# Comparison of gefitinib, erlotinib and afatinib in non-small cell lung cancer: a meta-analysis

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***Short title:*** Gefitinib vs erlotinib vs afatinib in NSCLC

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***Abbreviations*:** EGFR TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; NSCLC, non-small cell lung cancer; HR, hazard ratio; RR, risk ratio; CI, confidence interval.

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***Novelty and Impact*:** This study synthesized direct evidence on the comparative effects of gefitinib, erlotinib and afatinib in non-small cell lung cancer. The three

agents had comparable efficacy in first-line treatment of patients with *EGFR* mutations, but gefitinib had a generally more favorable safety profile. Afatinib was more effective than erlotinib as second-line treatment of patients with advanced squamous cell carcinoma. These findings should inform clinical decision-making in the treatment of non-small cell lung cancer.

**ABSTRACT**

Gefitinib, erlotinib and afatinib are three widely used epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) for treating advanced non-small cell lung cancer (NSCLC) with proven efficacy. We undertook a systematic review and meta-analysis to synthesize existing studies with direct comparisons of EGFR TKIs in NSCLC in terms of both efficacy and safety. Eight randomized trials and 82 cohort studies with a total of 17621 patients were included for analysis. Gefitinib and erlotinib demonstrated comparable effects on progression-free survival (hazard ratio [HR], 1.00; 95% confidence interval [CI], 0.95 to 1.04), overall survival (HR, 0.99; 95% CI, 0.93 to 1.06), overall response rate (risk ratio [RR], 1.05; 95% CI, 1.00 to 1.11), and disease control rate (RR, 0.98; 95% CI, 0.96 to 1.01), which did not vary considerably with *EGFR* mutation status, ethnicity, line of treatment, and baseline brain metastasis status. Gefitinib was associated with more grade 3/4 liver dysfunction, but tended to have lower rates of dose reduction, treatment discontinuation, total grade 3/4 adverse events (RR, 0.78; 95% CI 0.65 to 0.94), and a number of specific adverse events such as rash and diarrhea. No solid evidence was found that afatinib had greater efficacy than gefitinib or erlotinib in first-line treatment of *EGFR*-mutant NSCLC. However, afatinib was more effective than erlotinib as second-line treatment of patients with advanced squamous cell carcinoma. The grade 3/4 adverse events rate of afatinib was comparable to that of erlotinib but higher than that of gefitinib.

## BACKGROUND

Gefitinib and erlotinib are two small-molecule, first-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) that were approved more than 10 years ago and have since been widely used as first-line treatment of advanced non-small cell lung cancer (NSCLC) in chemotherapy-naive patients, or as second- or later-line treatment after failure of chemotherapy.[1] Compared with standard chemotherapy, EGFR TKIs are effective in improving progression-free survival but not overall survival.[2] Greater efficacy of EGFR TKIs is associated with East Asian ethnicity, female sex, non-smoking status, adenocarcinoma pathological type,[3,4] and most pronouncedly *EGFR* mutations.[2] In particular, EGFR TKIs are superior to standard chemotherapy at various lines in *EGFR*-mutant NSCLC, but become inferior in *EGFR*-wild-type patients in terms of progression-free survival and overall response rate.[2,5] In 2013, afatinib, a second-generation EGFR TKI, was also approved for treating advanced NSCLC. It is used as first-line treatment of patients with exon 19 deletions or exon 21 (L858R) substitution mutations or second-line treatment of those with advanced squamous cell carcinoma after failure of platinum-based chemotherapy.[6,7]

While the efficacy of gefitinib, erlotinib and afatinib is well established, their comparative effects are less understood, mainly because published randomized controlled trials that directly compared the three agents or any two of them are relatively rare.[8-10] Indeed, there are good reasons to question the interchangeability of the three agents. For example, erlotinib and gefitinib are reversible EGFR TKIs, while afatinib is an irreversible ErbB-family blocker and reported to be effective against tumors carrying T790M mutation, a major mechanism for acquired resistance to EGFR TKIs.[11] Gefitinib and erlotinib, who have similar chemical structures and mechanisms of action, are also different from each other in some aspects, which may lead to differential treatment effects. First, they differ in the substituents attached to the quinazoline and anilino rings, which may have important clinical implications.[12] Second, the pharmacokinetics of the two agents is also different. For example, when administered at their recommended doses (250 mg/day for gefitinib; 150 mg/day for erlotinib), the area under curve of the plasma concentrations of erlotinib is seven times higher than that of gefitinib.[8,13] These differences have led to the assumption that erlotinib is more effective and at the same time associated with more adverse events than gefitinib. Indeed, studies have shown that gefitinib is effective in *EGFR*-mutant patients only, while erlotinib has efficacy versus placebo in *EGFR*-wild-type patients as well.[3,14]

Some researchers have tried to compare the three agents or two of them indirectly based on randomized controlled trials that evaluated each agent against control, in which no within-study direct comparisons of the agents were available.[9,15-17] However, the indirect approach itself is controversial,[18] and the findings from indirect comparisons conducted by different research groups were inconsistent. For example, Lee et al concluded that erlotinib was significantly more efficacious than gefitinib through indirect comparison based on two published trials, one for erlotinib (OPTIMAL) and one for gefitinib (IPASS),[15] whereas Haaland et al stated that there was no statistically significant difference in the efficacy of the two agents based on eight trials involving gefitinib, erlotinib, and afatinib.[17]

A review published in the New England Journal of Medicine in 2011 clearly pointed out that no direct comparison of gefitinib versus erlotinib had been conducted and thus no definitive conclusions could be drawn regarding their comparative effects.[1] For the comparison of afatinib with gefitinib and erlotinib, a more recent review highlighted the same problem.[10] In 2012, a phase II randomized controlled trial conducted in Korea directly compared gefitinib with erlotinib for the second-line treatment of advanced NSCLC, but it was small in sample size (48 patients for each group) and failed to yield any statistically significant results on progression-free survival, overall survival, overall response rate, disease control rate, or safety.[8,19] To our knowledge, that was the only randomized trial with direct comparison of gefitinib with erlotinib that had been published in full text before the present systematic review started, although several relevant randomized trials emerged later.

On the other hand, our pilot literature search showed that quite a number of observational cohort studies have been published to directly compare different EGFR TKIs in terms of effectiveness, safety, or both. However, a problem of such studies is that their results, compared with those of randomized controlled trials, are generally more susceptible to confounding. For example, due to lack of randomization, patient characteristics that may influence the efficacy of the two agents, such as female, non-smokers, adenocarcinoma, and *EGFR* mutation status, could be imbalanced between treatment groups. Here we report a systematic review and meta-analysis synthesizing the direct evidence, randomized or not, on the comparative effects of EGFR TKIs in NSCLC, with important potential confounding factors taken into account.

## METHODS

### *Data sources and literature search*

We performed a systematic search of PubMed, EMBASE, The Cochrane Central

Register of Controlled Trials, Chinese Biomedical Literature Database (in Chinese), and China National Knowledge Infrastructure (in Chinese) from their respective inception through 17 December 2016, limited to "human studies" where possible, with no restrictions placed on the time, language and format (abstract or full text) of publication. The keywords used for literature search included gefitinib, erlotinib, afatinib, non-small cell lung cancer, and their variations or synonyms. The abstracts of 40 American Society of Clinical Oncology and European Society of Medical Oncology meetings, including their annual meetings and the meetings related to lung cancer, were reviewed, two major trial registration websites (i.e. www.clinicaltrials.gov/ and www.who.int/ictrp/) were searched, and the reference lists of eligible studies and relevant reviews were also scrutinized, to identify additional studies.

***Study selection***

Titles and abstracts of all identified records were screened to judge their relevance. Full texts of the studies seemingly fulfilling the inclusion criteria were obtained for further assessment. To be eligible for the present systematic review, original studies had to be randomized controlled trials or cohort studies that directly compared the three EGFR TKIs, i.e. gefitinib monotherapy, erlotinib monotherapy, afatinib monotherapy, or any two of them, in NSCLC patients and reported results on at least one of the following outcomes, i.e. progression-free survival, overall survival, overall response rate (complete response plus partial response), disease control rate (complete response plus partial response and stable disease), and safety, including treatment tolerability and adverse events. Completely duplicate records of a same study from different data sources were excluded, while partially duplicate records were combined to obtain a full picture of the study concerned.

***Data extraction***

The following data was extracted from each eligible study: (i) bibliographic information, such as first author, country, and publication year; (ii) clinical and pathological characteristics of patients, such as the number of patients included for the present systematic review, mean or median age, percentage of female, percentage of non-smokers, stage of cancer, pathological type of cancer, percentage of *EGFR*-mutant patients, Eastern Cooperative Oncology Group performance status, and line of treatment; (iii) main study results, such as hazard ratio (HR) and 95% confidence interval (CI) for progression-free survival, HR and 95% CI for overall survival, number of patients with response to treatment, and number of cases with adverse events; and (iv) information that did not belong to any of the previous

categories but was related to the methodological quality of studies (see the "risk of bias assessment" section below).

Investigators of original studies were contacted as needed to clarify ambiguities in reported methods or results or to seek additional data not included in published reports. If not explicitly reported in original papers and still not available after contact with investigators, HRs were estimated based on other data reported, for example, survival curves, using such methods as the one developed by Parmar et al.[20] Data extraction was completed independently by two reviewers. Disagreements between the two were settled by revisiting original papers and discussion until consensus was reached.

***Risk of bias assessment***

As mentioned above, both randomized controlled trials and cohort studies were included in this systematic review. The risk of bias in randomized controlled trials was assessed using the Cochrane Collaboration's tool and classified as "low" or "others" for convenience of analysis.[21] The Newcastle-Ottawa scale[22] adapted to this systematic review was employed to assess the risk of bias in cohort studies, with emphasis on comparability between gefitinib and erlotinib groups in terms of the factors that are commonly believed to be able to significantly affect the efficacy of the two agents, such as ethnicity, gender, smoking status, pathology, *EGFR* mutation status, and line of treatment. According to the Newcastle-Ottawa scale, a score ranging from 0 to 9 was assigned to each study, with 9 representing the lowest risk of bias.[22] For convenience of analysis, studies with a score of 7 to 9 were referred to as the low-risk-of-bias group. Risk of bias assessment was done independently by two reviewers. Disagreements between the two were resolved by revisiting the original paper and discussion. Unsettled disagreements were referred to a third researcher for final decision.

***Data synthesis and analysis***

The primary outcome was progression-free survival and secondary outcomes included overall survival, overall response rate, disease control rate, and safety. The comparative effects of EGFR TKIs on progression-free survival and overall survival were measured by HR with 95% CI, with HR>1 meaning that the efficacy of intervention group is inferior to that of reference group and HR<1 meaning the opposite. The comparative effects of overall response rate, disease control rate, and safety were measured by risk ratio (RR) with 95% CI. For overall response rate and disease control rate, RR>1 means that the efficacy of intervention group is greater than that of reference group, while RR<1 means the opposite. For safety, RR>1 means

that the safety profile of intervention group is worse than that of reference group, while RR<1 means the opposite.

For each outcome, the effect estimates (HR or RR) from relevant studies were combined using the random-effects model to produce a summary estimate. Statistical heterogeneity among studies was measured by Cochran's Q test and the $I^2$ statistic.[23,24] A P value ≤0.10 for the Q test or an $I^2 \geqslant 50\%$ was suggestive of substantial heterogeneity. Subgroup analyses were conducted according to *EGFR* mutation status, ethnicity, line of treatment, and baseline brain metastasis status to see if the comparative effects of gefitinib versus erlotinib would vary with these important clinical factors and to explore the source of substantial heterogeneity, if present. Sensitivity analyses were conducted by restricting the meta-analyses to the studies with low risk of bias only to demonstrate the impact of study quality on the overall results. Begg's funnel plot and Egger's test were used to examine the possibility of publication bias where 10 or more studies were available.[25] All analyses were performed with RevMan software, version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), and STATA software, version 11.0 (StataCorp LP, College Station, TX, USA). A P value <0.05 suggested statistical significance for all analyses except for the tests of heterogeneity and between-subgroup difference, for which the statistical significance level was set at $\alpha$=0.10.

## RESULTS

### *Study selection and characteristics*

The flow of study selection is shown in Figure 1. Of the 3208 records identified by our literature search, 90 eligible studies with 17621 patients (9529, 7401, and 691 in the gefitinib, erlotinib, and afatinib groups, respectively) were included for this systematic review.[12,19,26-115] Twelve of the 90 studies were available as conference abstracts only.[26-31,32-35,95,110,111] For one of the abstract-only studies, detailed results were obtained by communication with their investigators.[34] The data of two studies were obtained from more than one source.[36-39]

The characteristics of included studies are shown in Table 1. Except one global multicenter trial, most of the other studies were conducted in East Asia. Specifically, 44 studies were from China, 13 from Korea, 12 from Japan, six from Taiwan, four from Italy, three from US, two from UK, two from Spain, and one each from Netherlands, France, and Thailand. Eighty studies were retrospective cohort studies, two prospective cohort studies,[40,98] and eight randomized controlled trials.[19,32,87,93,97,103,109,110] Eighty-eight studies (16014 patients), three studies (807

patients)[89,97,98] and three studies (1047 patients) were available for the comparisons of gefitinib versus erlotinib, gefitinib versus afatinib, and erlotinib versus afatinib,[89,98,103] respectively, with two studies (607 patients) of them providing within-study comparison of the three agents.[89,98] Twenty-nine studies included *EGFR*-mutant patients only, one study included *EGFR*-wide-type patients only, while the others included both or did not specify the *EGFR* status of patients. Fourteen studies were conducted in first-line settings, 21 in ≥second-line settings, and the others in both or did not specify the line of treatment. Fifty-one, 45, 61, 51, and 47 studies provided data on progression-free survival, overall survival, overall response rate, disease control rate, and safety, respectively. Twenty-five of the 90 eligible studies were regarded as with low risk of bias.

***Gefitinib versus erlotinib: efficacy***

Meta-analyses of studies with relevant data showed that the effects of gefitinib versus erlotinib on progression-free survival (HR, 1.00; 95% CI, 0.95 to 1.04, P=0.89; heterogeneity $I^2$=56%, P<0.0001; Figure 2), overall survival (HR, 0.99; 95% CI, 0.93 to 1.06, P=0.82; heterogeneity $I^2$=42%, P=0.002; Figure 3), overall response rate (RR, 1.05; 95% CI, 1.00 to 1.11, P=0.05; heterogeneity $I^2$=0%, P=0.55; Appendix A), and disease control rate (RR, 0.98; 95% CI, 0.96 to 1.01, P=0.22; heterogeneity $I^2$=0%, P=0.54; Appendix B) were all comparable. Substantial heterogeneity was observed in the meta-analyses for progression-free survival and overall survival.

***Gefitinib versus erlotinib: safety***

The results about safety are presented in detail in Appendix C. Briefly, there was a consistent trend towards fewer dose reduction (RR, 0.34; 95% CI, 0.21 to 0.54, P<0.0001; heterogeneity $I^2$=32%, P=0.15), treatment discontinuation (RR 0.94; 95% CI 0.67 to 1.31, P=0.70; heterogeneity $I^2$=25%, P=0.23), any-grade adverse events (RR, 0.92; 95% CI 0.75 to 1.14, P=0.47; heterogeneity $I^2$=86%, P=0.0001), grade 3/4 adverse events (RR, 0.78; 95% CI 0.65 to 0.94, P=0.01; heterogeneity $I^2$=0%, P=0.72) and deaths due to adverse events (RR, 0.51; 95% CI 0.13 to 1.97, P=0.33; heterogeneity $I^2$=0%, P=0.66) with gefitinib than with erlotinib, although only the results about dose reduction and grade 3/4 adverse events reached statistical significance.

In terms of specific adverse events, gefitinib was associated with more grade 3/4 liver dysfunction (RR, 2.88; 95% CI, 1.56 to 5.28, P=0.0007; heterogeneity $I^2$=0%, P=0.68), but fewer grade 3/4 rash (RR, 0.43; 95% CI, 0.27 to 0.70, P=0.0005; heterogeneity $I^2$=28%, P=0.11), any-grade diarrhea (RR, 0.83; 95% CI, 0.75 to 0.93, P=0.0007; heterogeneity $I^2$=15%, P=0.23), any-grade nausea/vomiting (RR, 0.60;

95% CI, 0.43 to 0.85, P=0.003; heterogeneity $I^2$=48%, P=0.02), and grade 3/4 paronychia (RR, 0.19; 95% CI, 0.04 to 0.84, P=0.03; heterogeneity $I^2$=0%, P=0.41) as compared with erlotinib. Gefitinib also appeared to be associated with lower incidence of some other adverse events such as asthenic conditions (RR 0.50; 95% CI, 0.24 to 1.01, P=0.05), oral ulcer (RR 0.50; 95% CI, 0.25 to 1.04, P=0.06), pruritus (RR 0.72; 95% CI, 0.50 to 1.03, P=0.07), desquamation, eye change, stomatitis and constipation, but the results were not statistically significant, or the number of studies with relevant data was very limited. No significant difference was found in the incidence of such commonly mentioned adverse events as interstitial lung disease, neutropenia, anorexia and oral ulcer between the two treatment groups.

***Comparison of afatinib with gefitinib and erlotinib***

The effects of afatinib were investigated in four studies, including two observational ones directly comparing the three agents on progression-free survival[89] or selected adverse events,[98] one randomized trial comparing afatinib with gefitinib on all efficacy and safety outcomes,[97] and one randomized trial comparing afatinib with erlotinib on all efficacy and safety outcomes.[103]

Compared with gefitinib, afatinib appeared to be associated with longer progression-free survival as first-line treatment of *EGFR* mutant patients,[89,97] but the benefit was considerably different between studies (>18 versus 11.4 months in the observational one; 11.0 versus 10.9 months in the randomized trial), and there was no evidence that afatinib prolonged overall survival.[97]

Compared with erlotinib, afatinib appeared to have similar efficacy in terms of progression-free survival as first-line treatment of *EGFR* mutant patients,[89] but was associated with longer progression-free survival (2.6 vs 1.9 months, HR 0.81, 95% CI, 0.69 to 0.96) and overall survival (7.9 vs 6.8 months, HR 0.81, 95% CI, 0.69 to 0.95) as second-line treatment of patients with advanced squamous cell carcinoma of the lung.[103]

In terms of safety, there was a consistent trend that the overall incidence of grade 3/4 adverse events of afatinib was comparable to that of erlotinib but higher than that of gefitinib.[97,98,103] This finding coincides with the results on comparative effects of gefitinib versus erlotinib as reported above. Compared with gefitinib, afatinib caused more diarrhea and rash but fewer liver dysfunction.[97] Compared with erlotinib, afatinib caused more diarrhea and stomatitis but fewer rash.[103]

***Subgroup, sensitivity and publication bias analyses***

Subgroup analyses showed that the comparative effects of gefitinib versus erlotinib did not differ considerably with *EGFR* mutation status, ethnicity, and line of treatment

(Appendix D). Although gefitinib appeared to be associated with better overall survival and fewer grade 3/4 adverse events in the first-line treatment subgroup, all subgroup differences were not statistically significant. Comparative effects of the two agents in the subset of patients with brain metastases were similar to those in the overall population.

In sensitivity analyses where only the studies with low risk of bias were included, the summary estimates for progression-free survival, overall survival, overall response rate, disease control rate, any-grade adverse events, and grade 3/4 adverse events were 1.02 (95% CI 0.96~1.09, P=0.54; heterogeneity $I^2$=37%, P=0.06), 1.00 (95% CI 0.92~1.09, P=1.00; heterogeneity $I^2$=0%, P=0.82), 1.01 (95% CI 0.91~1.11, P=0.91; heterogeneity $I^2$=15%, P=0.29), 0.99 (95% CI 0.96~1.03, P=0.74; heterogeneity $I^2$=0%, P=0.60), 0.92 (95% CI 0.75~1.14, P=0.47; heterogeneity $I^2$=86%, P=0.0001),and 0.80 (95% CI 0.65~0.98, P=0.03; heterogeneity $I^2$=0%, P=0.48), respectively, all of which were very close, both qualitatively and quantitatively, to the results of overall meta-analyses as reported above. However, the results of studies with low risk of bias tended to be more homogeneous than those in the overall meta-analyses.

For the comparison of gefitinib with erlotinib, funnel plots constructed based on the data for progression-free survival, overall survival, overall response rate, disease control rate, and grade 3/4 adverse events are shown in Appendix E, which are all visually symmetric. Egger's tests for asymmetry yielded no statistically significant results, indicating no evidence for publication bias. For the comparison of afatinib with gefitinib or erlotinib, the number of studies was too small for investigation of publication bias.

## DISCUSSION

This systematic review synthesized 90 studies with direct comparisons of two or three EGFR TKIs, the majority of which comparing gefitinib with erlotinib. It was found that gefitinib had similar efficacy but a generally more favorable safety profile as compared with erlotinib. Specifically, gefitinib was associated with more grade 3/4 liver dysfunction, but tended to have lower rates of dose reduction, treatment discontinuation, total adverse events, fatal or non-fatal, and a number of specific adverse events. The data on comparative effects of afatinib versus gefitinib or erlotinib is limited. There is no solid evidence that afatinib had greater efficacy, especially in terms of overall survival benefit, than the other two agents in first-line treatment of *EGFR*-mutant NSCLC. However, afatinib was more effective than erlotinib as second-line treatment of patients with advanced squamous cell carcinoma.

The overall grade 3/4 adverse events rate of afatinib was comparable to that of erlotinib but higher than that of gefitinib.

These findings differ to varying degrees from those of previously published indirect comparisons of gefitinib with erlotinib.[9,15-17] For example, Lee et al compared the gefitinib with erlotinib for first-line treatment of *EGFR*-mutant NSCLC indirectly based on only two large trials and concluded that erlotinib was significantly more efficacious than gefitinib (progression-free survival: HR=0.33, 95% CI 0.19 to 0.58).[15] Another three indirect comparisons of gefitinib, erlotinib and afatinib based on systematic review of randomized trials found that the three agents had similar efficacy.[9,16,17] Among these indirect comparisons, however, Haaland et al (11 trials, 3 EGFR TKIs and various chemotherapies) found that the "adverse event profiles were similar among TKIs";[16] Liang et al (12 trials, 4 EGFR TKIs and various chemotherapies) found that gefitinib was associated with fewer grade 3/4 rash and diarrhea than erlotinib and afatinib;[17] Haspinger et al (9 trials, 3 EGFR TKIs and various chemotherapies) found that gefitinib was associated with similar rates of diarrhea and rash, but more hypertransaminasemia, as compared with erlotinib, and that both agents caused lower adverse events rates than did afatinib.[9] The discrepancy between these indirect comparisons is obvious. It could be due to the different number of studies, patients and treatments included for comparison, or even the validity of the indirect approach itself. The present systematic review settled existing controversies by including studies with direct comparison of EGFR TKIs only. It provides a full view of the comparative effects of gefitinib, erlotinib and afatinib on a variety of outcomes.

The finding that gefitinib and erlotinib have comparable efficacy but different safety profiles is not completely the same as expected. Although the bioavailability of erlotinib 150 mg/day (equal to the maximum tolerated dose) is three-fold higher than that of gefitinib 250 mg/day (one-third of the maximum tolerated dose),[116,117] which could partly explain the less tolerability and more toxicities with erlotinib, the anticancer efficacy of erlotinib is however not greater than that of gefitinib. A potential explanation for this is that gefitinib, after absorbed, accumulates significantly more in tumor tissue than in plasma, in contrast with the clinical pharmacokinetics of erlotinib.[118,119]

The findings of this systematic review have important clinical implications. As there is no solid evidence that gefitinib, erlotinib and afatinib differ much in efficacy, gefitinib seems to be generally more preferable than the other two agents, in view of their safety profiles, for first-line treatment of patients with *EGFR*-mutant NSCLC. For second-line treatment of advanced squamous cell carcinoma, currently available evidence suggests that afatinib is generally a better choice than erlotinib. However,

this does not necessarily mean that gefitinib and afatinib are always optimal in the two settings, respectively. Clinical decision-making regarding which agent to use should also take patients' physical status, resources and values into account, which is often not straightforward. For example, gefitinib could be more suitable for patients with poor gastrointestinal function, while erlotinib or afatinib could be better for those with poor liver functions. In addition, the prices of and reimbursement or discounting schemes for different agents, if any, could be different within health systems.[48,57,72,120] Thus, the out-of-pocket costs of different EGFR TKIs treatments should be balanced against the suffering from and costs required for management of toxicities induced by these agents.

This systematic review has several strengths. First, it summarized the direct evidence on comparative effects of different EGFR TKIs, which is scientifically more solid than indirect evidence. Second, it compiled a large, comprehensive dataset, which allowed us to obtain precise estimates and conduct subgroup analyses according to important factors. Importantly, there was no evidence for publication bias. Third, between-study statistical heterogeneity was not significant in most of the main meta-analyses, especially in the ones restricted to studies with low risk of bias. Although the majority of included studies were observational and potential imbalance in patient characteristics between gefitinib and erlotinib groups could be of concern, sensitivity analyses that included the studies with low risk of bias only showed that the summary estimates were robust and very close to those from the overall meta-analyses.

A major limitation of this systematic review is that the number of studies available for comparison of afatinib with gefitinib, erlotinib, or both, was very limited. This prevented us from drawing a firm conclusion about their comparative effects in some settings. For example, for second-line treatment of advanced squamous cell carcinoma, currently available evidence suggests that afatinib has greater efficacy than does erlotinib, but whether afatinib outperforms gefitinib or not in risk-benefit ratio is unclear. The same question exists in some other settings as well and thus remains to be clarified. A further limitation of the present work is that data on low-grade adverse events are lacking, mainly because most of the included studies did not report them separately. Low-grade adverse events may impair patient' quality of life more than transient grade 3/4 adverse events. Thus, future studies are suggested to pay attention to this issue.

As shown by this systematic review, dose reduction occurs significantly more in erlotinib group than in gefitinib group, but the two groups achieved comparable efficacy. This implies that erlotinib might be administered at a lower-than-standard dose to reduce adverse events while retaining its efficacy. In fact, retrospective studies

have shown that patients who were treated with reduced dose of erlotinib down to 25 mg/day had similar or even better prognosis compared to those who were treated with the agent at standard dose, although prospective studies are needed to validate this finding.[121-123] To complicate matters, similar evidence exists for gefitinib as well.[121,124,125] Thus, there seems to be room for adjusting the doses of both agents to minimize toxicity while retaining maximum efficacy. Further studies on this issue are warranted.

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**Conflicts of interest statement**

The authors declare no conflict of interest.

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**Figure legends**

Figure 1. Flow chart of study selection.

Figure 2. Comparative effects of gefitinib versus erlotinib on progression-free survival of patients with non-small cell lung cancer. Results are presented as individual and pooled hazard ratios with 95% confidence intervals. A hazard ratio statistically significantly smaller than 1 means that the progression-free survival of patients treated with gefitinib is better than with erlotinib, while a hazard ratio statistically significantly greater than 1 means the opposite.

Figure 3. Comparative effects of gefitinib versus erlotinib on overall survival of patients with non-small cell lung cancer. Results are presented as individual and pooled hazard ratios with 95% confidence intervals. A hazard ratio statistically significantly smaller than 1 means that the overall survival of patients treated with gefitinib is better than that with erlotinib, while a hazard ratio statistically significantly greater than 1 means the opposite.