# 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 other chemotherapeutics in EGFR-mutated NSCLC.

**MATERIALS AND METHODS:** Up to April 27$^{th}$, 2020, PubMed, Embase, Medline, Scopus, Cochrane library, and ClinicalTrials.gov were searched with the following keywords: "non-small cell lung cancer" AND "advanced" AND "epidermal growth factor receptor" AND "tyrosine kinase inhibitor" AND "randomized controlled trials." 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 event (SAE). 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 of 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:** NSCLC; EGFR-TKI; Efficacy; Safety; 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 compared EGFR-TKIs such as gefitinib, erlotinib, afatinib, and osimertinib 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. Unlike the definite effect of EGFR-TKIs extending PFS, 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 might be not updated to include 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 event (AE) 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 27$^{th}$, 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 be compare EGFR-TKI monotherapy to standard first-line chemotherapy, consisting of one or more of 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 have to focus only on patients with EGFR-activating mutations, 5) studies should report at least one of the PFS, OS, or AE as outcomes, and 6) studies should be published either as full articles or as informative abstracts.

The 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 on 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. 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, AE, and severe AE [SAE] 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 the 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, SAE, 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 previous meta-analyses and searching an updated database 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 the 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 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 lead 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 all subgroups. 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 SAE 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 found to be more associated with EGFR-TKI therapy, while nausea, anorexia, fatigue, anemia, and neutropenia were more common with 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.

## 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] demonstrated 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 the 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 evidences 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]. One study by 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. in 2014 and Sequist et al. 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. But, rates of SAEs for the next-generational drugs afatinib and osimertinib were comparable to the first-generational EGFR-TKIs.

Our study has several points of strength. 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.

**Funding information:** Neither financial support nor any sort of sponsorship was received for this study.

**Conflict of Interests/Competing Interests:** The authors declare no conflict of interests.

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## 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 + Gemcitabin | 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

## 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

## 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

## FIGURE LEGENDS

**Figure 1.** Forest plot of progression-free survival comparing EGFR-TKI with standard chemotherapy in patients with EGFR mutated advanced-stage non-small cell lung cancer.

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

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