

Zuyao Yang 

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

Zuyao Yang^{1,2}, Allan Hackshaw³, Qi Feng¹, Xiaohong Fu¹, Yuelun Zhang¹, Chen Mao^{1,4} and Jinling Tang^{1,2,4,*}

¹Division of Epidemiology, the Jockey Club School of Public Health and Primary Care, the Chinese University of Hong Kong, Hong Kong, China

²The Hong Kong Branch of the Chinese Cochrane Centre, the Chinese University of Hong Kong, Hong Kong, China

³Cancer Research UK and University College London Cancer Trials Centre, 90 Tottenham Court Rd, London W1T 4TJ, United Kingdom

⁴Shenzhen Key Laboratory for Health Risk Analysis, Shenzhen Research Institute of the Chinese University of Hong Kong, Shenzhen, Guangdong Province, China

*Correspondence to: Jinling Tang, 4/F, School of Public Health Building, Prince of Wales Hospital, Shatin, New Territories, Hong Kong, Tel.: (+852) 2252 8779, Fax: (+852) 2645 3098, Email: jltang@cuhk.edu.hk

Short title: Gefitinib vs erlotinib vs afatinib in NSCLC

Keywords: Gefitinib, erlotinib, afatinib, non-small cell lung cancer, meta-analysis

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.

Article category: Research articles; Cancer Therapy and Prevention

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', doi: 10.1002/ijc.30691

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-naïve 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 scale²² 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 $I^2 \geq 50\%$ 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 \geq 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 survival⁸⁹ 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's 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.

Funding support

This work was supported in part by the Faculty Postdoctoral Fellowship Scheme from Faculty of Medicine, the Chinese University of Hong Kong.

Conflicts of interest statement

The authors declare no conflict of interest.

Acknowledgements

We thank the authors of some original studies who provided additional data to us for this meta-analysis.

References

1. Cataldo VD, Gibbons DL, Pérez-Soler R, Quintás-Cardama A. Treatment of non-small-cell lung cancer with erlotinib or gefitinib. *N Engl J Med* 2011;364:947-55.
2. Lee CK, Brown C, Gralla RJ, Hirsh V, Thongprasert S, Tsai CM, Tan EH, Ho JC, Chu da T, Zaatar A, Osorio Sanchez JA, Vu VV, Au JS, Inoue A, Lee SM, GebSKI V, Yang JC. Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: a meta-analysis. *J Natl Cancer Inst* 2013;105:595-605.
3. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, Campos D, Maoleekoonpiroj S, Smylie M, Martins R, van Kooten M, Dediu M, Findlay B, Tu D, Johnston D, Bezjak A, Clark G, Santabárbara P, Seymour L; National Cancer Institute of Canada Clinical Trials Group. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123-32.
4. Thatcher N, Chang A, Parikh P, Rodrigues Pereira J, Ciuleanu T, von Pawel J, Thongprasert S, Tan EH, Pemberton K, Archer V, Carroll K. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 2005;366:1527-37.
5. Lee JK, Hahn S, Kim DW, Suh KJ, Keam B, Kim TM, Lee SH, Heo DS. Epidermal growth factor receptor tyrosine kinase inhibitors vs conventional chemotherapy in non-small cell lung cancer harboring wild-type epidermal growth factor receptor: a meta-analysis. *JAMA* 2014;311:1430-7.
6. U.S. Food and Drug Administration. Giotrif (afatinib) tablets, for oral use. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/201292s000lbl.pdf. Accessed on February 18, 2016.
7. European Medicines Agency. Giotrif (afatinib). http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicine_s/002280/human_med_001698.jsp&mid=WC0b01ac058001d124. Accessed on February 18, 2016.
8. Bronte G, Rolfo C, Giovannetti E, Cicero G, Pauwels P, Passiglia F, Castiglia M, Rizzo S, Vullo FL, Fiorentino E, Van Meerbeeck J, Russo A. Are erlotinib and gefitinib interchangeable, opposite or complementary for non-small cell lung cancer treatment? Biological, pharmacological and clinical aspects. *Crit Rev Oncol Hemato* 2014;89:300-13.
9. Haspinger ER, Agustoni F, Torri V, Gelsomino F, Platania M, Zilembo N, Gallucci R, Garassino MC, Cinquini M. Is there evidence for different effects

- among EGFR-TKIs? Systematic review and meta-analysis of EGFR tyrosine kinase inhibitors (TKIs) versus chemotherapy as first-line treatment for patients harboring *EGFR* mutations. *Crit Rev Oncol Hematol* 2015;94:213-27.
10. Asami K, Atagi S. Comparing the efficacy of gefitinib, erlotinib, and afatinib in non-small cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations. *Austin J Lung Cancer Res* 2016;1:1003.
 11. Li D, Ambrogio L, Shimamura T, Kubo S, Takahashi M, Chirieac LR, Padera RF, Shapiro GI, Baum A, Himmelsbach F, Rettig WJ, Meyerson M, Solca F, Greulich H, Wong KK. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. *Oncogene* 2008;27:4702-11.
 12. Togashi Y, Masago K, Fujita S, Hatachi Y, Fukuhara A, Nagai H, Sakamori Y, Kim YH, Mio T, Mishima M. Differences in adverse events between 250 mg daily gefitinib and 150 mg daily erlotinib in Japanese patients with non-small cell lung cancer. *Lung Cancer* 2011;74:98-102.
 13. Frohna P, Lu J, Eppler S, Hamilton M, Wolf J, Rakhit A, Ling J, Kenkare-Mitra SR, Lum BL. Evaluation of the absolute oral bioavailability and bioequivalence of erlotinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in a randomized, crossover study in healthy subjects. *J Clin Pharmacol* 2006;46:282-90.
 14. Augustin A, Lamerz J, Meistermann H, Golling S, Scheiblich S, Hermann JC, Duchateau-Nguyen G, Tzouros M, Avila DW, Langen H, Essioux L, Klughammer B. Quantitative chemical proteomics profiling differentiates erlotinib from gefitinib in *EGFR* wild-type non-small cell lung carcinoma cell lines. *Mol Cancer Ther* 2013;12:520-9.
 15. Lee VW, Schwander B, Lee VH. Effectiveness and cost-effectiveness of erlotinib versus gefitinib in first-line treatment of epidermal growth factor receptor-activating mutation-positive non-small-cell lung cancer patients in Hong Kong. *Hong Kong Med J* 2014;20:178-86. .
 16. Liang W, Wu X, Fang W, Zhao Y, Yang Y, Hu Z, Xue C, Zhang J, Zhang J, Ma Y, Zhou T, Yan Y, Hou X, Qin T, Dinglin X, Tian Y, Huang P, Huang Y, Zhao H, Zhang L. Network meta-analysis of erlotinib, gefitinib, afatinib and icotinib in patients with advanced non-small-cell lung cancer harboring *EGFR* mutations. *PLoS One* 2014;9:e85245.
 17. Haaland B, Tan PS, de Castro G Jr, Lopes G. Meta-analysis of first-line therapies in advanced non-small-cell lung cancer harboring EGFR-activating mutations. *J Thorac Oncol* 2014;9:805-11.
 18. Song F, Loke YK, Walsh T, Glenny AM, Eastwood AJ, Altman DG. Methodological problems in the use of indirect comparisons for evaluating

- healthcare interventions: survey of published systematic reviews. *BMJ* 2009;338:b1147.
19. Kim ST, Uhm JE, Lee J, Sun JM, Sohn I, Kim SW, Jung SH, Park YH, Ahn JS, Park K, Ahn MJ. Randomized phase II study of gefitinib versus erlotinib in patients with advanced non-small cell lung cancer who failed previous chemotherapy. *Lung Cancer* 2012;75:82-8.
 20. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998;17:2815-34.
 21. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
 22. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses.
http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed on July 25, 2014.
 23. Deeks JJ, Higgins JP, Altman DG, eds. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JP, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org. Accessed on July 25, 2014.
 24. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
 25. Sterne JAC, Egger M, Moher F, eds. Chapter 10: Addressing reporting biases. In: Higgins JP, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org. Accessed on July 25, 2014.
 26. Arriola E, Gomez RG, Diz P, Majem M, Aguillo MM, Valdivia J, Paredes A, Torres JMS, Peralta S, Barneto IC, Gonzalez MC. Observational retrospective study to describe the management of advanced epidermal growth factor receptor (EGFR) mutated (M+) non-small cell lung cancer (NSCLC) patients (pts) in Spain (NCT01795352). *J Clin Oncol* 2014;32(suppl): abstr e19133.
 27. Berros JP, Esteban E, Villanueva N, Jimenez P, Vieitez J.M. Gutierrez E. Alvarez C. Perez Q. Ruiz A.L. Rubi D. Gefitinib and erlotinib in advanced non-small-cell lung cancer (NSCLC) patients: A retrospective review from the hospital universitario central de Asturias. In: 3rd European Lung Cancer Conference; Apr

- 18-21, 2012; Geneva, Switzerland. Abstract 7.
28. Caristi N, Franchina T, Proto C, Chiofalo G, Toscano G, Scimone A, Zanghì M, Berenato R, Briguglio R, Denaro N, Noto L, Adamo V. Second-line therapy in advanced non-small cell lung cancer: Cytotoxic agents or tyrosine kinase inhibitors? Our experience. In: 2011 ASCO Annual Meeting; Jun 3-7, 2011; Chicago, US. Abstract 18063.
29. Franchina T, Adamo B, Caristi N, Chiofalo G, Toscano G, Colonese F, Denaro N, Ricciardi GR, Russo A, Adamo V. Activity and safety of gefitinib and erlotinib in metastatic non-small cell lung cancer (NSCLC): A comparative analysis. In: 2010 ASCO Annual Meeting; Jun 4-8, 2010; Chicago, US. Abstract 18110.
30. Grossi F, Defferrari C, Brianti A, Dal Bello MG, Catania G, Pronzato P. Difference in skin toxicity incidence between erlotinib (E) and gefitinib (G) in the treatment of advanced non-small-cell lung cancer (NSCLC). In: 34th Congress of the European Society for Medical Oncology (ESMO); Sep 12-16, 2008; Stockholm, Sweden. Abstract 106-107.
31. Jang SH, Park GY, Park S, Hwang YI, Kim DG, Jung KS, Lee KW, Chung HS. Prediction of treatment response EGFR tyrosine kinase inhibitors by direct sequencing method for EGFR mutation in non-squamous non-small cell lung cancer. In: 14th World Conference on Lung Cancer; Jul 3-7, 2011; Aksterdam, The Netherlands. Abstract S1282.
32. Urata Y, Katakami N, Morita S, Kaji R, Yoshioka H, Seto T, Satouchi M, Iwamoto Y, Kanehara M, Fujimoto D, Ikeda N, Murakami H, Daga H, Oguri T, Goto I, Imamura F, Sugawara S, Saka H, Nogami N, Negoro S, Nakagawa K, Nakanishi Y. Randomized phase III study comparing Gefitinib with Erlotinib in patients with previously treated advanced lung adenocarcinoma: WJOG 5108L. *J Clin Oncol* 2016;34:3248-57.
33. Lee JH, Lee KE, Ryu YJ, Chun EM, Chang JH. Comparison of gefitinib and erlotinib for patients with advanced Non-Small-Cell lung cancer. *Tuberc Respir Dis (Seoul)* 2009;66:280-7.
34. Morise M, Goto K, Umemura S, Goto K, Umemura K, Matsumoto S, Yoh K, Niho S, Ohmatsu H, Nagai K, Ohe Y. Clinicopathological analysis of long-term (more than 2 years) progression-free survivors treated with epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) in patients with EGFR mutation-positive non-small cell lung cancer. In: 15th World Conference on Lung Cancer; Oct 27-30, 2013; Sydney, Australia. Abstract 753.
35. Wang Z, Wu LY, Yang J, Wang B, Huang Y, Zhou Q, Xu C. EGFR tyrosine kinase inhibitor in advanced non-small cell lung cancer with wild-type EGFR. In: 2011 ASCO Annual Meeting ; Jun 3-7, 2011; Chicago, US. Abstract 18072.

36. Zhang J, Liu S, Zhang J, Ban LY, Zhou T. Effect and cost-efficacy analysis of the second-line treatment of advanced non-small cell lung cancer. *Chin Clin Oncol* 2012;17:908-11.
37. Zhang J. Efficacy and cost-effectiveness analysis of the second-line treatment for advanced non-small-cell lung cancer [master's thesis]. Dalian, China: Dalian Medical University; 2011.
38. Zhang XQ, Li Y, Ni J, Liu GL. Clinical effect and pharmacoeconomics of gefitinib and erlotinib in advanced non-small-cell lung cancer. *Chin J New Drugs Clin Rem* 2009;11:837-40.
39. Zhang X, Li Y, Ni J, Liu GL. Clinical effect and pharmacoeconomics of gefitinib and erlotinib in advanced non-small-cell lung cancer. In: *The 2nd Conference on Anti-tumor Pharmacy*; Oct 16, 2009; Shanghai, China. Abstract 51-54.
40. Park SJ, Kim HT, Lee DH, Kim KP, Kim SW, Suh C, Lee JS. Efficacy of epidermal growth factor receptor tyrosine kinase inhibitors for brain metastasis in non-small cell lung cancer patients harboring either exon 19 or 21 mutation. *Lung Cancer* 2012;77:556-60.
41. Hong W, Lin BC, Zhang BB, Mao WM, Zhang YP. Association between GNAS1 T393C polymorphism and therapeutic efficacy of tyrosine kinase inhibitor in pretreated advanced non-small cell lung cancer with unknown EGFR mutation status. *Chin J Lung Cancer* 2014;17:321-6.
42. Hotta K, Kiura K, Takigawa N, Yoshioka H, Harita S, Kuyama S, Yonei T, Fujiwara K, Maeda T, Aoe K, Ueoka H, Kamei H, Umemura S, Moritaka T, Segawa Y, Kawai H, Bessho A, Kato K, Tabata M, Tanimoto M. Comparison of the incidence and pattern of interstitial lung disease during erlotinib and gefitinib treatment in Japanese patients with non-small cell lung cancer. *J Thorac Oncol* 2010;5:179-84.
43. Kim ST, Lee J, Kim JH, Won YW, Sun JM, Yun J, Park YH, Ahn JS, Park K, Ahn MJ. Comparison of gefitinib versus erlotinib in patients with nonsmall cell lung cancer who failed previous chemotherapy. *Cancer* 2010;116:3025-33.
44. Koo DH, Kim K, Choi CM, Lee DH, Lee JC, Lee JS, Jang SJ, Kim SW. EGFR-TKI is effective regardless of treatment timing in pulmonary adenocarcinoma with EGFR mutation. *Cancer Chemother Pharmacol* 2014;75:197-206.
45. Lim SH, Lee JY, Sun JM, Ahn JS, Park K, Ahn MJ. Comparison of clinical outcomes following gefitinib and erlotinib treatment in non-small-cell lung cancer patients harboring an epidermal growth factor receptor mutation in either exon 19 or 21. *J Thorac Oncol* 2014;9:506-11.
46. Peng L. Efficacy of erlotinib and gefitinib on advanced non-small cell lung

cancer and analysis of survival associated factors. Beijing, China: Medical School of Chinese PLA; 2010.

47. Popat S, Barbachano Y, Ashley S, Norton A, O'Brien M. Erlotinib, docetaxel, and gefitinib in sequential cohorts with relapsed non-small cell lung cancer. *Lung Cancer* 2008;59:227-31.
48. Shao YY, Shau WY, Lin ZZ, Chen HM, Kuo R, Yang JC, Lai MS. Comparison of gefitinib and erlotinib efficacies as third-line therapy for advanced non-small-cell lung cancer. *Eur J Cancer* 2013;49:106-14.
49. Shin HJ, Kim TO, Kang HW, Chi SY, Ban HJ, Kim SO, Kwon YS, Oh IJ, Kim KS, Kim YI, Lim SC, Kim YC. Comparison of therapeutic efficacy of gefitinib and erlotinib in patients with squamous cell lung cancer. *Tuberc Respir Dis* 2011;71:15-23.
50. Takeda M, Okamoto I, Nakagawa K. Survival outcome assessed according to tumor response and shrinkage pattern in patients with EGFR mutation-positive non-small-cell lung cancer treated with gefitinib or erlotinib. *J Thorac Oncol* 2014;9:200-4.
51. Yoshida T, Yamada K, Azuma K, Kawahara A, Abe H, Hattori S, Yamashita F, Zaizen Y, Kage M, Hoshino T. Comparison of adverse events and efficacy between gefitinib and erlotinib in patients with non-small-cell lung cancer: a retrospective analysis. *Med Oncol* 2013;30:349.
52. Zheng L, Lin BC, Song ZB, Xie F, Hong W, Feng J, Shao L, Zhang Y. Relationship between BIM gene polymorphism and therapeutic efficacy in the retreatment of advanced non-small cell lung cancer with tyrosine kinase inhibitor. *Chin J Lung Cancer* 2013;16:632-8.
53. Bai J, Chen M. Comparison research of efficacy of erlotinib and gefitinib for lung cancer. *Guide of China Medicine* 2013;11:567-8.
54. Chen HJ, Yang JJ, Yan HH, Wang Z, Wang BC, Huang YS, Wu YL. Survival benefit and failure patterns of EGFR-TKIs in elderly patients with advanced non-small cell lung cancer. *J Third Mil Med Univ* 2012;34:2047-50.
55. Chen XP, Hang XS, Gao X, Xu WH, Li C, Zhao J. Adverse drug reaction of gefitinib in threparty for patients with advanced non-small cell lung cancer. *Chin J Hemorh* 2009;19:579-82.
56. Emery IF, Bettelli C, Auclair PL, Carrier K, Hayes DM. Response to gefitinib and erlotinib in non-small cell lung cancer: a retrospective study. *BMC Cancer* 2009;9:333.
57. Fan WC, Yu CJ, Tsai CM, Huang MS, Lai CL, Hsia TC, Tien YJ, Huang SF, Wu CH, Chou KT, Lee YC, Perng RP, Chen YM. Different efficacies of erlotinib and gefitnib in Taiwanese patients with advanced non-small cell lung cancer: a

- retrospective multicenter study. *J Thorac Oncol* 2011;6:148-55.
58. Hong J, Kyung SY, Lee SP, Park JW, Jung SH, Lee JI, Park SH, Sym SJ, Park J, Cho EK, Shin DB, Lee JH. Pemetrexed versus gefitinib versus erlotinib in previously treated patients with non-small cell lung cancer. *Korean J Intern Med* 2010;25:294-300.
59. Jiang B, Li J, Wan P, Gong P. Clinical Research of EGFR-TKIs in the treatment of patients with advanced non-small cell lung cancer. *Prog Mod Biomed* 2013;13:1489-92.
60. Jung M, Kim SH, Lee YJ, Hong S, Kang Y, Kim SK, Chang J, Rha, SY, Kim JH, Kim JD, Cho BC. Prognostic and predictive value of CEA and CYFRA 21-1 levels in advanced non-small cell lung cancer patients treated with gefitinib or erlotinib. *Exp Ther Med* 2011;2:685-93.
61. Kappers I, Vollebergh MA, van Tinteren H, Korse CM, Nieuwenhuis LL, Bonfrer JM, Klomp HM, van Zandwijk N, van den Heuvel MM. Soluble epidermal growth factor receptor (sEGFR) and carcinoembryonic antigen (CEA) concentration in patients with non-small cell lung cancer: correlation with survival after erlotinib and gefitinib treatment. *Ecancermedicallscience* 2010;4:178.
62. Li J, Li X, Ren S, Chen X, Zhang Y, Zhou F, Zhao M, Zhao C, Chen X, Cheng N, Zhao Y, Zhou C, Hirsch FR. MiR-200c overexpression is associated with better efficacy of EGFR-TKIs in non-small cell lung cancer patients with EGFR wild-type. *Oncotarget* 2014;5:7902-16.
63. Li JJ, Qu LL, Wei X, Gao HJ, Wang WX, Qin HF, Tang CH, Guo WF, Wang H, Liu XQ. Clinical Observation of EGFR-TKI as a first-line therapy on advanced non-small cell lung cancer. *Chin J Lung Cancer* 2012;15:299-304.
64. Lin GN, Peng JW, Liu PP, Liu DY, Xiao JJ, Chen XQ. Elevated neutrophil-to-lymphocyte ratio predicts poor outcome in patients with advanced non-small-cell lung cancer receiving first-line gefitinib or erlotinib treatment. *Asia Pac J Clin Oncol*. 2014 Oct 31. doi: 10.1111/ajco.12273. [Epub ahead of print]
65. Locatelli-Sanchez M, Couraud S, Arpin D, Riou R, Bringuier PP, Souquet PJ. Routine EGFR molecular analysis in non-small-cell lung cancer patients is feasible: exons 18-21 sequencing results of 753 patients and subsequent clinical outcomes. *Lung* 2013;191:491-9.
66. Lu L. Acts of clinical and pathological features treated by EGFR-TKI in the prognosis of NSCLC patients. Suzhou, China: Soochow University; 2012.
67. Ma YX, Huang Y, Zhao HY, Liu JL, Chen LK, Wu HY, Zhou NN. The cost-effectiveness analysis of gefitinib or erlotinib in the treatment of advanced

- EGFR mutant non-small cell lung cancer patients. *Chin J Lung Cancer* 2013;16:203-10.
68. Ren S, Su C, Wang Z, Li J, Fan L, Li B, Li X, Zhao C, Wu C, Hou L, He Y, Gao G, Chen X, Ren J, Li A, Xu G, Zhou X, Zhou C, Schmid-Bindert G. Epithelial phenotype as a predictive marker for response to EGFR-TKIs in non-small cell lung cancer patients with wild-type EGFR. *Int J Cancer* 2014;135:2962-71.
 69. Suzumura T, Kimura T, Kudoh S, Umekawa K, Nagata M, Matsuura K, Tanaka H, Mitsuoka S, Yoshimura N, Kira Y, Nakai T, Hirata K. Reduced CYP2D6 function is associated with gefitinib-induced rash in patients with non-small cell lung cancer. *BMC Cancer* 2012;12:568.
 70. Wang DZ, Chen N, Guo CY, Wei R, Han SH, Pan NQ. Analysis of efficacy and survival associated factors of TKI on old advanced non-small cell lung cancer. *Chin J Geriatr Care* 2014;12:15-8.
 71. Wang H, Zhang D. Comparison of the efficacy of gefitinib and erlotinib as a second line treatment for advanced non-small cell lung cancer. *J Pract Med* 2012;28:3444-6.
 72. Wu JY, Wu SG, Yang CH, Chang YL, Chang YC, Hsu YC, Shih JY, Yang PC. Comparison of gefitinib and erlotinib in advanced NSCLC and the effect of EGFR mutations. *Lung Cancer* 2011;72:205-12.
 73. Wu WS, Chen YM, Tsai CM, Shih JF, Chiu CH, Chou KT, Lai SL, Wu CH, Luo YH, Huang CY, Lee YC, Perng RP, Whang-Peng J. Erlotinib has better efficacy than gefitinib in adenocarcinoma patients without EGFR-activating mutations, but similar efficacy in patients with EGFR-activating mutations. *Exp Ther Med* 2012;3:207-13.
 74. Wu X, Zhang HY, Lv WZ, Lin Z. Comparison of clinical effects and safety between gefitinib and erlotinib in treatment of patients with NSCLC. *Chin J Misdiagn* 2011;11:3534-6.
 75. Yan Y, Liu Y, Lai C. Adverse events and nursing care of gefitinib and erlotinib therapies for non-small-cell lung cancer. *Chin J Mod Nurs* 2009;15:1066-7.
 76. Zhang C. Clinical observation of adverse events in target therapy for advanced non-small cell lung cancer. *Hainan Med J* 2014;25:2273-4.
 77. Zhang XY, Xu LY, Wang H, Zhu YZ, Liu Z, Yue WT, Tang JF, Wu W, Liu Z, Wu YH, Zhang CY, Shi YK, Wang MZ, Shi HL, Li MZ, Meng QY, Guo LL, Wang JH, Li XB. The relationship between EGFR mutations and response and prognosis of tyrosine kinase inhibitors in advanced non-small-cell lung cancer. *Chin J Lung Cancer* 2008;11:206-13.
 78. Zhao LD, Li JL, Wang Y, Wang B, Wang HY, Hao XB, Cui CX, Zhang XR, Shi YK. Factors affecting the sensitivity of EGFR-TKI treatment in advanced

- non-small cell lung cancer. *Chin J Oncol* 2011;33:217-21.
79. Bai H, Xiong LW, Han BH. Clinical observation of gefitinib and erlotinib for brain metastase of non-small cell lung cancer. *Chin Clin Oncol* 2015;20:1028-31.
80. Bie L, Li M, Chen B, Lv H, Han L, Zou H, Zhang W, Fan Q, Wang L, Chen X, Luo S. Clinical effect and pharmacoeconomics analysis of EGFR-TKI in the treatment of advanced non-small cell lung cancer. *J Basic Clin Oncol* 2016;29:143-6.
81. Chanprapaph K, Pongcharoen P, Vachiramon V. Cutaneous adverse events of epidermal growth factor receptor inhibitors: A retrospective review of 99 cases. *Indian J Dermatol Venereol Leprol* 2015;81:547.
82. Gao X. Clinical analysis of non-small cell lung adenocarcinoma targeted therapy. *J North Pharm* 2015;12:157.
83. Guan Q. Clinical comparison of erlotinib and gefitinib in the treatment of non - small cell lung cancer with brain metastases. *World Latest Medicine Information* 2015;15:85.
84. He H, Yang ZZ, Li Q, Zhang ZM, Lan BH, Xiao H, Wu Y, Li J. Prognostic analysis of advanced non-small cell lung cancer patients with EGFR mutations in response to first-line treatment with EGFR-TKIs. *J Third Military Med Univ* 2016;38:761-5.
85. Hirano R, Uchino J, Ueno M, Fujita M, Watanabe K. Low-dose Epidermal Growth Factor Receptor (EGFR)-Tyrosine Kinase Inhibition of EGFR Mutation-positive Lung Cancer: Therapeutic Benefits and Associations Between Dosage, Efficacy and Body Surface Area. *Asian Pac J Cancer Prev* 2016;17:785-9.
86. Jackman DM, Yeap BY, Sequist LV, Lindeman N, Holmes AJ, Joshi VA, Bell DW, Huberman MS, Halmos B, Rabin MS, Haber DA, Lynch TJ, Meyerson M, Johnson BE, Jänne PA. Exon 19 deletion mutations of epidermal growth factor receptor are associated with prolonged survival in non-small cell lung cancer patients treated with gefitinib or erlotinib. *Clin Cancer Res* 2006;12:3908-14.
87. Jin Y, Dai LL, Chen XH, Qin BB, Feng J, Shen B. The efficacy of ebrain metastasis. *Oncology Progress* 2016;14:458-60.
88. Kashima J, Okuma Y, Miwa M, Hosomi Y. Survival of patients with brain metastases from non-small cell lung cancer harboring EGFR mutations treated with epidermal growth factor receptor tyrosine kinase inhibitors. *Med Oncol* 2016;33:129.
89. Kuan FC, Li SH, Wang CL, Lin MH, Tsai YH, Yang CT. Analysis of progression-free survival of first-line tyrosine kinase inhibitors in patients with non-small cell lung cancer harboring leu858Arg or exon 19 deletions. *Oncotarget*

2017;8:1343-53.

90. Lee E, Keam B, Kim DW, Kim TM, Lee SH, Chung DH, Heo DS. Erlotinib versus gefitinib for control of leptomeningeal carcinomatosis in non-small-cell lung cancer. *J Thorac Oncol* 2013;8:1069-74.
91. Li YY, Li L, Lv EJ. Comparison of erlotinib and gefitinib in the treatment of non-small cell lung cancer with brain metastases. *Chin J Clin Res* 2015;28:1308-10.
92. Lin JJ, Cardarella S, Lydon CA, Dahlberg SE, Jackman DM, Jänne PA, Johnson BE. Five-Year Survival in EGFR-Mutant Metastatic Lung Adenocarcinoma Treated with EGFR-TKIs. *J Thorac Oncol* 2016;11:556-65.
93. Lin QX, Zhang QT, Zhen RN, Tan YD, Wang ZG. Efficacy of gefitinib and erlotinib in the treatment of EGFR gene sensitive mutations in patients with advanced NSCLC. *Chin J of Oncol Prev and Treat* 2016;8:171-3.
94. Liu LH. Effect and safety comparison of smoking for gefitinib and erlotinib in EGFR gene mutation in treatment of patients with advanced NSCLC. *World Latest Medicine Information* 2015;15:18-9.
95. Margetts J. A regional audit of outcomes of NSCLC patients treated first line with EGFR inhibitors. <http://www.nescn.nhs.uk/wp-content/uploads/2015/02/3-EGFR-audit-for-7-5-12.pdf>. Accessed on February 18, 2017.
96. Otsuka T, Mori M, Yano Y, Uchida J, Nishino K, Kaji R, Hata A, Hattori Y, Urata Y, Kaneda T, Tachihara M, Imamura F, Katakami N, Negoro S, Morita S, Yokota S. Effectiveness of tyrosine kinase inhibitors in Japanese patients with non-small cell lung cancer harboring minor epidermal growth factor receptor mutations: results from a multicenter retrospective study (HANSHIN Oncology Group 0212). *Anticancer Res* 2015;35:3885-91.
97. Park K, Tan EH, O'Byrne K, Zhang L, Boyer M, Mok T, Hirsh V, Yang JC, Lee KH, Lu S, Shi Y, Kim SW, Laskin J, Kim DW, Arvis CD, Kölbeck K, Laurie SA, Tsai CM, Shahidi M, Kim M, Massey D, Zazulina V, Paz-Ares L. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. *Lancet Oncol* 2016;17:577-89.
98. Passaro A, Di Maio M, Del Signore E, Gori B, de Marinis F. management of nonhematologic toxicities associated with different EGFR-TKIs in advanced NSCLC: a comparison analysis. *Clin Lung Cancer* 2014;15:307-12.
99. Qu WF. Clinical effect of erlotinib on non-small cell lung cancer and its impact on immunoglobulin levels and T-lymphocyte subsets. *Practical Journal of Cardiac Cerebral Pneumal and Vascular Disease* 2015;23:73-5.

100. Ruan Y, Jiang J, Guo L, Li Y, Huang H, Shen L, Luan M, Li M, Du H, Ma C, He L, Zhang X, Qin S. Genetic association of curative and adverse reactions to tyrosine kinase inhibitors in Chinese advanced non-small cell lung cancer patients. *Sci Rep* 2016;6:23368.
101. Sato S, Kurishima K, Miyazaki K, Kodama T, Ishikawa H, Kagohashi K, Tamura T, Homma S, Satoh H, Hizawa N. Efficacy of tyrosine kinase inhibitors in non-small-cell lung cancer patients undergoing dose reduction and those with a low body surface area. *Mol Clin Oncol* 2014;2:604-8.
102. Song C, Xu LY, Qiao JJ, Li M, Zhao JB, Sun LM. Efficacy and safety of EGFR-TKIs as first-line treatment in 112 elder patients with advanced non-small cell lung cancer. *J Dalian Med Univ* 2015;37:282-5.
103. Soria JC, Felip E, Cobo M, Lu S, Syrigos K, Lee KH, Göker E, Georgoulas V, Li W, Isla D, Guclu SZ, Morabito A, Min YJ, Ardizzoni A, Gadgeel SM, Wang B, Chand VK, Goss GD; LUX-Lung 8 Investigators. Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial. *Lancet Oncol* 2015;16:897-907.
104. Suh KJ, Keam B, Kim M, Park YS, Kim TM, Jeon YK, Kim DW, Chung DH, Kim YW, Heo DS. Serum neuron-specific enolase levels predict the efficacy of first-line epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in patients with non-small cell lung cancer harboring EGFR mutations. *Clin Lung Cancer* 2016;17:245-52.
105. Togashi Y, Masago K, Masuda S, Mizuno T, Fukudo M, Ikemi Y, Sakamori Y, Nagai H, Kim YH, Katsura T, Mishima M. Cerebrospinal fluid concentration of gefitinib and erlotinib in patients with non-small cell lung cancer. *Cancer Chemother Pharmacol* 2012;70:399-405.
106. Wang J. Clinical observation of first-generation targeted drugs in the treatment of advanced NSCLC. *Modern Med J* 2015;43:1423-4.
107. W84. Weng XL. Clinical effect and pharmacoeconomics of gefitinib and erlotinib in advanced non-small-cell lung cancer. *Chin Med Pharm* 2015;5:100-2.
108. Wu YH, Wu WB, Zhang J, Gu LJ. Observation of clinical efficacy of EGFR-TKI for brain metastases in non-small cell lung cancer with EGFR mutation. *J Clin Pulmonary Med* 2016;21:2168-71.
109. Xie YL, Liang JZ, Su N. Gefitinib versus Erlotinib as first-line treatment for patients with advanced EGFR mutationpositive non-small-cell lung cancer. *J South Med Univ* 2015;35:446-9.
110. Yang JJ, Zhou Q, Yan HH, Zhang XC, Chen HJ, Tu HY, Wang Z, Xu CR, Su J, Huang YS, Wang BC, Jiang BY, Bai XY, Zhong WZ, Yang XN, Wu YL. A

- randomized controlled trial of Erlotinib versus Gefitinib in advanced non-small-cell lung cancer harboring EGFR mutations (CTONG0901). *J Thorac Oncol* 2015;10: abstract 2762.
111. Yang M, Tan EC, Chen Y. Gefitinib, Erlotinib and Chemotherapy as Second-Line Treatment for Patient with Advanced Non-Small Lung Cancer (NSCLC). *Value Health* 2016;19:A885.
112. Ying H, Yang XD, Sun Z, Ning X, Wang Y, Bai C, Chen S, Wang Y. Lifestyle risks exposure and response predictor of gefitinib in patients with non-small cell lung cancer. *Med Oncol* 2014;31:220.
113. Zhang JX, Cai D, Li SY, Zhou CZ, Qin YY, OUYANG M. Clinical comparison of erlotinib and gefitinib in non-small cell lung cancer with brain metastases. *Chin J Cancer Prev Treat* 2015;22:285-8.
114. Zhang YJ, Li HB, Li XD, Liu XC, Han JC. Clinical effect and safety of gefitinib and erlotinib second line treatment of lung adenocarcinoma. *Chin J Clin Pharmacol* 2015;31:899-901.
115. Zhu Y, Du Y, Liu H1, Ma T1, Shen Y, Pan Y. Study of efficacy and safety of pulsatile administration of high-dose gefitinib or erlotinib for advanced non-small cell lung cancer patients with secondary drug resistance: A single center, single arm, phase II clinical trial. *Thorac Cancer* 2016;7:663-9.
116. Baselga J, Rischin D, Ranson M, Calvert H, Raymond E, Kieback DG, Kaye SB, Gianni L, Harris A, Bjork T, Averbuch SD, Feyereislova A, Swaisland H, Rojo F, Albanell J. Phase I safety, pharmacokinetic, and pharmacodynamic trial of ZD1839, a selective oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with five selected solid tumor types. *J Clin Oncol* 2002;20:4292-302.
117. Hidalgo M, Siu LL, Nemunaitis J, Rizzo J, Hammond LA, Takimoto C, Eckhardt SG, Tolcher A, Britten CD, Denis L, Ferrante K, Von Hoff DD, Silberman S, Rowinsky EK. Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. *J Clin Oncol* 2001;19:3267-79.
118. McKillop D, Partridge EA, Kemp JV, Spence MP, Kendrew J, Barnett S, Wood PG, Giles PB, Patterson AB, Bichat F, Guilbaud N, Stephens TC. Tumor penetration of gefitinib (Iressa), an epidermal growth factor receptor tyrosine kinase inhibitor. *Mol Cancer Ther* 2005;4:641-9.
119. Rukazenzov Y, Speake G, Marshall G, Anderton J, Davies BR, Wilkinson RW, Mark Hickinson D, Swaisland A. Epidermal growth factor receptor tyrosine kinase inhibitors: similar but different? *Anticancer Drugs* 2009;20:856-66. .
120. Greenhalgh J, Bagust A, Boland A, Dwan K, Beale S, Hockenhull J, Proudlove C,

Dundar Y, Richardson M, Dickson R, Mullard A, Marshall E; The Liverpool Reviews and Implementation Group (LRiG). Erlotinib and gefitinib for treating non-small cell lung cancer that has progressed following prior chemotherapy (review of NICE technology appraisals 162 and 175).

<http://www.nice.org.uk/guidance/gid-tag347/documents>. Accessed on December 12, 2014.

121. Sato S, Kurishima K, Miyazaki K, , Kodama T, Ishikawa H, Kagohashi K, Tamura T, Homma S, Satoh H, Hizawa N. Efficacy of tyrosine kinase inhibitors in non-small-cell lung cancer patients undergoing dose reduction and those with a low body surface area. *Mol Clin Oncol* 2014;2:604-8.
122. Takashima N, Kimura T, Watanabe N, Umemura T, Katsuno S, Arakawa K, Fukatsu M, Nakamura N, Nishiyama O, Kataoka K, Kondoh Y, Taniguchi H. Prognosis in patients with non-small cell lung cancer who received erlotinib treatment and subsequent dose reduction due to skin rash. *Onkologie* 2012;35:747-52.
123. Yeo WL, Riely GJ, Yeap BY, Lau MW, Warner JL, Bodio K, Huberman MS, Kris MG, Tenen DG, Pao W, Kobayashi S, Costa DB. Erlotinib at a dose of 25 mg daily for non-small cell lung cancers with *EGFR* mutations. *J Thorac Oncol* 2010;5:1048-53.
124. Satoh H, Inoue A, Kobayashi K, Maemondo M, Oizumi S, Isobe H, Gemma A, Saijo Y, Yoshizawa H, Hagiwara K, Nukiwa T. Low-dose gefitinib treatment for patients with advanced non-small cell lung cancer harboring sensitive epidermal growth factor receptor mutations. *J Thorac Oncol* 2011;6:1413-7.
125. Sim SH, Keam B, Kim DW, Kim TM, Lee SH, Chung DH, Heo DS. The gefitinib dose reduction on survival outcomes in epidermal growth factor receptor mutant non-small cell lung cancer. *J Cancer Res Clin Oncol* 2014;140:2135-42.

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.

Table 1. Characteristics of the studies included for analysis

Study	Country	Design	Comparison	Patients	Median age (year)	Female (%)	Non-Smoker (%)	ECOG PS	Stage	Adenocarcinoma (%)	EGFR Mutations (%)	$\geq 2^{\text{nd}}$ -line (%)	Risk of Bias
Arriola 2014*	Spain	RC	G vs E	100/24	72	62	55	≥ 0	--	94	100	0	Other
Bai H 2015	China	RC	G vs E	38/29	<65	69	78	0-4	IV	100	100	100	Low
Bai J 2013	China	RC	G vs E	102/102	53	51	--	--	--	41	--	--	Other
Berros JP 2012*	Spain	RC	G vs E	17/114	58	23	29	0-3	IIIb/IV or recurrent	81	--	100	Other
Bie LY 2016	China	RC	G vs E	43/38	56	53	73	0-3	IV	88	100	0	Other
Caristi N 2011*	Italy	RC	G vs E	20/24	66	34	--	0-2	IIIb/IV	43	--	100	Other
Chanpraph K 2015	Thailand	RC	G vs E	24/75	61	42	--	--	--	--	--	99	Other
Chen H 2012	China	RC	G vs E	51/20	70	52	63	0-2	III/IV	94	69	44	Other
Chen X 2009	China	RC	G vs E	25/24	--	45	51	0-4	IV	65	--	--	Other
Emery IF 2009	USA	RC	G vs E	115/45	67	53	6	1.3-7 (median)	IIIb/IV or recurrent	43	--	>50	Other
Fan WC 2011	Taiwan	RC	G vs E	715/407	<70	45	53	≥ 0	IIIb/IV	77	--	59	Other
Franchina T 2010*	Italy	RC	G vs E	42/40	65	29	27	0-2	IIIb/IV	45	--	100	Other
Gao XP 2015	China	RC	G vs E	30/30	58	47	--	--	--	100	--	--	Other
Grossi F	Italy	RC	G vs E	31/16	--	--	--	--	--	--	--	--	Other

2010*														her
Guan	Q	China	RC	G vs E	22/21	53	49	--	0-1	IV	--	--	--	Ot
2015														her
He	H	China	RC	G vs E	70/44	<60	51	62	0-2	--	95	100	0	Lo
2016														w
Hirano	R	Japan	RC	G vs E	10/16	71	42	46	0-1	III/I	81	--	--	Ot
2016										V or				her
										recu				
										rrrent				
Hong	J	Korea	RC	G vs E	20/17	64	46	54	0-2	IIIb/	70	--	100	Ot
2010										IV				her
Hong	W	China	RC	G vs E	41/75	<60	47	63	0-2	III/I	75	--	100	Lo
2014										V				w
Hotta	K	Japan	RC	G vs E	330/2	67	38	39	0-4	II-I	76	--	>57	Lo
2010					09					V or				w
										recu				
										rrrent				
Jackman		USA	RC	G vs E	23/9	67	63	47	0-3	IIIb/	75	100	50	Ot
DM 2006										IV				her
Jang	SH	Korea	RC	G vs E	24/12	--	50	58	--	--	92	31	--	Ot
2011*														her
Jiang	B	China	RC	G vs E	35/57	67	64	52	0-2	IIIb/	71	--	100	Ot
2013										IV				her
Jin	Y	China	RC	G vs E	50/50	62	57	--	0-2	IV	--	54	--	Lo
2016			T											w
Jung	M	Korea	RC	G vs E	72/51	55	43	48	0-2	IIIb/	59	30	>68	Ot
2011										IV				her
Kappers	I	Nethe	RC	G vs E	64/31	59	47	21	--	III/I	67	--	--	Ot
2010		rlands								V				her
Kashima		Japan	RC	G vs E	11/11	68	86	82	0-4	IV	--	100	0	Lo
J 2016														w
Kim	ST	Korea	RC	G vs E	171/1	58	53	67	≥0	IIIb/	86	--	>14	Lo
2010					71					IV				w
Kim	ST	Korea	RC	G vs E	48/48	59	85	94	1-2	IIIb/	91	35	100	Lo
2012			T							IV				w
										or				
										recu				
										rrrent				

Koo DH 2014	Korea	RC	G vs E	166/5 6	<70	70	74	0-3	IIIb/ IV	87	100	56	Lo w
Kuan F 2016	Taiwan	RC	G vs E vs A	304/6 3/81	<65	61	75	≥0	IIIb/ IV	100	100	0	Lo w
Lee E 2013	Korea	RC	G vs E	11/14	53	72	76	0-4	IV	92	68	52	Ot her
Lee JH 2009*	Korea	RC	G vs E	52/34	64	38	--	--	IIIb/ IV or recu rrent	--	--	--	Ot her
Li J 2012	China	RC	G vs E	26/28	60	74	82	≥0	IIIb/ IV	98	100	0	Ot her
Li J 2014	China	RC	G vs E	53/97	59	44	73	0-3	IIIb/ IV or recu rrent	67	53	100	Ot her
Li Y 2015	China	RC	G vs E	37/36	53	44	38	0-4	IV	93	--	--	Lo w
Lim SH 2014	Korea	RC	G vs E	121/1 21	58	56	64	≥0	IIIb/ IV	98	100	74	Lo w
Lin GN 2014	China	RC	G vs E	24/57	<65	40	--	≥0	IIIb/ IV	59	100	0	Ot her
Lin JJ 2016	USA	RC	G vs E	16/12 1	60	77	96	--	IV or recu rrent	100	100	32	Ot her
Lin QX 2016	China	RC T	G vs E	25/25	64	62	--	0-2	IIIb/ IV	--	100	--	Ot her
Liu L 2015	China	RC	G vs E	28/22	--	--	46	--	IIIb/ IV	--	100	--	Ot her
Locatelli- Sanchez M 2013	France	RC	G vs E	47/37	66	63	60	0-3	IIIb/ IV	96	100	60	Ot her
Lu L 2012	China	RC	G vs E	127/3 7	62	73	85	0-3	III/I V	88	--	70	Ot her
Ma Y	China	RC	G vs E	49/17	62	44	65	0-1	IIIb/	88	100	65	Ot

2013										IV				her
Margetts J 2015*	UK	RC	G vs E	59/9	69	57	76	--	IIIb/IV	88	100	0	Ot	
Morise M 2013*	Japan	RC	G vs E	170/24	65	64	58	0-3	IIIb/IV or recu rrent	97	100	38	Ot	
Otsuka T 2015	Japan	RC	G vs E	35/9	66	50	41	0-3	IIIb/IV	91	100	70	Lo	
Park K 2016	Korea	RC T	G vs A	159/160	63	62	67	0-1	IIIb/IV	99	100	0	Lo	
Park SJ 2012	Korea	PC	G vs E	22/6	58	61	61	0-3	IIIb/IV	--	100	79	Ot	
Passaro A 2014	Italy	PC	G vs E vs A	51/56 /52	--	--	--	--	--	--	78	--	Ot	
Peng L 2010	China	RC	G vs E	210/91	<65	59	56	0-2	IIIb/IV	76	--	55	Ot	
Popat S 2008	UK	RC	G vs E	85/29	66	47	9	0-3	IIIb/IV or recu rrent	45	--	100	Ot	
Qu WF 2015	China	RC	G vs E	50/50	52	38	28	0-3	III/I V	49	--	--	Lo	
Ruan Y 2016	China	RC	G vs E	63/134	60	40	64	--	III/I V	--	--	--	Ot	
Ren S 2014	China	RC	G vs E	60/142	59	45	59	0-3	IV	66	48	91	Ot	
Sato S 2014	Japan	RC	G vs E	213/69	66	56	55	0-4	IIIb/IV or recu rrent	86	34	--	Ot	
Shao YY 2013	Taiwan	RC	G vs E	566/267	62	47	--	--	IIIb/IV or recu	80	--	100	Ot	

										rrent					
Shin HJ	Korea	RC	G vs E	100/8	65	8	9	≥0	III/I	0	--	>94	Ot		
2013				2					V				her		
Song C	China	RC	G vs E	68/15	75	53	60	--	IIIb/	83	--	0	Ot		
2015									IV				her		
Soria JC	Globa	RC	E vs A	397/3	65	16	6	0-2	III/I	0	--	100	Lo		
2015	l	T		98					V				w		
Suh KJ	Korea	RC	G vs E	146/5	65	70	74	0-3	IIIb/	97	100	0	Ot		
2016									IV				her		
Suzumura T	Japan	RC	G vs E	232/8	67	55	46	≥0	IIIb/	95	45	--	Ot		
2012				6					IV				her		
Takeda M	Japan	RC	G vs E	57/11	69	77	77	0-3	IIIb/	99	100	44	Lo		
2014									IV				w		
									or						
									recu						
									rrent						
Togashi Y	Japan	RC	G vs E	85/69	67	51	42	0-4	IIIb/	82	38	>42	Ot		
2011									IV				her		
Togashi Y	Japan	RC	G vs E	9/6	65	59	65	≥0	IV	88	100	71	Ot		
2012													her		
Urata Y	Japan	RC	G vs E	279/2	67	54	50	0-2	IIIb/	100	66	100	Lo		
2016		T		80					IV				w		
									or						
									recu						
									rrent						
Wang DZ	China	RC	G vs E	52/46	>60	47	37	0-1	IIIb/	55	--	0	Ot		
2014									IV				her		
Wang HY	China	RC	G vs E	41/42	≤60	39	28	0-3	IIIb/	72	--	100	Ot		
2012									IV				her		
Wang J	China	RC	G vs E	25/25	>60	--	--	0-3	IIIb/	--	--	--	Ot		
2015									IV				her		
									or						
									recu						
									rrent						
Wang Z	China	RC	G vs E	17/34	61	26	--	--	IV	71	0	--	Ot		
2011*													her		
Weng XL	China	RC	G vs E	38/34	57	39	--	0-3	IIIb/	82	--	100	Lo		
2015									IV				w		

Wu JY	Taiwan	RC	G vs E	440/276	67	50	62	≥ 0	IIIb/IV	85	52	46	Other
Wu WS	Taiwan	RC	G vs E	124/100	--	52	28	0-4	IIIb/IV	100	65	67	Other
Wu X	China	RC	G vs E	24/20	55	52	78	≥ 0	IIIb/IV	84	--	89	Other
Wu YH	China	RC	G vs E	34/39	≤ 65	58	68	0-4	IIIb/IV	100	100	92	Low
Xie YL	China	RC	G vs E	27/23	63	60	--	0-2	IIIb/IV	--	100	0	Other
Yan Y	China	RC	G vs E	28/20	87	2	--	--	--	--	--	--	Other
Yang JJ	China	RC	G vs E	128/128	--	--	--	0-2	IIIb/IV	--	100	36	Low
Yang M	Taiwan	RC	G vs E	1570/1646	--	--	--	--	IIIb/IV	--	--	100	Other
Ying H	China	RC	G vs E	198/75	61	44	55	0-2	III/I V	84	52	82	Other
Yoshida T	Japan	RC	G vs E	107/35	65	59	56	0-3	III/I V or recurrent	84	49	>28	Low
Zhang CW	China	RC	G vs E	71/54	62	42	--	--	III/I V	--	--	--	Other
Zhang J	China	RC	G vs E	40/40	50	43	--	1-2	IIIb/IV	61	--	100	Other
Zhang JX	China	RC	G vs E	79/113	65	59	67	0-3	IV	100	100	0	Low
Zhang X	China	RC	G vs E	34/25	57	47	56	0-3	IIIb/IV	75	37	78	Other
Zhang X	China	RC	G vs E	50/50	59	51	--	0-3	IIIb/IV	83	--	100	Other
Zhang YJ	China	RC	G vs E	41/45	60	52	--	0-2	IIIb/IV or recurrent	100	--	100	Low
Zhao L	China	RC	G vs E	135/3	57	58	75	--	IIIb/IV	87	--	93	Other

2011					1					IV				her
Zheng	L	China	RC	G vs E	48/75	≤60	50	64	≥1	IIIb/	79	--	100	Lo
2013										IV				w
Zhu	YZ	China	RC	G vs E	29/13	<65	50	50	0-3	IV	100	100	62	Ot
2016														her

Abbreviations: ECOG PS, the Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor gene; RC, retrospective cohort; G, gefitinib; E, erlotinib; RCT, randomized controlled trial; A, afatinib; PC, prospective cohort. -- Not available/applicable. * Only abstracts are available.





