Introduction

Based on results from seven prospective phase III randomized trials comparing first-line epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) to platinum-doublet chemotherapy as first-line treatment of non-small cell lung cancer (NSCLC) patients harboring activating EGFR mutations (*EGFRm*), it is now well-established that EGFR TKI offers superior improvement in progression-free survival (PFS) [1–7]. Exploratory univariate analyses of three of the seven clinical trials (WJTOG3405, EURTAC, and LUX-Lung-3 [LL3]) suggested that *EGFRm* NSCLC patients who had a previous smoking history (former or current smoker) did not seem to derive a statistical PFS improvement when EGFR TKI was compared with platinum-doublet chemotherapy. In WJTOG3405, the hazard ratio (HR) for PFS among ever-smokers was 0.58 (95% confidence interval [CI]: 0.29–1.12) [1]. In EURTAC, the HR for PFS for current smokers was 0.56 (95% CI: 0.15–2.15), and that for former smokers was 1.05 (95% CI: 0.40–2.74) [4]. In LL3, the HR for PFS for current/ex-smokers was 1.04 (95% CI: 0.54–1.98), and that for recent light former smokers was 0.50 (95% CI: 0.19–1.34) (stopped >1 year ago and <15 pack years) [5]. On the other hand, exploratory univariate analyses in two of the six trials (OPTIMAL and LUX-Lung-6 [LL6]) did show statistical significant PFS benefit among former/current smoker from first-line EGFR TKIs. The HR for PFS among former/current smokers in OPTIMAL was 0.21 (95% CI: 0.09–0.49) [3]. The HR for PFS among current or ex smokers in LL6 was 0.46 (95% CI: 0.22–1.00) [6]. Two remaining trials (NEJ002 and ENSURE) have not reported univariate analysis by smoking status [2, 7]. Given that up to one-third of *EGFRm* patients had a previous smoking history [8], we performed a meta-analysis to analyze the role of smoking status and other potential predictive factors that may influence clinical outcome in *EGFRm* patients receiving first-line EGFR TKIs. In particular, we incorporated previously unpublished results of the univariate analysis of the NEJ002 trial outcome into this current meta-analysis.

Materials and Methods

Study Eligibility and Identification

All prospective randomized phase III trials enrolling *EGFRm* NSCLC patients comparing EGFR TKI and platinum doublet chemotherapy (chemotherapy) as first-line treatment for advanced NSCLC were eligible for inclusion. Trials were identified from the MEDLINE database using PubMed using the combination of the following terms (without the quotation marks): "non-small cell lung cancer," "epidermal growth factor," and "randomized controlled trial." Abstracts from conference proceedings of the American Society of Clinical Oncology, the European Society for Medical Oncology, and the World Conference of Lung Cancer were reviewed to identify unpublished studies. All searches were limited to human studies and the English language.

Data Extraction

Information recorded from each trial including study name, year of publication or conference presentation, demographic area (age, gender, region of enrollment), methods of determining *EGFR* mutations, smoking status, type of platinum-doublet chemotherapy, and specific EGFR TKI were abstracted. All studies were retrieved independently by two investigators (Y.H. and S.Y.) to assess the reliability of data extraction. After selection of potential studies, the investigators reviewed each other's selected studies and excluded inappropriate studies with the agreement of both. Disagreements were adjudicated by a third reviewer after referring to the original articles.

We extracted log-transformed HRs and corresponding 95% CI for PFS using a random-effect model to assess efficacy within several subgroups: smoking status (never-smokers versus ever-smokers [former and current smokers if the distinction is made in the trial]), age (<65 versus ≥65 years), gender (male versus female), *EGFR* mutation type (exon 19 deletion versus L858R substitution), ethnicity (Asians versus non-Asians), and EGFR TKI (gefitnib, erlotinib, and afatinib). Comparison of the pooled HRs was performed by metaregression analysis. HRs for former and current smokers were pooled as one HR for ever-smokers. A $p < .05$ was considered statistically significant, and all reported p values were two-sided. The I^2 statistics were used to assess heterogeneity across studies, and $I^2 < 25$, $25 \leq I^2 < 50$, and $50 \leq I^2$ were interpreted as signifying low-level, intermediate-level, and high-level heterogeneity, respectively. The Egger's test and Begg's funnel plots were calculated using Comprehensive Meta-Analysis version 2 (Biostat Inc., Englewood, NJ, http://biostat.com). All other statistical analyses were performed with SPSS version 21 (SPSS, Chicago, IL, http://www-01.ibm.com/software/analytics/spss/) or SAS version 9.4 (SAS Inc., Cary, NC, http://www.sas.com).

Results

Clinical Trials

A total of 280 articles were identified, of which 132 articles were excluded primarily because only two of the three search criteria were present in the articles despite using the three combined search criteria (Fig. 1). We eventually identified seven (six published and one presented) (WJTOG3405, NEJ002, EURTAC, OPTIMAL, LL3, LL6, and ENSURE) eligible trials (Fig. 1). PFS was the primary endpoint for all seven trials, and assessment scans were performed every 6 weeks for 5 trials (EURTAC, OPTIMAL, LL3, LL6, and ENSURE) and 8 weeks for 2 trials (WJTOG3405 and NEJ002). The eligibility criteria were similar among all 7 trials with 3 trials (OPTIMAL, EURTAC, and ENSURE) allowing performance status up to 2. Gefitinib, erlotinib, and afatinib were investigated in two, three and two trials, respectively. The chemotherapy regimens investigated were platinum (carboplatin/cisplatin)-based with paclitaxel, docetaxel, gemcitabine, and pemetrexed. Five trials randomized patients 1:1 to EGFR TKIs and two trials (LL3 and LL6) randomized patients 2:1 to EGFR TKIs to chemotherapy. Five trials stratified the randomization by the type of *EGFR* mutations (OPTIMAL, EURTAC, ENSURE, LL3, and LL6), but only one trial stratified the randomization by smoking status (OPTIMAL). Three trials allowed (NEJ002, LL3, and LL6) enrollment of *EGFRm* patients with uncommon mutations in addition to the two common types of EGFR mutations (exon 19 deletion and L858R substitution). Details and primary results of all seven trials are summarized in Table 1.

Patient Characteristics and Common *EGFRm* Types

Among the total of 1,649 *EGFRm* patients analyzed from the 7 prospective randomized phase III trials, 65.1% were female,

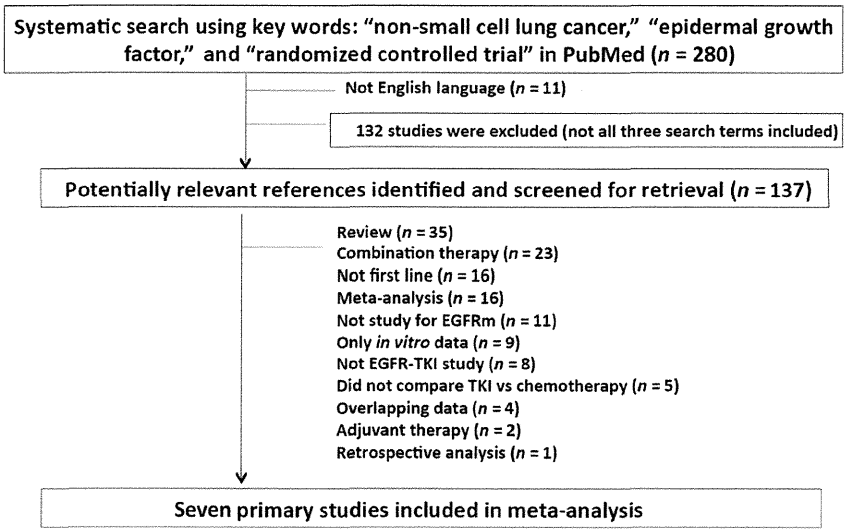


Figure 1. Trial selection process.
Abbreviations: EGFR, epidermal growth factor receptor; EGFRm, mutated EGFR; TKI, tyrosine kinase inhibitor.

84.8% had stage 4 disease, 96.1% had adenocarcinoma histology, and 52.9% had exon 19 deletion (Table 2). Of the total 1,649 patients, 950 (57.6%) were randomized to EGFR TKIs, and 699 (42.4%) were randomized to platinum-doublet chemotherapy.

Approximately 70.0% of the *EGFRm* patients were never-smokers. All the *EGFRm* patients were randomized in a similar proportion to EGFR TKIs (70.0% never-smokers) and chemotherapy (69.8% never-smokers) by smoking status (Table 2). Additionally, among never-smokers, 57.7% of them were randomized to EGFR TKI essentially equal to the 57.3% of ever-smokers, who were also randomized to EGFR TKI.

The vast majority of the patients enrolled in the 7 randomized trials were Asians (83.7%), and they were randomized to a similar proportion to EGFR TKIs (84.2%) and chemotherapy (83.0%) (Table 2). Among the common *EGFRm* mutations (exon 19 deletion and L858R substitution), 56.1% were exon 19 deletion, and 43.9% were L858R substitution. Among Asian *EGFRm* patients, 54.7% had exon 19 deletion, and 45.3% had L858R substitution. Among non-Asian *EGFRm* patients, 63.0% had exon 19 deletion, and 37.0% had L858R substitution. Among *EGFRm* patients with exon 19 deletions, 57.4% were randomized to EGFR TKI, and among *EGFRm* patients with L858R substitution, 56.6% were randomized to EGFR TKI. Among *EGFRm* patients with common *EGFR* mutation randomized to EGFR TKI, 56.4% had exon 19 deletion. In a similar proportion, among *EGFRm* patients with common *EGFR* mutations randomized to platinum-doublet chemotherapy, 56.6% had exon 19 deletion.

Among the patients randomized to EGFR TKI, 49.7% of the patients were randomized to receive afatinib, 29.3% were randomized to receive erlotinib, and 21.1% were randomized to receive gefitinib. Among the patients randomized to receive platinum-doublet chemotherapy, 37.8% were randomized to receive cisplatin/gemcitabine, 16.5% were randomized to receive cisplatin/pemetrexed, 15.8% were randomized to receive carboplatin/paclitaxel, 14.3% were randomized to receive carboplatin/gemcitabine, 13.2% were randomized to receive cisplatin/docetaxel, and 2.4% were randomized to receive carboplatin/docetaxel.

All seven randomized trials demonstrated significant PFS improvement of EGFR TKIs over platinum-doublet chemotherapy. The median PFS in patients who received EGFR TKI ranged from 9.2 to 13.1 months, whereas the range of median PFS in patients who received platinum-doublet chemotherapy was 4.6 to 6.9 months (Table 1).

PFS Benefits of EGFR TKIs by Smoking Status

The PFS HRs by smoking status for NEJ002 [2, 9–10] and ENSURE have not been previously presented or published, but we were able to obtain the individual NEJ002 patient data (smoking status, gender, type of *EGFR* mutation, age) from the North East Japan study group but not the data from ENSURE. Hence, the meta-analysis on smoking status was based on 86.8% of the total population (excluding the ENSURE patient population). The PFS HR for never-smokers in the NEJ002 trial was 0.27 (95% CI: 0.18–0.41), whereas the PFS HR for ever-smokers in NEJ002 was 0.46 (95% CI: 0.28–0.74). Therefore, the meta-analysis was based on 86.8% of the total patient population. The pooled PFS HR for never-smokers was 0.29 (95% CI: 0.21–0.39), whereas the pooled PFS HR for ever-smokers was 0.54 (95% CI: 0.38–0.76). Metaregression analysis of the HRs was significant, with a p value of .007 (Fig. 2A).

PFS Benefits of EGFR TKIs by the Two Common *EGFR* Mutations

The PFS HR for patients with exon 19 deletion in the NEJ002 trial was 0.24 (95% CI: 0.15–0.38), whereas the PFS HR for patients with L858R in NEJ002 was 0.32 (95% CI: 0.20–0.53). The pooled PFS HR for *EGFR* exon 19 deletion was 0.25 (95% CI: 0.19–0.31), whereas the pooled PFS HR for L858R substitution was 0.44 (95% CI: 0.34–0.57). Metaregression analysis of the HRs was significant, with a p value of $<.001$ (Fig. 2B).

PFS Benefits of EGFR TKIs by Ethnicity

The pooled PFS HR for Asians was 0.33 (95% CI: 0.24–0.46), whereas the pooled PFS HR for non-Asians was 0.48 (95% CI: 0.28–0.84). Metaregression analysis of the HRs was not significant ($p = .261$) (Fig. 2C).

Table 1. List of the characteristics of the seven randomized trials

Trial	Number of patients	Region	Platinum-doublet chemotherapy	EGFR TKI	Randomization	*EGFR* mutation analysis	Stratifications	Median PFS (months)			
								Chemo	EGFR TKI	HR (95% CI)	*p*
WJTOG 3405	177	Japan	Cisplatin/ docetaxel	Geftinib	1:1	Exon 19 (fragment analysis) L858R (Cyclease method) Direct sequencing, PNA-LNA PCR	Stage IV: institution, stage (IIIB vs. V), sex Postoperative recurrence: institution, postoperative adjuvant chemotherapy (yes vs. no), interval between surgery and recurrence (<1 yr vs. ≥1 yr)	6.3	9.2	0.489 (0.336–0.710)	<.0001
NEJ002	230	Japan	Carboplatin/ paclitaxel	Gefitinib	1:1	PNA-LNA PCR clamp	Sex, stage, institution	5.4	10.8	0.30 (0.22–0.41)	<.0001
EURTAC[a]	174	Spain France Italy	Cisplatin/ gemcitabine Cisplatin/ docetaxel Carboplatin/ gemcitabine Carboplatin/ docetaxel	Erlotinib	1:1	PCR length analysis (exon 19) L858R (TaqMan 5′ nuclease PCR)	*EGFR* mutation type, PS	5.2	9.7	0.37 (0.25–0.54)	<.0001
OPTIMAL	165	China	Carboplatin/ gemcitabine	Erlotinib	1:1	PCR length analysis (exon 19) L858R (Cycleave real-time PCR)	*EGFR* mutation type, smoking status, histology	4.6	13.1	0.16 (0.10–0.26)	<.0001
ENSURE	217	China Malaysia Philippines	Cisplatin/ gemcitabine	Erlotinib	1:1		*EGFR* mutation type, PS, gender, country	5.6	11.1	0.43 (0.29–0.64)	<.0001
LL3	1,269	Asia Europe North America South America Australia	Cisplatin/ pemetrexed	Afatinib	2:1	Therascreen EGFR 29	*EGFR* mutation type, race	6.9	11.1	0.47 (0.34–0.65)	0.0001
LL6	364	China Thailand South Korea	Cisplatin/ gemcitabine	Afatinib	2:1	Therascreen EGFR 29	*EGFR* mutation type, PS, gender, country	5.6	11.0	0.28 (0.20–0.39)	<.0001

[a]Cisplatin/gemcitabine (40.7%); carboplatin/gemcitabine (32.6%); carboplatin/docetaxel (19.8%); cisplatin/docetaxel (7.0%).

Abbreviations: CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; PCR, polymerase chain reaction; PFS, progression-free survival; PNA-LNA, peptide nucleic acid-locked nucleic acid; PS, performance status; TKI, tyrosine kinase inhibitor; yr, year.

Table 2. Clinicopathologic characteristics of the patients (total, EGFR TKI, and doublet chemotherapy) analyzed by the meta-analysis

	Total (%)	EGFR TKI (%)	Platinum-doublet chemotherapy (%)
N	1,649	950	699
Age	1,477[a]		
<65	970 (65.7)	—	—
≥ 65	507 (34.3)	—	—
Smoking status			
Never-smoker	1,155 (70.0)	667 (70.0)	488 (69.8)
Ever-smoker	494 (30.0)	283 (30.0)	211 (30.2)
Sex			
Male	576 (34.9)	343 (36.1)	233 (33.3)
Female	1,073 (65.1)	607 (63.9)	466 (66.7)
Ethnicity			
Asian	1,380 (83.7)	800 (84.2)	580 (83.0)
Non-Asian	269 (16.3)	150 (15.8)	119 (17.0)
Histology			
Adenocarcinoma	1,584 (96.1)	916 (96.4)	668 (95.6)
Other	65 (3.9)	34 (3.6)	31 (4.4)
Stage			
III	160 (9.7)	90 (9.5)	70 (10.0)
IV	1,399 (84.8)	814 (85.7)	585 (83.7)
Postoperative relapse	90 (5.5)	46 (4.8)	44 (6.3)
EGFR mutation			
Exon 19 deletion	872 (52.9)	502 (52.8)	370 (52.9)
L858R	685 (41.5)	388 (40.8)	297 (42.5)
Other	92 (5.6)	60 (6.3)	32 (4.6)
Clinical trials			
WJTOG3405	172 (10.4)	86 (9.1)	86 (12.3)
NEJ002	224 (13.6)	114 (12.0)	110 (15.7)
OPTIMAL	154 (9.3)	82 (8.6)	72 (10.3)
EURTAC	173 (10.5)	86 (9.1)	87 (12.4)
LUX-Lung-3	345 (20.9)	230 (24.2)	115 (16.5)
LUX-Lung-6	364 (22.1)	242 (25.5)	122 (17.5)
ENSURE	217 (13.2)	110 (11.6)	107 (15.3)

[a]Lack of data in the WJTOG3405 study.
Abbreviations: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

PFS Benefits of EGFR TKIs by Age

Although the breakdown by patients' age was presented in ENSURE, the PFS HR by age for ENSURE has not been presented. The PFS HR for patients less than 65 years old in the NEJ002 trial was 0.25 (95% CI: 0.15–0.41), whereas the PFS HR for patients aged 65 and older in NEJ002 was 0.34 (95% CI: 0.22–0.52). The pooled PFS HR for patients less than 65 years old was 0.32 (95% CI: 0.23–0.46), whereas the pooled PFS HR for patients aged 65 and older was 0.31 (95% CI: 0.21–0.47). Metaregression analysis of the HRs was not significant ($p = .904$) (Fig. 2D).

PFS Benefits of EGFR TKIs by Gender

The PFS HR for female patients in the NEJ002 trial was 0.25 (95% CI: 0.17–0.38), whereas the PFS HR for male patients in NEJ002 was 0.48 (95% CI: 0.30–0.77). The pooled PFS HR for female patients was 0.31 (95% CI: 0.23–0.40), whereas the pooled PFS HR for male patients was 0.43 (95% CI: 0.32–0.57). Metaregression analysis of the HRs was not significant ($p = .090$) (Fig. 2E).

PFS Benefits of EGFR TKIs by EGFR TKI

The pooled PFS HR for gefitnib over platinum-doublet chemotherapy was 0.38 (95% CI: 0.24–0.59), the pooled PFS HR for erlotinib over chemotherapy was 0.30 (95% CI: 0.20–0.44), and the pooled PFS HR for afatinib was 0.41 (95% CI: 0.24–0.68). Metaregression analysis showed the *p* value between erlotinib and gefitinib to be 0.43, whereas the *p* value between erlotinib and afatinib was .37 (Fig. 2F).

Publication Bias

Potential publication bias was evaluated using the Egger's test and Begg's funnel plots with log-transformed hazards calculated from prevalence rate as the outcome and their

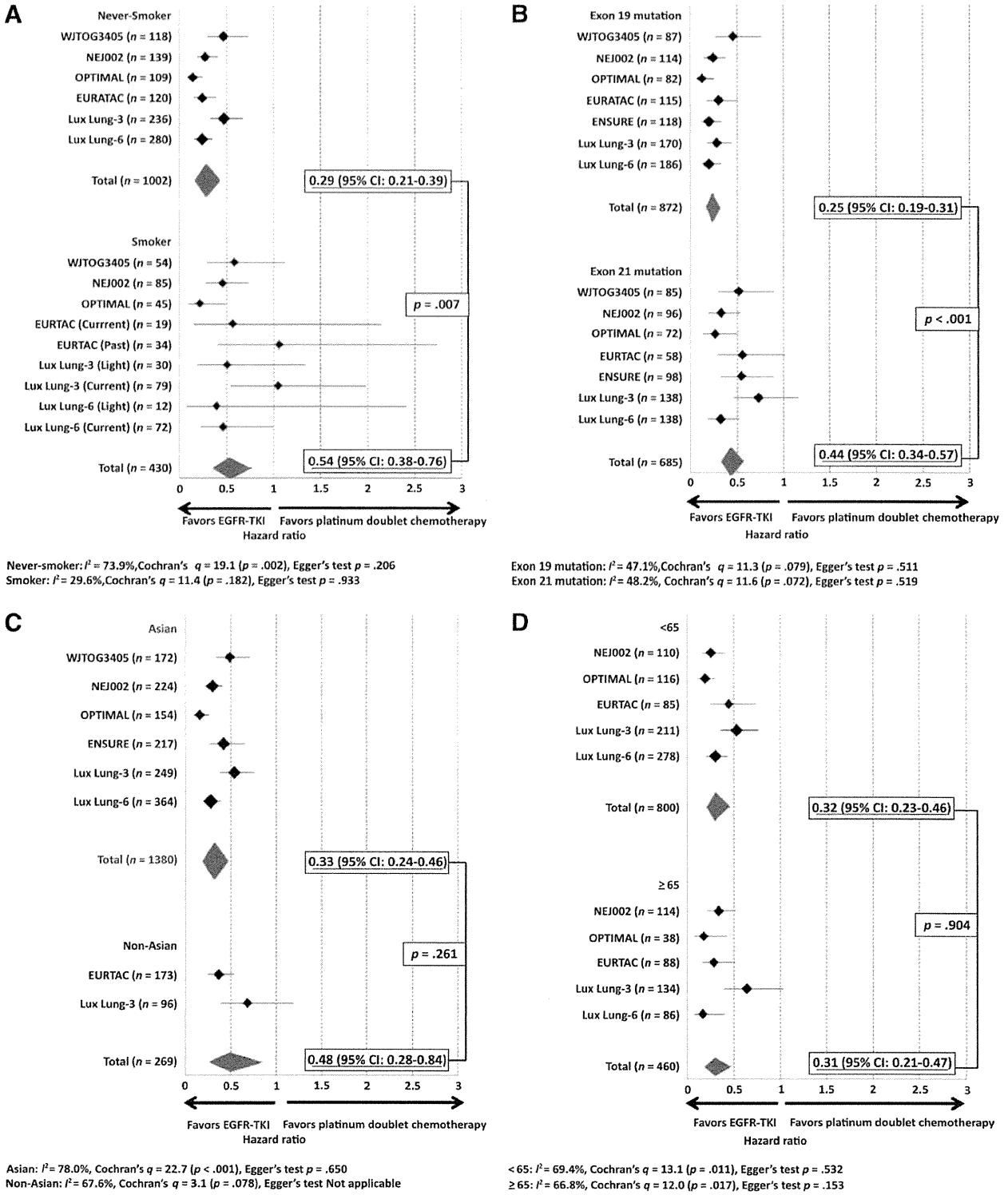


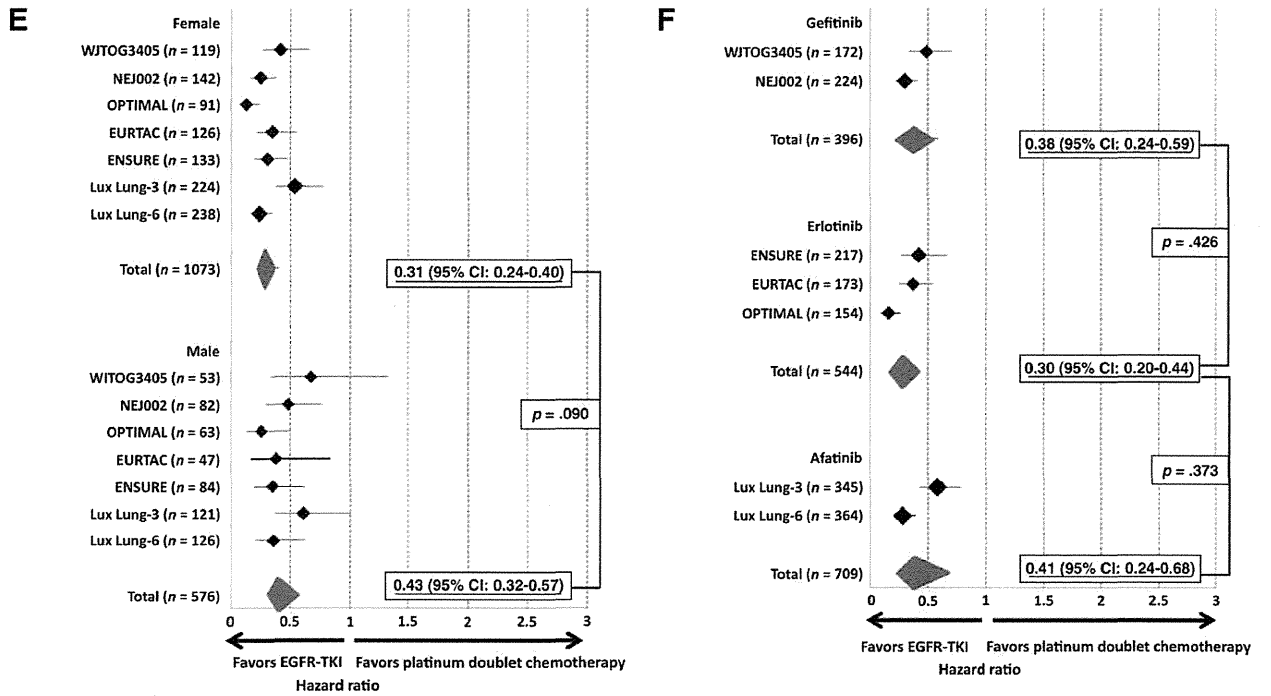
Figure 2. Pooled hazard ratios (HRs) and metaregression analysis of pooled HRs of EGFR TKI compared with platinum-doublet chemotherapy. **(A):** HRs and metaregression analysis according to smoking status. **(B):** HRs and metaregression analysis according to two common types of *EGFR* mutation. **(C):** HRs and metaregression analysis according to ethnicity. **(D):** HRs and metaregression analysis according to age. **(E):** HRs and metaregression analysis according to gender. **(F):** HRs and metaregression analysis according to type of EGFR TKI.

Abbreviations: CI, confidence interval; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

standard errors as the index for accuracy. The funnel plots were symmetrical, and the Egger's tests for all study were shown in Figure 2A–2F. These data indicate that there is little evidence of publication bias.

Discussion

In this meta-analysis, we have shown that patients with advanced *EGFRm* NSCLC benefited in terms of PFS from first-line EGFR TKI when compared with platinum-doublet



Female: I^2=71.7%, Cochran's q = 21.2 (p = .002), Egger's test p = .206
Male: I^2= 15.3%, Cochran's q = 7.0 (p = .313), Egger's test p = .593

Gefitinib: I^2= 74.7%, Cochran's q = 3.9 (p = .049), Egger's test Not applicable
Erlotinib: I^2= 79.9%, Cochran's q = 9.9 (p = .007), Egger's test p = .546
Afatinib: I^2 = 90.1%, Cochran's q = 10.1 (p = .001), Egger's test Not applicable

Figure 2. Continued.

chemotherapy regardless of smoking status, although there was a significant difference in the HRs for PFS benefit favoring patients without a smoking history. Although activating *EGFR* mutations are very common among NSCLC patients who were never-smokers, it is important to note that approximately 30% of the *EGFRm* patients in this meta-analysis had a history of tobacco use. Our results indicated that the efficacy of EGFR TKI may be less efficacious in *EGFRm* patients who had a smoking history. This is likely due to the difference in the genetic background of *EGFR* mutated NSCLC between never-smokers and ever-smokers. It has been demonstrated from comprehensive genomic profiling in adenocarcinoma between never-smokers and ever-smokers that the mutation burden (including point mutations) is at least 10-fold higher among adenocarcinoma patients who were ever-smokers [11, 12]. Furthermore, these point mutations in ever-smokers tend to occur in DNA mismatch repair genes, likely leading to secondary resistance to EGFR TKI or activation of bypass pathways [12]. Finally, the frequency of transversion increased with increasing tobacco smoke exposure. Transversion involves a purine to pyrimidine mutation or vice versa and is more likely to lead to structure changes in protein that harbors the transversion. Another potential mechanistic explanation to our observation of better PFS achieved with EGFR TKI in never-smokers compared with ever-smokers is that cigarette smokes have been shown in vitro to activate bypass signaling pathways that overcome the blockade of activated *EGFRm* by EGFR TKIs [13, 14]. Furthermore, active smoking has been shown to decrease the bioavailability of erlotinib by 50% [15, 16]. Thus active cigarette smoking during EGFR TKI treatment may directly and indirectly reduce the efficacy of EGFR TKI. Although we cannot rule out the less likely interpretation of the results of this meta-analysis is that platinum-doublet chemotherapy may be more efficacious in *EGFRm* patients with a history of smoking, the narrow range of median PFS from platinum-doublet chemotherapy indicated that the difference, if present, is very subtle.

Kim et al. [17] have also recently reported that smoking history is detrimental to NSCLC patients with *EGFRm* receiving EGFR TKIs. They showed that PFS was significantly shorter among *EGFRm* NSCLC patients receiving EGFR TKIs who were ever-smokers than never-smokers primarily from EGFRm patients with a ≥30-pack year smoking habit [18]. The disease control rate and overall response rate (ORR) to EGFR TKIs were also significantly lower among *EGFRm* patients with a ≥30-pack year smoking history [17]. The advantage of our meta-analysis was that all *EGFRm* patients were treated with first-line EGFR TKIs, whereas the patients in Kim et al. received EGFR TKIs as first to fourth lines of therapy. Additionally, our meta-analysis included previously unpublished predictive factor analysis from NEJ002. Furthermore, the patients in this meta-analysis were well balanced by gender, ethnicity, and type of *EGFR* mutation. Given that ORR was not the primary endpoint of any of the seven trials and not reported according to smoking status, we could not analyze any potential difference in ORR among *EGFRm* patients receiving EGFR TKIs by smoking status. We could also not analyze PFS outcome by the amount of tobacco smoke exposure because none of the seven trials systemically reported outcome according to exposure by pack years. We did not include IPASS [18] or First-SIGNAL [19] trials because both trials mainly enrolled never-smokers, the analysis of the *EGFRm* subgroup was retrospective, and a significant amount of

patients had unknown *EGFR* mutation status. Although three of the seven trials did not show that the PFS HRs by smoking were positive, as shown in Figure 2A almost all the HRs by smoking status were in the left of the Forest plot (HR < 1), with only former smokers from EURTAC and current smokers from LUX-Lung 3 lying just to the right of the Forest plot. Thus our results are consistent with what has been observed in individual trials and indicate the importance of performing this meta-analysis.

Finally, this meta-analysis also demonstrates that EGFR TKI is significantly more effective in conferring PFS benefit against exon 19 deletion than against L858R substitution when compared with platinum-doublet chemotherapy. In vitro data have demonstrated that gefitinib and erlotinib both have a higher affinity for the exon 19 deletion than L858R mutation [20], resulting in inhibition of the kinase activity of mutated exon 19 deletion EGFR much faster and tighter with both EGFR TKIs [21]. As early as in 2006, clinical observations have reported that exon 19 deletion seems to derive longer PFS from EGFR TKI than L858R substitution [22, 23]. Indeed five of the seven randomized trials in this meta-analysis had already been stratified for the type of *EGFR* mutation, whereas only one trial was stratified for smoking status. Liang et al. [24] performed a similar metaregression analysis on the two common *EGFR* mutations and demonstrated that exon 19 deletion conferred significant longer PFS than L858R substitution when treated with EGFR TKIs. Recently a pooled analysis of LL3 and LL6 demonstrated significant overall survival benefit of afatinib over platinum-doublet chemotherapy among *EGFRm* patients with exon 19 deletions [25], providing further strengthening evidence that the two common activating *EGFRm* mutations should be treated differently. Similar proportions of *EGFRm* patients with exon 19 deletion and L858R mutation received EGFR TKI and platinum-doublet chemotherapy, respectively, in this meta-analysis. However, we could not analyze the role of smoking status in determining the PFS outcome by EGFR TKI according to the type of *EGFRm* because the breakdown of the types of *EGFRm* by smoking status was not presented in any of the seven randomized trials.

The incidence of NSCLC patients with *EGFRm* is highest among Asians [26] and could be as high as 62% in one molecular epidemiology study among newly diagnosed treatment-naïve advanced adenocarcinoma in seven Southeast Asian regions including mainland China [27]. More importantly, the percentage of *EGFRm* among heavy Asian smokers (>50 pack years) in the same study was as high as 31.4% [27]. Furthermore 20.7% of the *EGFRm* patients were active smokers [27]. It is unlikely that these *EGFRm* patients with >50 pack years of smoking had the same genetic background in their tumors as *EGFRm* patients who were never-smokers. Thus *EGFRm* NSCLC patients represent a diverse group of patients with both intrinsic different genetic and environmental exposure. While the presence of activating *EGFR* mutations defines a unique molecular subtype of lung cancer, *EGFRm* lung cancer is likely to be a fairly heterogeneous disease in terms of underlying genomic alterations. Next generation sequencing techniques such as targeted paralleling sequencing, whole exome sequencing, and whole genome sequencing will reveal much more genetic heterogeneity between never-smokers and ever-smokers, potentially allowing better fine-tuning of personalized therapy with EGFR TKIs.

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Disclosures

Akihito Kubo: Chugai (H); **Takayasu Kurata:** AstraZenaca , Eli Lilly, Boehringer Ingelheim, Taiho, Pfizer (H); **Makoto Maemondo:** AstraZeneca, Chugai, Boehringer (H). The other authors indicated no financial relationships.

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