS benefit in favor of chemotherapy in the overall population and for the exon 21 L858R subgroup. Despite exclusion of these studies, the overall conclusion of this study remains unchanged (Supplementary Figure 3, available online).

Discussion

In this IPD meta-analysis, there was no OS advantage of gefitinib or erlotinib over platinum-based chemotherapy despite demonstrating substantial PFS benefit. There was also no statistically significant difference in OS for EGFR-TKI vs chemotherapy in all subgroups defined by *EGFR* mutation type or other baseline clinical characteristics. In contrast, for PFS, treatment with EGFR-TKI, compared with chemotherapy, was associated with a 63.0% overall reduction in the risk of disease progression or death. Furthermore, the relative effect of EGFR-TKI compared with chemotherapy on PFS was 42.9% greater for patients with exon 19 deletions than for those with exon 21 L858R, consistent with LUX-Lung 3 (62%) (7) and LUX-Lung 6 (38%) (8) trial findings, respectively.

The most plausible explanation for the lack of OS benefit despite PFS advantage with first-generation EGFR-TKI therapy is the effect of salvage treatments received at disease progression. Our examination of available postprogression treatment and outcomes data supports this hypothesis. Postprogression treatments with either chemotherapy or EGFR-TKI were not balanced across the randomly assigned groups. More patients in the chemotherapy arm had EGFR-TKI salvage therapy at disease progression than those who had salvage chemotherapy in the EGFR-TKI arm (73.8% vs 65.9%). At least 5% did not receive any treatment at disease progression, more in the EGFR-TKI arm than the chemotherapy arm (9.1% vs 0.6%).

Consistent with previous studies (18,19), our data indicate that pretreatment with chemotherapy does not diminish the impact of EGFR-TKI. In our exploratory analysis, patients treated with EGFR-TKI following disease progression had statistically significantly longer OS than those who were treated with chemotherapy (median OS 21.5 vs 15.9 months). Our previous meta-analysis estimated that the benefit of second and subsequent lines of therapy (HR for PFS = 0.34, 95% CI = 0.20 to 0.60) is comparable with that of firstline therapy (HR for PFS = 0.43, 95% CI = 0.38 to 0.49) when EGFR-TKI and chemotherapy were compared (19). A population-based study has further demonstrated that median OS has doubled from 13.6 months to 27.2 months before and after gefitinib approval in Japan for treatment of *EGFR*-mutated advanced NSCLC (20). The median OS of 27.2 months is comparable with the pooled median OS of 25.9 months from the included RCTs in this meta-analysis. Therefore, the lack of apparent OS benefit in the relative comparison of the randomized treatments might be largely confounded by very effective salvage treatment with EGFR-TKI at disease progression, and hence it is not possible to estimate the true overall randomized treatment effect.

There is controversy about whether improvement in PFS without a corresponding increase in OS is a meaningful end

Table 2. Second and subsequent therapies after disease progression, by randomized treatment overall

Second and subsequent lines of therapy	Randomized treatment, No. (%)	
	Chemotherapy	EGFR-TKI
EGFR-TKI	377 (73.8)	44 (8.9)
Chemotherapy	56 (11.0)	325 (65.9)
None	3 (0.6)	45 (9.1)
Other or unknown	75 (14.7)	79 (16.0)
Total	511	493

*EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor.

point for determining efficacy for novel therapies (21). In a recent study, the US Food and Drug Administration analyzed 14 RCTs of advanced NSCLC and reported no association between OS and PFS, suggesting that PFS is a poor surrogate for OS (22). However, among the included studies, there were only two RCTs comparing EGFR-TKI and chemotherapy as firstline therapy for EGFR-mutated advanced NSCLC. We expect the relative PFS improvement with treatment to be greater than the OS improvement because of crossover or other unknown reasons. Furthermore, in using PFS as a trial end point, double-blinding, placebo-controlled design, and independent radiological review for progression have the role of minimizing bias associated with this end point (23). Among the included trials in this meta-analysis, none could be double blinded, and independent radiological reviews were performed in only four studies. Whether PFS is a valid surrogate for OS in RCTs that compare EGFR-TKI against chemotherapy in *EGFR*-mutated advanced NSCLC remains uncertain and requires more research.

In advanced *EGFR*-mutant NSCLC, systemic therapy is generally palliative, and hence improvement in quality of life (QOL) is also an important end point. Multiple RCTs comparing EGFR-TKI against chemotherapy have demonstrated that upfront EGFR-TKI treatment is associated with a more pronounced improvement in cancer-related symptoms (3,7,24–26). The improvement in QOL does not appear to be just due to EGFR-TKI being a better-tolerated treatment because *EGFR* wild-type patients had inferior QOL when treated with EGFR-TKI in the IPASS trial (26). Therefore, even in the absence of apparent lack of relative benefit of EGFR-TKI over chemotherapy for OS, upfront EGFR-TKI treatment is still recommended for QOL improvement in these patients.

This meta-analysis has several strengths. We performed a comprehensive review and analyses using IPD from six large RCTs with long-term OS data to investigate the study questions. As IPD were available, we were able to estimate treatment effects within subgroups of different common *EGFR* mutations as well as other clinical characteristics. There are also limitations of this study. Data on postprogression therapies in several of the included RCTs were collected post hoc and hence might not have captured all therapies received. Nine percent of the postprogression therapies were also unknown. As the median OS from disease progression was 4.4 months for patients whose postprogression therapies were unknown, we speculate that most of these patients did not receive any systemic treatment at disease progression. We acknowledged that because there were more patients randomly assigned to EGFR-TKI arm, OS from postprogression could be skewed by those patients. Our grouping of patients to define their postprogression therapies might be too simplistic and not reflective of the true overall

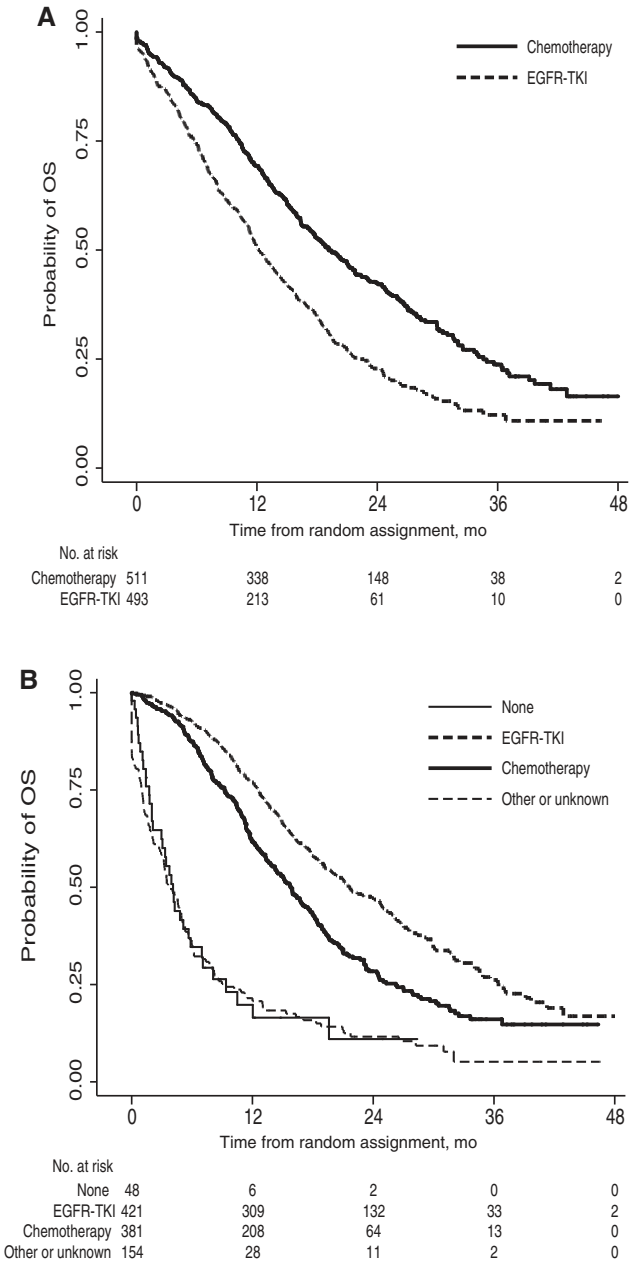

Figure 4. Overall survival outcome following disease progression of randomized treatments. **A)** Kaplan-Meier curve comparing overall survival from disease progression according to the randomized arms. **B)** Kaplan-Meier curve comparing overall survival after disease progression between the different actual treatments received after disease progression. OS = overall survival.

treatment received if some patients were treated with multiple lines of different classes of therapies. Hence, our analyses for differences in OS between different postprogression treatments should be considered exploratory and hypothesis generating as they are nonrandomized comparisons where crossover was not mandated in all studies. We were unable to control for all possible confounders, in particular for those patients who died without documented progression, and hence the patients who were analyzed in the postprogression phase were different from the overall population that entered the randomized studies. Work is currently ongoing to improve estimation of the treatment effect using novel statistical approaches, particularly in this

Table 3. Prognostic values of baseline characteristics in univariate and multivariable Cox regression analyses

Baseline characteristics	No.	Median, mo	Univariate		Multivariable (n = 1228)	
			HR (95% CI)	P*	HR (95% CI)	P*
Overall survival						
Sex						
Male	384	24.77	1.00		1.00	
Female	847	26.41	0.88 (0.76 to 1.03)	.11	0.83 (0.69 to 1.00)	.05
Smoking						
Never smoker	918	25.92	1.00		1.00	
Ever smoker	313	26.48	1.10 (0.93 to 1.31)	.27	1.00 (0.82 to 1.23)	.99
Performance status						
0	430	33.97	1.00		1.00	
1	725	24.08	1.43 (1.22 to 1.69)	<.001	1.43 (1.21 to 1.69)	<.001
2	76	15.66	2.76 (2.04 to 3.73)	<.001	2.71 (2.00 to 3.67)	<.001
Age, y						
<65	784	25.59	1.00		1.00	
≥65	447	26.61	0.90 (0.77 to 1.06)	.20	0.90 (0.77 to 1.06)	.20
Histological subtype						
Adenocarcinoma	1168	26.28	1.00		1.00	
Nonadenocarcinoma	63	22.93	1.18 (0.86 to 1.61)	.31	1.08 (0.79 to 1.48)	.63
Cancer stage						
IV	988	23.95	1.00		1.00	
IIIB	155	30.95	0.70 (0.55 to 0.88)	.002	0.68 (0.54 to 0.85)	<.001
Postoperative recurrence	85	42.70	0.50 (0.34 to .074)	<.001	0.54 (0.36 to 0.80)	.002
Progression-free survival						
Sex						
Male	383	7.89	1.00		1.00	
Female	844	7.50	1.02 (0.89 to 1.18)	.74	1.07 (0.90 to 1.26)	.46
Smoking						
Never smoker	916	7.93	1.00		1.00	
Ever smoker	311	7.04	1.06 (0.91 to 1.23)	.48	1.10 (0.92 to 1.31)	.31
Performance status						
0	429	8.59	1.00		1.00	
1	723	7.49	1.40 (1.21 to 1.62)	<.001	1.33 (1.15 to 1.55)	<.001
2	75	6.48	2.45 (1.83 to 3.28)	<.001	2.38 (1.78 to 3.19)	<.001
Age, y						
<65	782	7.20	1.00		1.00	
≥65	445	8.21	0.77 (0.67 to 0.88)	<.001	0.77 (0.67 to 0.89)	<.001
Histological subtype						
Adenocarcinoma	1164	7.76	1.00		1.00	
Nonadenocarcinoma	63	6.35	1.06 (0.76 to 1.44)	.73	1.07 (0.78 to 1.46)	.68
Cancer stage						
IV	985	7.30	1.00		1.00	
IIIB	155	7.93	0.87 (0.71 to 1.06)	.16	0.87 (0.71 to 1.06)	.16
Postoperative recurrence	84	9.97	0.49 (0.37 to 0.67)	<.001	0.54 (0.39 to 0.73)	<.001

*Hazard ratios, 95% confidence intervals, and P values were estimated from Cox regression models. These tests were two-sided. CI = confidence interval; HR = hazard ratio.

setting with possible selection bias and competing risks, for better interpretation of results from postprogression therapy. We assumed that gefitinib and erlotinib in the experimental arms of the RCTs have equivalent therapeutic efficacy. A similar assumption was made for the different platinum-based chemotherapies in the control arms. A recent study demonstrates the efficacy of afatinib in treatment of some types of uncommon *EGFR* mutations (13). This question cannot be addressed in this meta-analysis of gefitinib and erlotinib as most of the included RCTs excluded uncommon *EGFR* mutations.

In conclusion, despite statistically significant relative PFS benefit, OS did not statistically significantly differ between gefitinib or erlotinib vs chemotherapy in advanced NSCLC with common *EGFR* mutations. This result is likely due to effective subsequent therapy with EGFR-TKI at disease progression in patients randomly assigned to chemotherapy. Upfront EGFR-TKI treatment is still recommended over chemotherapy as firstline treatment in this population.

Notes

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