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Efficacy and safety of epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) monotherapy for advanced EGFR-mutated non-small cell lung cancer: systematic review and meta-analysis

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Abstract. – OBJECTIVE: It is controversial whether there is efficacy or safety benefit of epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) in advanced EGFR-mutated non-small cell lung cancer (NSCLC) compared to standard chemotherapy. We aim to assess the efficacy and safety of EGFR-TKIs compared to another chemotherapeutics in EGFR-mutated NSCLC.

MATERIALS AND METHODS: Up to April 27th, 2020, PubMed, Embase, Medline, Scopus, Cochrane library, and ClinicalTrials.gov were searched for articles or trials meeting the inclusion criteria. After filtering, 230 eligible studies were initially identified. Data extraction followed PRISMA and included outcomes were progression-free survival (PFS), overall survival (OS), and severe adverse events (SAEs). Direct and indirect meta-analyses were generated in the context of log-linear mixed-effects models, with fixed effects for each relative comparison and random effects for each study.

RESULTS: The results showed that EGFR-TKI therapy had improved PFS with a hazard ratio (HR) of 0.40 (95% CI: 0.36-0.44, $p<0.001$) compared to standard chemotherapy. Nevertheless, the EGFR-TKIs showed no benefit on OS (HR: 0.96, 95% CI: 0.83-1.10, $p=0.556$). In the analysis of adverse events, EGFR-TKIs had fewer SAEs than standard chemotherapy (HR: 0.29, 95% CI: 0.26-0.33, $p<0.001$).

CONCLUSIONS: Our systemic review indicates that EGFR-TKI therapy has improved PFS, and reduced SAEs compared to standard chemotherapy in advanced EGFR-mutated NSCLC.

Key Words:

Non-small cell lung cancer, Epidermal growth factor receptor, Tyrosine kinase, Meta-analysis.

Introduction

Lung cancer has a high incidence globally with high cancer-related mortality[1]. Specifically, non-small cell lung cancer (NSCLC) accounts for about 85% of all lung cancer and results in approximately 1.4 million deaths every year as it is often diagnosed at an advanced stage[2].

Epidermal growth factor receptor (EGFR) is an oncogene located on chromosome 7p11.2; it is one of the most important driver genes in lung cancer with activating mutations found in up to 20% of NSCLC, mainly adenocarcinoma. Its mutational status activates tumor growth and progression, stimulates cancer cell proliferation, invasion, and metastases, and inhibits apoptosis[3-5]. For patients having advanced NSCLC with activating mutations of the *EGFR* gene, EGFR-tyrosine kinase inhibitor (EGFR-TKI) is the standard treatment. Multiple randomized controlled trials (RCTs) have demonstrated improvement in progression-free survival (PFS) when EGFR-TKIs such as gefitinib, erlotinib, afatinib, and Osimertinib were compared to platinum-based chemotherapy[6-23].

However, there is controversy regarding whether there is an improvement of overall survival (OS) for EGFR-TKIs compared to standard chemotherapy in advanced EGFR mutated NSCLC. Some meta-analyses, such as studies by Guetz et al[24] and Lee et al[25] did not find any OS benefit. However, these meta-analyses used preliminary OS data of large RCTs, such as WJTOG3405 by Yoshioka et al[7] and NEJ002 by Maemondo et al[20], thus the results might have limited accuracy and have not included the most recent data. Another issue is that recent meta-analyses comparing the efficacy of EGFR-TKIs with that of chemotherapy did not include the results of newly developed second- or third-generation EGFR-TKIs, such as afatinib[25-27]. Moreover, quality assessment of relevant meta-analyses using the AMSTAR 2 tool showed that most of these were categorized as not having a high methodological quality.

Thus, the primary objective of this study was to determine the efficacy and adverse events (AEs) of all kinds of EGFR-TKIs, particularly including novel drugs, in patients with advanced EGFR-mutated NSCLC through meta-analyzing all relevant RCTs reporting updated OS data. Secondary objective was to test for interactions between different EGFR mutation types and other baseline characteristics that might be associated with EGFR-TKIs benefit.

Materials and Methods

Study Eligibility and Identification

Our study was performed according to a predefined written protocol registered in PROSPERO (CRD42020162429). Two investigators searched eligible RCTs independently up to April 27th, 2020, using electronic search databases including PubMed, Embase, Medline, Scopus, Cochrane library, and ClinicalTrials.gov with the following keywords: "non-small cell lung cancer" AND "advanced" AND "epidermal growth factor receptor" AND "tyrosine kinase inhibitor" AND "randomized controlled trials." We also checked the reference lists of relevant review articles to obtain additional RCTs.

Whenever several studies deal with overlapping patients, we retained only the final updated version as a primary reference to avoid duplication of information.

To be eligible, studies needed to meet all of the following criteria: (1) studies should be phase III RCTs, (2) patients should be clinically and pathologically diagnosed with advanced stage (stage IIIB or IV) NSCLC, (3) studies should compare EGFR-TKI monotherapy to standard first-line chemotherapy, consisting of one or more platinum-based therapies, taxanes, or gemcitabine, (4) EGFR mutation status should be available and at least 10 patients per treatment group should have *EGFR*-mutated NSCLC and efficacy analyses focus only on patients with EGFR-activating mutations, (5) studies should report at least one out of PFS, OS, or AEs as outcomes, and (6) studies should be published either as full-text articles or as informative abstracts. Studies that did not meet all the above inclusion criteria were excluded from the meta-analysis. Any disagreements were resolved by consensus, including a third author.

Quality Assessment

Two investigators independently evaluated the risk of bias of each eligible study based on the criteria described by the Cochrane handbook for Systematic Reviews by Cochrane Collaboration[28]. Specifically, we assessed the risk of bias of each category, such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias into low-risk, high-risk or unclear risk constellation. Any disagreements were resolved by consensus including a third author.

Data Extraction

Data selection and extraction were carried out by two investigators independently. We recorded details of the first author, year of publication, number of patients, number of participants with *EGFR* mutations, EGFR-TKI regimens, standard chemotherapy regimens, line of treatment, clinical data (i.e., *EGFR* mutation type, smoking history, and ECOG score), pathological (i.e. histology), demographic data (i.e., age, sex, ethnicity), treatment outcomes (i.e., PFS, OS, AEs, and severe AEs [SAEs] that is defined as AE having grade 3 and above in the assessment by Common Terminology Criteria for Adverse Events), *p*-value, hazard ratio (HR), and 95% confidence interval (CI). Although we considered the final updated version as a primary reference for studies with more than one publication, we extracted available data from all publications. Any disagreements were resolved by consensus, including a third author.

Data Synthesis

The measure of efficacy and safety was HR in overall analysis, but odds ratio (OR) in some subgroup analyses. If studies did not report HR, we indirectly obtained the HR using the methods described elsewhere[29]. Direct and indirect meta-analyses were generated in the context of log-linear mixed-effects models, similar to the model proposed by DerSimonian and Laird with fixed effects for each relative comparison and random effects for each study[30]. Heterogeneity across studies was tested and partially summarized using chi-squared test and I^2 statistics as proposed by Higgins and Thompson. $I^2 < 25$, $25 \leq I^2 < 50$, and $I^2 \geq 50$ were interpreted as signifying low-level, intermediate-level, and high-level heterogeneity, respectively[31,32]. AE rates were summarized separately for each therapy in the context of logistic mixed-effects models with a random effect for study. For AE summaries, the analyses were based on each study's full safety population, potentially a mix of patients with and without EGFR-activating mutations. A $p<0.05$ was considered a statistically significant difference. To test publication bias, the Egger's test and Begg's funnel plots were calculated using Comprehensive Meta-Analysis version 3[33]. This same protocol was performed for all subgroup analyses, which included EGFR-TKI regimen, age, smoking status, ECOG status, treatment line (first line *vs.* second line), EGFR mutation, histology type, cancer stage, SAEs, and all grades of AE.

Ethics and Funding Source

This study was a literature-based study, and as such, no ethics approval was needed. There was no funding source associated with the study design, collection, analysis, interpretation of the data, or writing of the report. All authors had full access to all the data.

Results

Overview of Literature Search and Study Characteristics

A total of 230 studies were retrieved initially for evaluation by identifying references of pre-

vious meta-analyses and performance of another search of the databases from May 1st, 2019 to April 27th, 2020. After title and abstract screening, 41 publications were evaluated in detail. Based on the inclusion and exclusion criteria described in the methods, a total of 18 RCTs[6-23] comparing the efficacy and toxicity of EGFR-TKI monotherapy versus standard chemotherapy were finally included in the meta-analysis. The search process is described in Figure 1. Table I summarizes the characteristics of the final 18 eligible studies.

Progression-Free Survival

A total of 16 phase III RCTs were included for meta-analysis of PFS comparing EGFR-TKIs with standard chemotherapy in advanced *EGFR*-mutated NSCLC patients. The pooling data showed improved PFS with EGFR-TKI therapy (HR: 0.40, 95% CI: 0.36-0.44, $p<0.001$), suggesting that EGFR-TKIs have PFS advantage compared to standard chemotherapy (Figure 2). The test of heterogeneity indicated high study-to-study variability with Q=48.0 on 15 degrees of freedom ($p<0.001$) and I^2 of 68.7%.

Subgroup analyses also demonstrated that EGFR-TKIs achieved PFS benefit in all subgroups except for NSCLC clinical-stage. For EGFR-TKI regimens, the pooled HR for gefitinib versus standard chemotherapy was 0.410 (95% CI: 0.350-0.481, $p<0.001$), erlotinib was 0.406 (95% CI: 0.229-0.718, $p=0.002$), and afatinib was 0.405 (95% CI: 0.198-0.826, $p=0.013$). Also, regardless of gender, smoking status, NSCLC pathologic type, *EGFR* mutational type, ECOG status, and treatment line, EGFR-TKI therapy resulted in improved PFS compared to standard chemotherapy in advanced *EGFR*-mutated NSCLC patients (Table II).

Overall Survival

A total of 10 phase III RCTs were included for meta-analysis of OS comparing EGFR-TKIs with standard chemotherapy in advanced *EGFR*-mutated NSCLC patients. The pooling data did not

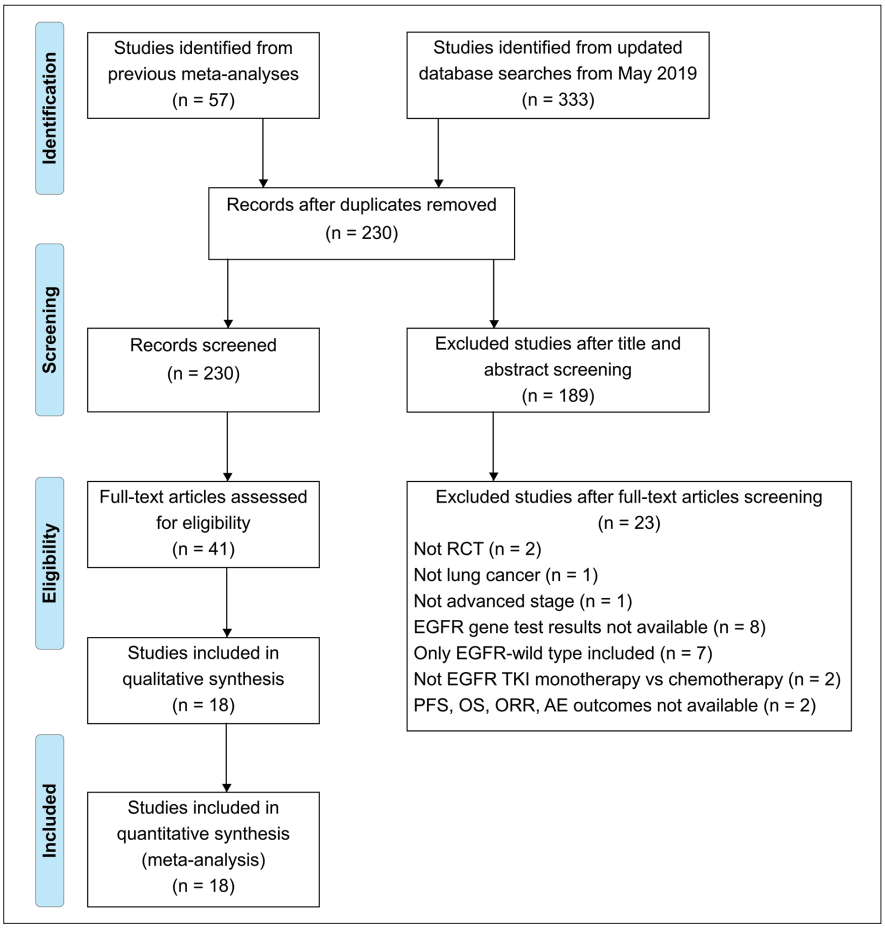

Figure 1. PRISMA flow chart of literature search.

Table I. Primary characteristics of eligible studies.

Author, year	Region	No. of Patients	Intervention	Control	Treatment line	EGFR-mutation (%)	Median age (years)	Men (%)	Smoker (%)	Hazard ratio (95% CI)*
Ye, 2019	Asia	98	Icotinib	Pemetrexed + Cisplatin	1	100	N/A	40.8	24.5	N/A
Yoshioka, 2019	Asia	177	Gefitinib	Cisplatin + Docetaxel	1	100	64	30.8	31.4	0.489 (0.336-0.710)
Akamatsu, 2018	Asia	419	Osimertinib	Pemetrexed + Carboplatin/ Cisplatin	2, 3, 4	100	62.3	35.8	35.1	0.3 (0.23-0.41)
Shi, 2017	Asia	296	Icotinib	Cisplatin + Pemetrexed	1	100	56	29.8	21.4	0.61 (0.43-0.87)
Han, 2017	Asia	81	Gefitinib	Pemetrexed + Carboplatin	1	100	N/A	43.2	30.1	0.35 (0.21-0.609)
Wu, 2015	Asia	217	Erlotinib	Cisplatin + Gemcitabine	1	100	56.8	38.7	29.5	0.43 (0.29-0.64)
Wu, 2014	Asia	364	Afatinib	Cisplatin + Gemcitabine	1	100	58	34.7	23.1	0.28 (0.20-0.39)
Kawaguchi, 2014	Asia	301	Erlotinib	Docetaxel	2, 3	22	67.5	71.4	74.8	1.22 (0.97-1.53)
Sequist, 2013	International	345	Afatinib	Pemetrexed + Cisplatin	1	100	61.3	35.1	31.6	0.58 (0.43-0.78)
Sun, 2012	Asia	135	Gefitinib	Pemetrexed	2	46.5	61	14.8	None	0.54 (0.37-0.79)
Rosell, 2012	Europe	174	Erlotinib	Cisplatin + Docetaxel/ Gemcitabine	1	100	65	27.2	30.6	0.37 (0.25-0.54)
Han, 2012	Asia	313	Gefitinib	Cisplatin + Gemcitabine	1	44.2	56.8	11.3	None	1.198 (0.944-1.520)
Ciuleanu, 2012	International	424	Erlotinib	Pemetrexed + Docetaxel	2	7.7	59	75.7	82.5	1.19 (0.97-1.46)
Zhou, 2011	Asia	165	Erlotinib	Carboplatin + Gemcitabine	1	100	57.9	40.9	29.2	0.16 (0.10-0.54)
Maemondo, 2010	Asia	230	Gefitinib	Carboplatin + Paclitaxel	1	100	63.3	36.4	38.2	0.322 (0.236-0.438)
Lee, 2009	Asia	313	Gefitinib	Cisplatin + Gemcitabine	1	50.9	57	11.3	None	0.737 (0.580-0.938)
Mok, 2009	Asia	1217	Gefitinib	Carboplatin + Paclitaxel	1	59.7	57	20.7	6.3	0.74 (0.65-0.85)
Kim, 2008	International	1466	Gefitinib	Docetaxel	2, 3, 4	14.8	60.5	65.1	79.7	1.04 (0.93-1.18)

No.: number, N/A: not available, *Hazard ratio for progression-free survival.

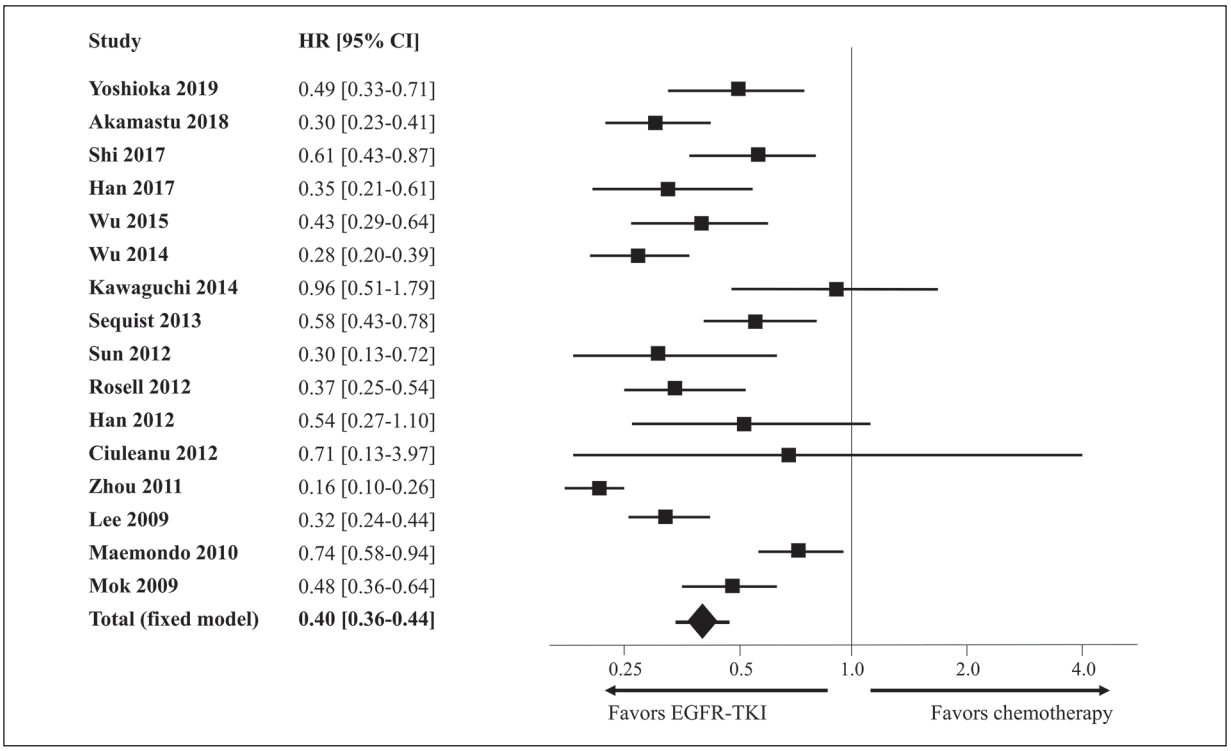

Figure 2. Forest plot of progression-free survival comparing EGFR-TKI with standard chemotherapy in patients with EGFR mutated advanced-stage non-small cell lung cancer.

show any OS advantage with EGFR-TKI therapy (HR: 0.96, 95% CI: 0.83-1.10, p=0.556). Neither EGFR-TKIs nor standard chemotherapy led to an OS advantage (Figure 3). The test of heterogeneity indicated low study-to-study variability with Q=5.27 on 9 degrees of freedom (p=0.810) and I^2 of 0%.

Subgroup analyses also demonstrated that EGFR-TKI therapy did not achieve OS benefit in any subgroup. Likewise, regardless of gender, smoking status, NSCLC clinical stage, NSCLC pathologic type, *EGFR* mutational type, ECOG status, and treatment line, EGFR-TKIs did not result in better OS rates than standard chemotherapy in advanced *EGFR* mutated NSCLC patients (Table II).

Adverse Events

A total of 13 phase III RCTs were included for meta-analysis of SAEs comparing EGFR-TKIs with standard chemotherapy in advanced EGFR-mutated NSCLC patients. The pooled data showed an SAE advantage with EGFR-TKI therapy (HR: 0.29, 95% CI: 0.26-0.33, p<0.001), suggesting that EGFR-TKIs cause fewer SAEs compared to standard chemotherapy (Figure 4). The test of heterogeneity indicated high study-to-study variability with Q=94.07 on 12 degrees of freedom (p<0.001) and I^2 of 87.24%.

In subgroup analyses of all grades of AEs, rash and diarrhea were more common in EGFR-TKI treated patients, while nausea, anorexia, fatigue, anemia, and neutropenia were more frequently observed in the group receiving standard chemotherapy. In subgroup analyses of SAEs, EGFR-TKIs treated patients showed more frequent aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevation, rash, and diarrhea, while patients treated with standard chemotherapy showed more frequent nausea, anorexia, fatigue, and neutropenia (Table III).

Publication Bias

Potential publication bias was evaluated using the Egger's test and Begg's funnel plots with log-transformed HR calculated from prevalence rate as the outcome and their standard errors as the index for accuracy. The funnel plots of PFS, OS, and SAE main findings were symmetrical. Funnel plots for subgroup analyses were also symmetrical. The data indicates that there is little evidence of publication bias.

Table II. Subgroup analyses of progression-free survival and overall survival.

		Progression-Free Survival					Overall Survival				
		No. of Studies	Effect size (95% CI)	*p*-value	Heterogeneity I^2 (*p*-value)	Egger's *p*-value	No. of Studies	Odds ratio, random (95% CI)	*p*-value	Heterogeneity I^2 (*p*-value)	Egger's *p*-value
EGFR-TKI regimen	Gefitinib	7	0.410 (0.350-0.481)	< 0.001	0% (0.438)	0.790	5	0.975 (0.804-1.182)	0.796	0% (0.526)	0.758
	Erlotinib	5	0.406 (0.229-0.718)	0.002	81.65% (< 0.001)	0.641	4	0.916 (0.693-1.212)	0.540	0% (0.583)	0.608
	Afatinib	2	0.405 (0.198-0.826)	0.013	90.18% (0.001)	N/A	–	–	–	–	–
Gender	Male	7	0.474 (0.352-0.638)	0.001	36.20% (0.152)	0.731	3	1.015 (0.701-1.469)	0.937	12.76% (0.318)	0.731
	Female	7	0.341 (0.239-0.487)	< 0.001	77.44% (< 0.001)	0.098	3	1.025 (0.810-1.297)	0.835	0% (0.833)	0.762
Age	Age < 65	4	0.343 (0.223-0.527)	< 0.001	73.79% (0.010)	0.704	–	–	–	–	–
	Age ≥ 65	4	0.284 (0.143-0.560)	< 0.001	75.07% (0.007)	0.091	–	–	–	–	–
Smoking	Smoker	6	0.520 (0.333-0.812)	0.004	54.10% (0.054)	0.118	3	0.984 (0.604-1.604)	0.949	39.29% (0.193)	0.428
	Never-smoker	9	0.362 (0.266-0.493)	< 0.001	71.46% (< 0.001)	0.508	4	1.025 (0.825-1.273)	0.825	0% (0.931)	0.951
Stage	Stage 3B	2	0.492 (0.184-1.319)	0.159	8.23% (0.297)	N/A	–	–	–	–	–
	Stage 4	2	0.343 (0.099-1.188)	0.091	94.46% (< 0.001)	N/A	–	–	–	–	–
Mutation	Exon 19 deletion	7	0.284 (0.191-0.423)	< 0.001	75.60% (< 0.001)	0.316	3	0.961 (0.678-1.361)	0.822	38.70% (0.196)	0.644
	Exon 21 L858R	7	0.494 (0.373-0.653)	< 0.001	45.71% (0.087)	0.339	3	1.101 (0.829-1.460)	0.507	0% ($p = 0.973$)	0.005
ECOG	ECOG 0-1	3	0.329 (0.144-0.753)	0.009	91.71% (< 0.001)	0.114	2	0.896 (0.705-1.139)	0.370	0% (0.964)	N/A
	ECOG 2-3	3	0.244 (0.092-0.648)	0.005	0% (0.977)	0.654	2	1.755 (0.671-4.593)	0.251	0% (0.346)	N/A
Histologic type	Adenocarcinoma	9	0.376 (0.280-0.507)	< 0.001	73.61% (< 0.001)	0.466	3	0.969 (0.755-1.243)	0.804	0% (0.999)	0.455
	Non-adenocarcinoma	2	0.237 (0.087-0.645)	0.005	0% (0.848)	N/A	–	–	–	–	–
Treatment line	First-line	12	0.397 (0.324-0.487)	< 0.001	69.18% (< 0.001)	0.468	8	0.969 (0.842-1.117)	0.667	0% (0.846)	0.825
	Second-line	4	0.464 (0.232-0.926)	0.030	74.28% (0.009)	0.466	2	0.531 (0.188-1.496)	0.231	0% (0.436)	N/A

No.: number, N/A: not available, *Hazard ratio for progression-free survival.

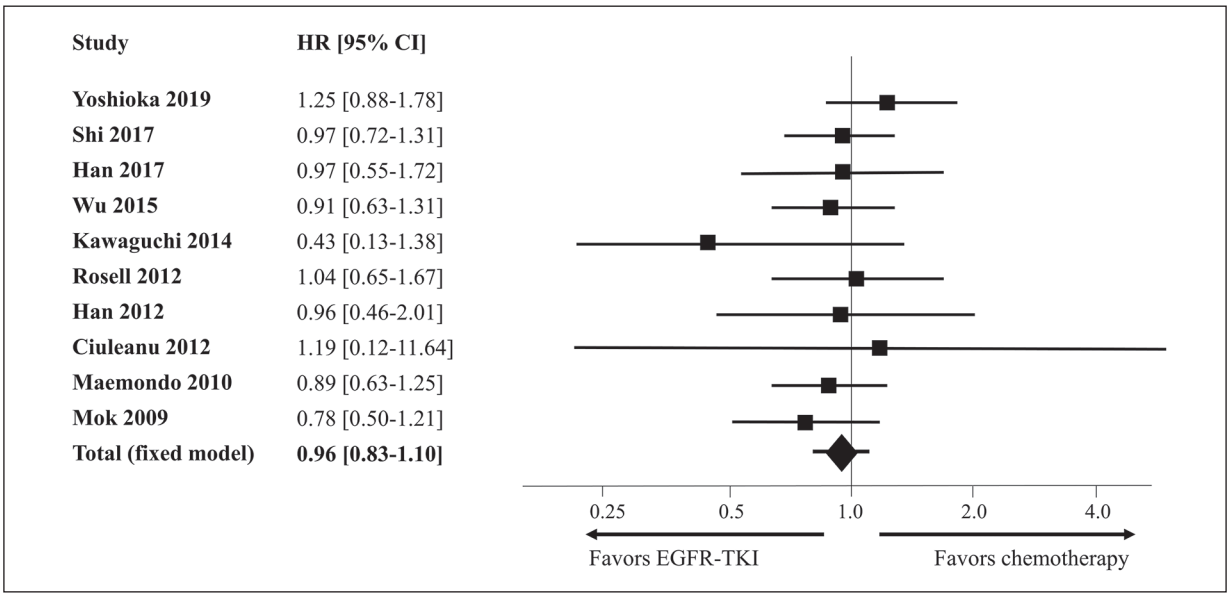

Figure 3. Forest plot of overall survival comparing EGFR-TKI with standard chemotherapy in patients with EGFR mutated advanced stage non-small cell lung cancer.

Discussion

NSCLC is a major driver of cancer-associated mortality. In *EGFR*-mutated NSCLC, EGFR-TKIs are well-tolerated and effective therapies associated with longer PFS times than chemotherapy[6-25]. However, whether OS is improved with EGFR-TKIs over platinum-based chemotherapy remains controversial. Past meta-analyses by Guetz et al.[24] and Lee et al.[25] demonstrat-

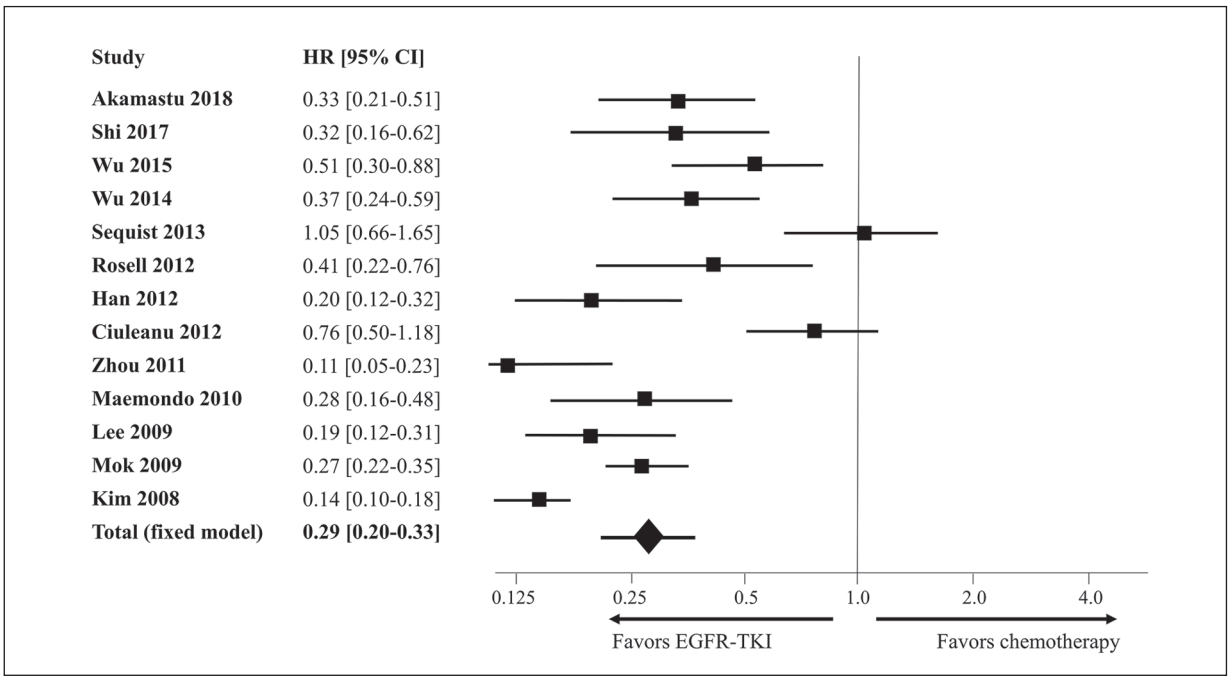

Figure 4. Forest plot of adverse events comparing EGFR-TKI with standard chemotherapy in patients with EGFR mutated advanced-stage non-small cell lung cancer.

Table III. Subgroup analyses of all grades and severe adverse events.

	No. of studies	Odds ratio, random (95% CI)	*p*-value	Heterogeneity I^2 (*p*-value)	Egger's *p*-value
All grades of AEs	8	0.534 (0.293-0.974)	0.041	48.38% (0.060)	0.158
SAEs*	13	0.314 (0.223-0.446)	< 0.001	87.24% (< 0.001)	0.453
All grades of AEs					
AST elevation	6	1.828 (0.871-3.840)	0.111	84.85% (< 0.001)	0.744
ALT elevation	8	1.510 (0.978-2.333)	0.063	65.82% (0.005)	0.933
Rash	17	21.79 (13.800-34.396)	< 0.001	86.05% (< 0.001)	0.005
Diarrhea	17	5.989 (3.506-10.231)	< 0.001	92.30% (< 0.001)	0.022
Stomatitis	8	2.338 (0.864-6.325)	0.094	94.31% (< 0.001)	0.561
Nausea	15	0.115 (0.060-0.220)	< 0.001	94.13% (< 0.001)	0.019
Anorexia	13	0.293 (0.178-0.483)	< 0.001	90.59% (< 0.001)	0.083
Fatigue	16	0.304 (0.238-0.388)	< 0.001	62.68% (< 0.001)	0.815
Anemia	15	0.145 (0.087-0.243)	< 0.001	82.68% (< 0.001)	0.014
Neutropenia	16	0.031 (0.020-0.048)	< 0.001	66.12% (< 0.001)	0.323
SAEs*					
AST elevation	6	4.357 (1.349-14.077)	0.014	37.21% (0.158)	0.663
ALT elevation	7	3.775 (1.397-10.201)	0.009	40.82% (0.119)	0.984
Rash	15	1.755 (0.671-4.593)	< 0.001	9.84% (0.343)	0.145
Diarrhea	13	2.258 (1.255-4.064)	0.007	31.62% (0.130)	0.020
Stomatitis	6	1.915 (0.425-8.633)	0.398	43.00% (0.118)	0.175
Nausea	10	0.188 (0.082-0.428)	< 0.001	48.88% (0.040)	0.414
Anorexia	11	0.408 (0.185-0.898)	0.026	75.09% (< 0.001)	0.984
Fatigue	13	0.319 (0.187-0.542)	< 0.001	55.36% (0.008)	0.356
Neutropenia	16	0.017 (0.011-0.027)	< 0.001	24.43% (0.178)	0.997

AEs: adverse events, SAEs: severe adverse events, AST: aspartate aminotransferase, ALT: alanine aminotransferase, *SAEs are defined as AEs with grade ≥3.

ed no OS improvement; both evaluated various first-line EGFR-TKIs but were limited by the inclusion of more preliminary OS data. Other studies by Wu et al[26], Li et al[27], and Jadad et al[28] also failed to include more recent therapies such as afatinib and osimertinib. Therefore, to overcome these methodological challenges, we comprehensively analyzed all RCTs to study the efficacy of EGFR-TKI monotherapy on PFS and OS in *EGFR*-mutated advanced NSCLC, compared to standard chemotherapy. As the result, we analyzed a total of 18 RCTs encompassing over 6,000 patients and found that EGFR-TKIs offered benefits of risk reduction in disease progression and in SAEs compared to standard chemotherapy. Benefits to PFS were maintained regardless of sex, age, smoking, genetic mutation, ECOG, histologic type, and treatment line (first or second). However, EGFR-TKIs were not associated with OS benefit, which remained across all subgroup analyses. Taken together, our study indicates that EGFR-TKIs have a clear PFS advantage, but they do not improve OS over platinum-based therapy.

It is currently uncertain whether PFS is a valid surrogate endpoint for OS in NSCLC. Although PFS has been suggested as a valid surrogate marker for other cancer types, it has not yet been validated in NSCLC[34]. The US Food and Drug Administration recently found a weak association between PFS and OS from 14 NSCLC RCTs, though this study only reported two trials of first-line EGFR-TKIs against platinum-based chemotherapy[35]. On the other hand, reliance on OS, particularly given crossover effects in many RCTs, may limit novel therapies having fewer AEs than traditional chemotherapy[36]. Despite several issues, since the care for advanced NSCLC is often focused on palliative intent such as an improved quality of life and reduction in toxicities, PFS benefit may be still an important factor in the evaluation and selection of treatment[37].

Of NSCLC driver mutations, *EGFR* mutations are the second most common, with several typical mutation locations[38]. The *EGFR* gene is located at chromosome 7p11.2. The most frequent mutations include deletion in exon 19 and L858R mutation in exon 21, but multiple other driver mutations also exist[39]. Primary and secondary driver mutations play a role in deciding type of EGFR-TKIs. For example, osimertinib is a preferred treatment option in patients with *EGFR* T790M mutations[40].

On the other hand, the response to treatment is not clearly correlated with mutation types. In Del19 or L858R mutated NSCLCs, there has been uncertainty as to whether one mutation responds better to EGFR-TKIs[41]. Many studies associated the Del19 mutation with better outcomes than L858R[42-44], while other studies report no survival differences between mutation types[45-47]. Del19 and L858R did not differ with respect to both PFS and OS in our study, providing further evidence that both mutations are sensitive to EGFR-TKIs at similar degrees.

Afatinib and osimertinib, second- and third-generation EGFR-TKIs are usually expected to be superior to first generation EGFR-TKIs. However, in that regard there are no clear evidence yet. The second-generation drug afatinib has been suggested to improve PFS and OS over platinum-based therapies and older EGFR-TKIs in advanced NSCLC by some meta-analyses, but not others[48-50]. Chen et al[51] found that osimertinib conferred both PFS and OS advantages over platinum-based doublet chemotherapy, though the authors disclosed limitations from heterogeneity and publication bias. An RCT of second, third, and fourth line osimertinib treatment included in our analysis described by Akamatsu et al. shows PFS benefit compared to standard therapy (HR: 0.3, 95% CI: 0.23-0.41) but to a similar degree as first-generation EGFR-TKIs (HR: 0.40, 95% CI: 0.36-0.44). Two RCTs by Wu et al[12] in 2014 and Sequist et al[14] in 2013 also demonstrated a PFS benefit of afatinib comparable with first-generation EGFR-TKIs. However, the OS data were unavailable for osimertinib and afatinib in our included RCTs. Even though osimertinib represents one of the most effective EGFR-TKI with the thus far longest reported PFS data[41], its value for OS requires further evaluation.

Besides drug efficacy, AEs are important considerations for cancer treatment. Our study indicates that EGFR-TKI therapy has a benefit of fewer SAEs compared to standard chemotherapy. Furthermore, the results suggest that EGFR-TKIs could be a preferred option for the patients with decreased general condition in advanced NSCLC. The rates of SAEs for the next-generational drugs afatinib and osimertinib were comparable to the first-generational EGFR-TKIs.

Our study has several strengths. Indeed, we only included RCTs that had already completed phase III, allowing for more complete data for newer EGFR-TKIs and OS outcomes. Furthermore, studies were largely consistent in using EGFR-TKIs as a first- or second-line treatment for Del19 or L858R mutated EGFR NSCLCs, which reduces the likelihood of introducing further heterogeneity in the examined patient populations from previous treatment. This study also has several limitations. Crossover treatment may have been a confounding factor even in a number of our included studies[7,9,10], which may explain the apparent lack of OS benefit in our study. Though evidence for bias was low, high study heterogeneity in the main and subgroup analyses suggest differences in experimental design and population characteristics between studies. Furthermore, most of the studies were conducted in Asia, and several did not report OS data or rates of SAEs, which may cause selection bias and limit relevant findings. Subgroup analyses were performed without controlling for several clinical parameters, including ethnicity, metastases, and genotype for resistance mutations, which may change the interpretation of our findings when delivering care. Specifically, the type of *EGFR* mutation, which can impact the efficacy of certain EGFR-TKIs over others, was not stratified in our analyses beyond exon 19 deletions and exon 21 L858R mutations. Additionally, OS data were limited for analyses for osimertinib and afatinib. However, our study contributes to increasing evidence that EGFR-TKIs provide a longer PFS together with a better toxicity profile for patients with advanced *EGFR*-mutated NSCLC over platinum-based chemotherapy and therefore supports their use in this patient group. Nevertheless, further research evaluating afatinib and osimertinib as first-line therapies for EGFR-mutated advanced NSCLC to confirm OS benefits in combination with investigations of treatment sequences based on molecular/mutation profiles are warranted.

Conclusions

Our systematic review with meta-analysis demonstrates that EGFR-TKIs induce superior PFS in patients with EGFR-mutated advanced NSCLC as compared to standard chemotherapy but do not improve OS. However, SAEs were also reduced in EGFR-TKI treatment relative to standard chemotherapy. Further studies evaluating afatinib and osimertinib as first-line treatments for NSCLC are warranted.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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