# Indirect comparison of the efficacy and safety of gefitinib and cetuximab-based therapy in patients with advanced non-small-cell lung cancer

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**Abstract.** The aim of this study was to systematically evaluate the efficacy and safety of gefitinib and cetuximab-based therapies in patients with advanced non-small-cell lung cancer (NSCLC). The studies to be used for the comparisons were selected from the available literature on gefitinib and cetuximab-based therapies compared to conventional chemotherapy in patients with advanced NSCLC. The meta-analysis was performed with RevMan 5.0 software and the Bucher approach was applied to conduct the indirect comparisons. A total of 4 studies, including 935 patients, on gefitinib therapy vs. conventional chemotherapy and 4 studies, including 1,015 patients, on cetuximab-based therapy vs. conventional chemotherapy, were used for indirect comparisons. As regards efficacy, the risk ratio (RR) of objective response rate and 1-year survival rate between gefitinib and cetuximab-based therapies in patients with advanced NSCLC were 0.99 [95% confidence interval (CI): 0.75-1.32; P=0.9584] and 0.85 (95% CI: 0.71-1.01; P=0.0696), respectively, and the mean difference of progression-free survival and overall survival (OS) were -0.15 (95% CI: -0.90 to 0.60; P=0.6946) and -1.84 (95% CI: -3.53 to -0.15; P=0.0331), respectively. As regards safety, the RR of grade 3/4 adverse events (AEs) was 0.29 (95% CI: 0.19-0.44; P=0.0001). The results demonstrated that cetuximab-based therapy was superior to gefitinib therapy in terms of OS and inferior to gefitinib therapy in terms of AEs, whereas there were no significant differences in terms of efficacy and safety between the two therapies on other endpoints adopted for advanced NSCLC. However, further well-designed randomized controlled trials and continuous studies are required to confirm our findings.

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## Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, with non-small-cell lung cancer (NSCLC) accounting for 80-85% of lung cancer cases (1). Chemotherapy combined with radiotherapy are traditionally used for the treatment of NSCLC. Over the last few years, targeted therapy has been gradually applied for the treatment of NSCLC and has been proven to be effective to a certain extent (2). Among the targeted drugs used for NSCLC, those acting on the epidermal growth factor receptor (EGFR) are attracting increasing attention, such as the tyrosine kinase inhibitor (TKI) gefitinib (Iressa; AstraZeneca, London, UK) and the monoclonal antibody cetuximab (Erbitux; Merck, Darmstadt, Germany). These two dtugs have similar mechanisms of action against NSCLC. In clinical practice, gefitinib may be administered orally alone, while cetuximab is administered intravenously in combination with chemotherapy. Gefitinib and cetuximab-based therapies have been proven to be effective for advanced NSCLC to a certain extent (3,4); however, there is currently no systematic review directly based on these two therapies and the differences between them in terms of efficacy and safety have not been determined.

Indirect comparisons are undertaken to address such issues. Using the same intervention as a bridge, the two therapies are compared with the intervention through a direct meta-analysis and, on the basis of the results, indirect comparisons are subsequently conducted. With conventional chemotherapy as the intervention, we performed a systematic evaluation for gefitinib and cetuximab-based therapies based on the most updated results of these studies and weighed the two therapies indirectly against the clinical benefits and toxicities, with the aim of providing references for clinical decisions for patients with advanced NSCLC.

## Materials and methods

*Literature search.* Several engines, including Medline, Embase, Elsevier, the Cochrane Library Register of Controlled Trials and the Science Citation Index, were searched for randomized controlled trials (RCTs) using the keywords 'random/trial', 'gefitinib', 'cetuximab', 'chemotherapy' and

'non-small-cell lung cancer/NSCLC'. The deadline for trial publication eligible for the analysis was April 30, 2013.

*Study selection.* The relevant studies were carefully selected using the following criteria: i) RCTs published in English; ii) patients with advanced (stage IIIB/IV) NSCLC and no obvious abnormalities of other organs; iii) comparison of gefitinib therapy vs. conventional chemotherapy (one or more combinations of cisplatin, carboplatin, docetaxel, gemcitabine, pemetrexed and vinorelbine) and cetuximab-based therapy vs. conventional chemotherapy; and iv) all or part of the data on objective response rate (ORR), 1-year survival, progression-free survival (PFS), overall survival (OS) and adverse events (AEs) were provided. Studies were excluded by any of the following criteria: i) objective unrelated to this study; ii) phase I clinical trial; iii) no controlled clinical trials; iv) no or insufficient mature data; and v) reviews, comments and case reports.

*Data extraction and conversion.* According to the recommended guidelines of the Cochrane Handbook for Systematic Reviews (5), the extraction form, created with Microsoft Excel, included author, year of publication, interventions, sample size, dose, clinical efficacy and AEs.

As for the data that could not be adopted directly, appropriate transforming was required. For qualitative data, number of events = effective sample size x event rate. For quantitative data, the conversion methods were as follows: When the confidence interval (CI) was provided within a group, i) if the sample size was $\geq$100, under the 95% CI, standard deviation (SD) = $\sqrt{N}$ x (upper limit of CI - lower limit of CI)/3.92); ii) if the sample size was $\leq$60, 3.92 was replaced with 2 x t value; iii) if the sample size was 60-100, either method was applicable. When CI was provided between the groups, standard error (SE) was estimated first with the method described above, where N = $n_1 + n_2$, and then SD was calculated with the formula SD = SE/ $\sqrt{1/n_1 + 1/n_2}$ (6).

*Quality assessment.* An open assessment of the trials was performed with the Jadad scale (7). The Jadad score ranged between 0 and 5 points with the major indicators of attrition and exclusions, randomization method and blinding. Studies scoring $\geq$3 were considered to be of high quality (8).

*Statistical methods.* Treatment A and C were compared with the intervention B and the direct evidence of AB and CB were obtained to conduct the indirect comparisons of AC (9). A meta-analysis was used to obtain the pooled AB and pooled CB using RevMan 5.0 software (The Cochrane Collaboration, Oxford, UK). The statistics were risk ratio (RR) for dichotomous variables and mean difference (MD) for numerical variables, together with the 95% CI. If the test for heterogeneity indicated good homogeneity (P>0.1 or $I^2 \leq$50%) between trials, the fixed-effects model was applied with the Mantel-Haeszel method (10); in the opposite case (P$\leq$0.1 or $I^2$>50%), the random-effects model [DerSimonian and Laird method (11)] was used.

The Bucher approach was applied for indirect comparisons. A comparison of A and C was conducted through the difference between pooled AB and pooled CB, namely $d_{AC} = d_{AB} - d_{CB}$.

The pooled effect size was measured by lnRR for dichotomous variables and MD for numerical variables. The variance of $d_{AC}$ equaled the sum of the variance of AB and CB, namely $Var(d_{AC}) = Var(d_{AB}) + Var(d_{CB})$. For $Var(d_{AB})$ and $Var(d_{CB})$, the computational formula was $Var(d) = [(upper limit of CI - lower limit of CI)/3.92]^2$. For dichotomous variables, 95% CI of $d_{AC} = \exp[d_{AC} \pm 1.96 \sqrt{Var(d_{AC})}]$ and for numerical variables, 95% CI of $d_{AC} = d_{AC} \pm 1.96 \sqrt{Var(d_{AC})}$. The hypothesis test was set for the results, as follows: $H_0$, $d_{AC}=0$; $H_1$, $d_{AC}\neq0$; and $Z_{AC}=|d_{AC}|/\sqrt{Var(d_{AC})}$, where $Z_{AC}$ exhibited a standard normal distribution as a test statistic. The null hypothesis was rejected if P<0.05 ($Z_{AC}$>1.96), i.e., if the effects between A and C exhibited a statistically significant difference (12).

## Results

*Description of selected studies.* A total of 104 articles were retrieved during the primary search, of which 8 studies met the predetermined inclusion criteria. A total of 4 studies (13-16), including 935 patients who were randomized to receive either gefitinib therapy or conventional chemotherapy, and another 4 studies (17-20), including 1,015 patients who received either cetuximab-based therapy or conventional chemotherapy, were included in the study. The main characteristics of the 8 studies are summarized in Table I.

All 8 studies were RCTs, of which 7 studies applied the proper methods of randomization. Attrition and exclusions were illustrated in detail, while double-blind methods were not mentioned. The included studies were considered to be of high quality, scoring 3 on the Jadad scale, except one study (13). The quality assessment of the studies is presented in Table II.

*Statistical analysis of efficacy and safety*
*ORR.* A total of 4 studies (13-16) compared gefitinib therapy vs. conventional chemotherapy and the remaining 4 studies (17-20) compared cetuximab-based therapy vs. conventional chemotherapy in terms of ORR. The pooled analysis of ORR using the fixed-effects model is presented in Fig. 1A and B. The RR for gefitinib therapy vs. conventional chemotherapy and cetuximab-based therapy vs. conventional chemotherapy was 1.31 (95% CI: 1.02-1.68) and 1.32 (95% CI: 1.15-1.52), respectively. Indirect comparisons between gefitinib and cetuximab-based therapies revealed no significant difference in ORR (RR=0.99; 95% CI: 0.75-1.32; P=0.9584; Table III).

*Survival rate.* A total of 2 studies (13,16) compared gefitinib therapy vs. conventional chemotherapy and 3 studies (17-19) compared cetuximab-based therapy vs. conventional chemotherapy in terms of 1-year survival rate. The pooled analysis of 1-year survival rate using the fixed-effects model is presented in Fig. 1C and D. The RR for gefitinib therapy vs. conventional chemotherapy and cetuximab-based therapy vs. conventional chemotherapy was 0.93 (95% CI: 0.81-1.06) and 1.10 (95% CI: 0.98-1.25), respectively. Indirect comparisons between gefitinib and cetuximab-based therapies revealed no significant difference in 1-year survival rate (RR=0.85; 95% CI: 0.71-1.01; P=0.0696; Table III).

*PFS.* A total of 4 studies (13-16) compared gefitinib therapy vs. conventional chemotherapy and the remaining 4 studies (17-20) compared cetuximab-based therapy vs. conven-

Table I. Characteristics of the 8 studies included in the meta-analysis.

| Study (year) | Group | Intervention | Treatment schedule | Phase | Cases | End point | (Refs.) |
|---|---|---|---|---|---|---|---|
| Kim et al | Treatment | Gefitinib | 250 mg/day p.o. | III | 733 | a-e | (13) |
| (2008) | Control | Doc | 75 mg/m$^2$ i.v. | III | 729 | a-e | |
| Mitsudomi | Treatment | Gefitinib | 250 mg/day p.o. | III | 88 | a,c,e | (14) |
| et al (2010) | Control | Cis + Doc | 80+60 mg/m$^2$ i.v. | III | 89 | a,c,e | |
| Morère et al | Treatment | Gefitinib | 250 mg/day p.o. | II | 43 | a,c-e | (15) |
| (2010) | Control | Gem | 1,250 mg/m$^2$ i.v. | II | 42 | a,c-e | |
| | Control | Doc | 75 mg/m$^2$ i.v. | II | 42 | a,c-e | |
| Ahn et al | Treatment | Gefitinib | 250 mg/day p.o. | II | 40 | a-c,e | (16) |
| (2012) | Control | Pem + Cis | 500+75 mg/m$^2$ i.v. | II | 33 | a-c,e | |
| Rosell et al | Treatment | Cetuximab + Cis + Vin | 400+80+25 mg/m$^2$ i.v. | II | 43 | a-e | (17) |
| (2008) | Control | Cis + Vin | 80+25 mg/m$^2$ i.v. | II | 43 | a-e | |
| Butts et al | Treatment | Cetuximab + Gem + Cis | 400+1,250+75 mg/m$^2$ i.v. | II | 65 | a-e | (18) |
| (2007) | Control | Gem + Cis | 1,250+75 mg/m$^2$ i.v. | II | 66 | a-e | |
| Pirker et al | Treatment | Cetuximab + Cis + Vin | 400+80+25 mg/m$^2$ i.v. | III | 557 | a-e | (19) |
| (2009) | Control | Cis + Vin | 80+25 mg/m$^2$ i.v. | III | 568 | a-e | |
| Lynch et al | Treatment | Cetuximab + Doc + Carbo | 400+75 mg/m$^2$ + curve ≤6 i.v. | III | 338 | a,c-e | (20) |
| (2010) | Control | Doc + Carbo | 75 mg/m$^2$ + curve ≤6 i.v. | III | 338 | a,c-e | |

[a]Objective response rate; [b]1-year survival rate; [c]progression-free survival; [d]overall survival; [e]grade 3/4 adverse events. Doc, docetaxel; p.o., *per os*; i.v., intravenously; cis, cisplatin; gem, gemcitabine; pem, pemetrexed; vin, vinorelbine; carbo, carboplatin.

Table II. Quality assessment of the 8 included studies by the Jadad scale.

| Author (year) | Randomization | Blinding | Attrition and exclusions | Jadad score | (Refs.) |
|---|---|---|---|---|---|
| Kim et al (2008) | 1 | 0 | 1 | 2 | (13) |
| Mitsudomi et al (2010) | 2 | 0 | 1 | 3 | (14) |
| Morère et al (2010) | 2 | 0 | 1 | 3 | (15) |
| Ahn et al (2012) | 2 | 0 | 1 | 3 | (16) |
| Rosell et al (2008) | 2 | 0 | 1 | 3 | (17) |
| Butts et al (2007) | 2 | 0 | 1 | 3 | (18) |
| Pirker et al (2009) | 2 | 0 | 1 | 3 | (19) |
| Lynch et al (2010) | 2 | 0 | 1 | 3 | (20) |

tional chemotherapy in terms of PFS. The pooled analysis of PFS using the fixed-effects model is presented in Fig. 2A and B. The MD for gefitinib therapy vs. conventional chemotherapy and cetuximab-based therapy vs. conventional chemotherapy was 0.06 (95% CI: -0.56 to 0.68) and 0.21 (95% CI: -0.21 to 0.63). Indirect comparisons between gefitinib and cetuximab-based therapies revealed no significant difference in PFS (MD=-0.15; 95% CI: -0.90 to 0.60; P=0.6946; Table III).

*OS*. A total of 2 studies (13,15) compared gefitinib therapy vs. conventional chemotherapy and 4 studies (17-20) compared cetuximab-based therapy vs. conventional chemotherapy in terms of OS. The pooled analysis of OS using the fixed-effects model is presented in Fig. 2C and D. The MD for gefitinib therapy vs. conventional chemotherapy and cetuximab-based therapy vs. conventional chemotherapy was -0.51 (95% CI: -1.76 to 0.75) and 1.33 (95% CI: 0.19-2.46). Indirect comparisons between gefitinib and cetuximab-based therapies

revealed that the latter exhibited a significant advantage over the former in terms of OS (MD=-1.84; 95% CI: -3.53 to -0.15; P=0.0331; Table III).

*Grade 3/4 AEs*. A total of 4 studies (13-16) compared gefitinib therapy vs. conventional chemotherapy and the remaining 4 studies (17-20) compared cetuximab-based therapy vs. conventional chemotherapy in terms of 3/4 AEs. The pooled analysis of 3/4 AEs using the fixed-effects model is shown in Fig. 3A, while the results using the random-effects model are shown in Fig. 3B. The RR for gefitinib therapy vs. conventional chemotherapy and cetuximab-based therapy vs. conventional chemotherapy was 0.67 (95% CI: 0.58-0.78) and 2.31 (95% CI: 1.55-3.44). Indirect comparisons between gefitinib and cetuximab-based therapies revealed that the former exhibited a significant advantage over the latter in terms of 3/4 AEs (RR=0.29; 95% CI: 0.19-0.44; P=0.0001; Table III).
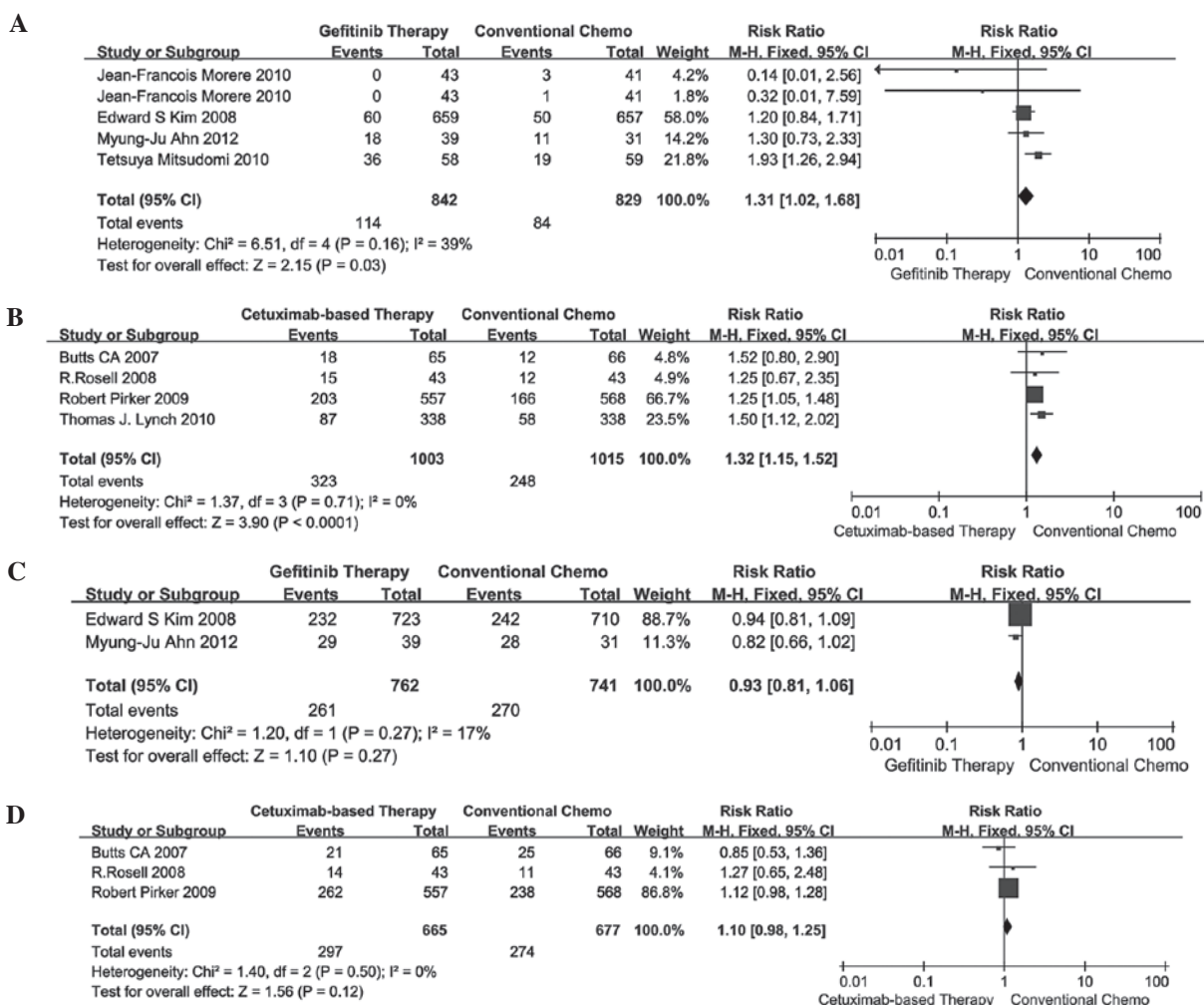
Figure 1. Meta-analysis of the risk ratio (RR) for (A and C) gefitinib therapy vs. conventional chemotherapy and (B and D) cetuximab-based therapy vs. conventional chemotherapy in terms of objective response rate (ORR) and 1-year survival rate, respectively. (A) Summary data and RR of gefitinib therapy vs. conventional chemotherapy in terms of ORR. (B) Summary data and RR of cetuximab-based therapy vs. conventional chemotherapy in terms of ORR. (C) Summary data and RR of gefitinib therapy vs. conventional chemotherapy in terms of 1-year survival rate. (D) Summary data and RR of cetuximab-based therapy vs. conventional chemotherapy in terms of 1-year survival rate. Chemo, chemotherapy; CI, confidence interval.

Table III. Results of indirect comparisons between gefitinib and cetuximab-based therapies.

| Indicator | RR/MD | 95% CI | P-value |
|---|---|---|---|
| Objective response rate | 0.99 | 0.75 to 1.32 | 0.9584 |
| One-year survival rate | 0.85 | 0.71 to 1.01 | 0.0696 |
| Progression-free survival | -0.15 | -0.90 to 0.60 | 0.6946 |
| Overall survival | -1.84 | -3.53 to -0.15 | 0.0331 |
| Grade 3/4 adverse events | 0.29 | 0.19 to 0.44 | 0.0001 |

RR, risk ratio; MD, mean difference; CI, confidence interval.

## Discussion

As demonstrated by the indirect comparisons, cetuximab-based therapy was found to be superior to TKIs, such as gefitinib, regarding efficacy. A recently published meta-analysis recommended that gefitinib therapy not be used for the management of patients with advanced NSCLC in the first-line setting (21).

Other studies also reported that the activity of EGFR-TKIs may be restricted to a subset of tumors with specific molecular characteristics, highlighting the need for appropriate patient selection (22,23). Furthermore, certain studies proved the OS benefit of cetuximab-based therapy and suggested that advanced NSCLC patients with high EGFR gene expression may benefit more from cetuximab-based therapy (24).

As regards safety, gefitinib appears to be superior to cetuximab-based therapy in terms of 3/4 AEs. Despite the limitations of the safety indicator itself, one plausible explanation for this discrepancy is the difference in the administration methods, i.e., the oral administration of gefitinib is considered to be safer compared to the intravenous administration of cetuximab. Another possible reason is that gefitinib is more uncomplicated and controllable compared to cetuximab-based therapy containing several chemotherapeutic drugs, such as cisplatin, docetaxel and gemcitabine, which is associated with more risks.

The indirect comparison adopted in our study is controversial. Certain investigators have suggested that indirect comparison compromises the randomness of original RCTs and inevitably induces bias (25). In the study of Bucher *et al* (26),
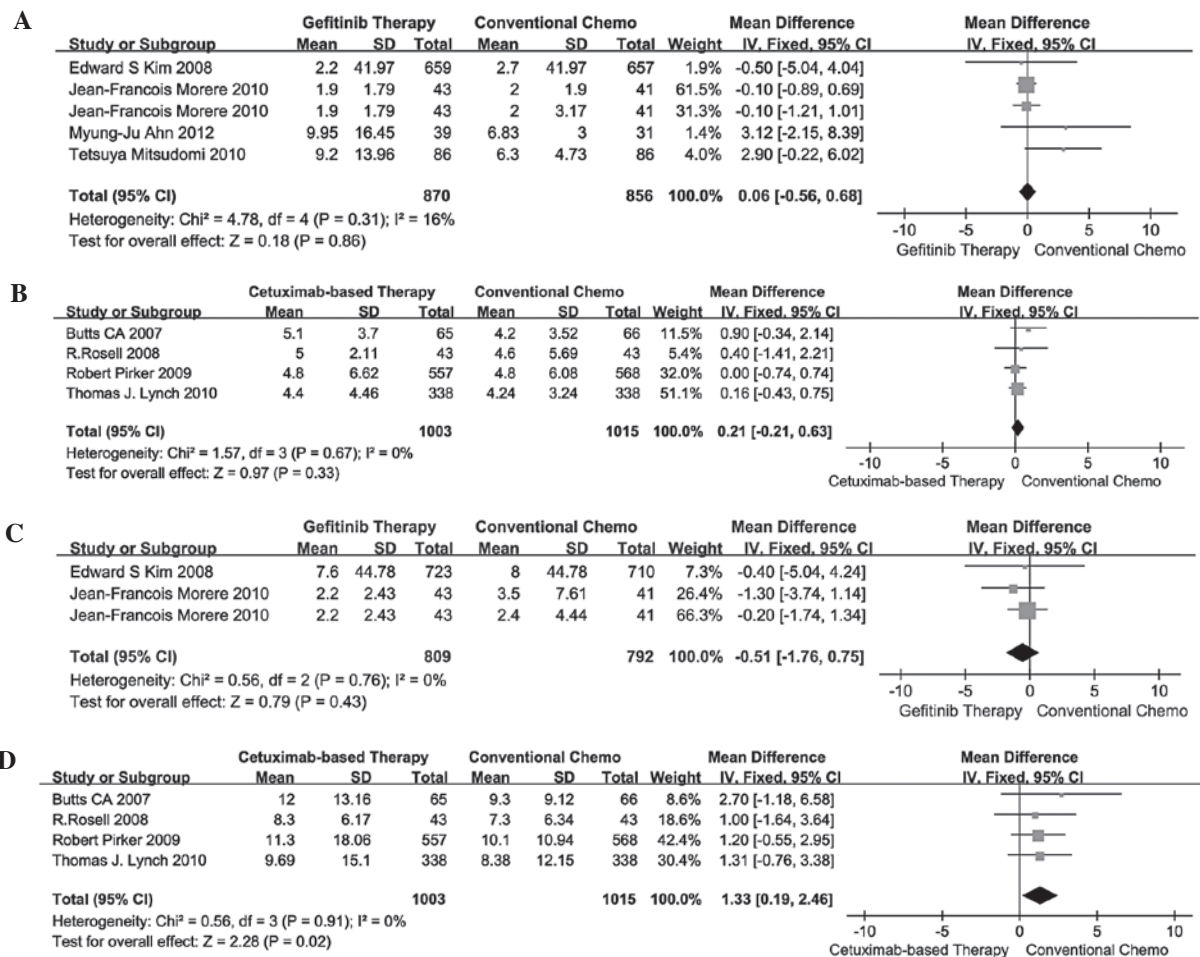
Figure 2. Meta-analysis of the mean difference (MD) for (A and C) gefitinib therapy vs. conventional chemotherapy and (B and D) cetuximab-based therapy vs. conventional chemotherapy in terms of progression-free survival (PFS) and overall survival (OS), respectively. (A) Summary data and MD of gefitinib therapy vs. conventional chemotherapy in terms of PFS. (B) Summary data and MD of cetuximab-based therapy vs. conventional chemotherapy in terms of PFS. (C) Summary data and MD of gefitinib therapy vs. conventional chemotherapy in terms of OS. (D) Summary data and MD of cetuximab-based therapy vs. conventional chemotherapy in terms of OS. Chemo, chemotherapy; SD, standard deviation; CI, confidence interval.
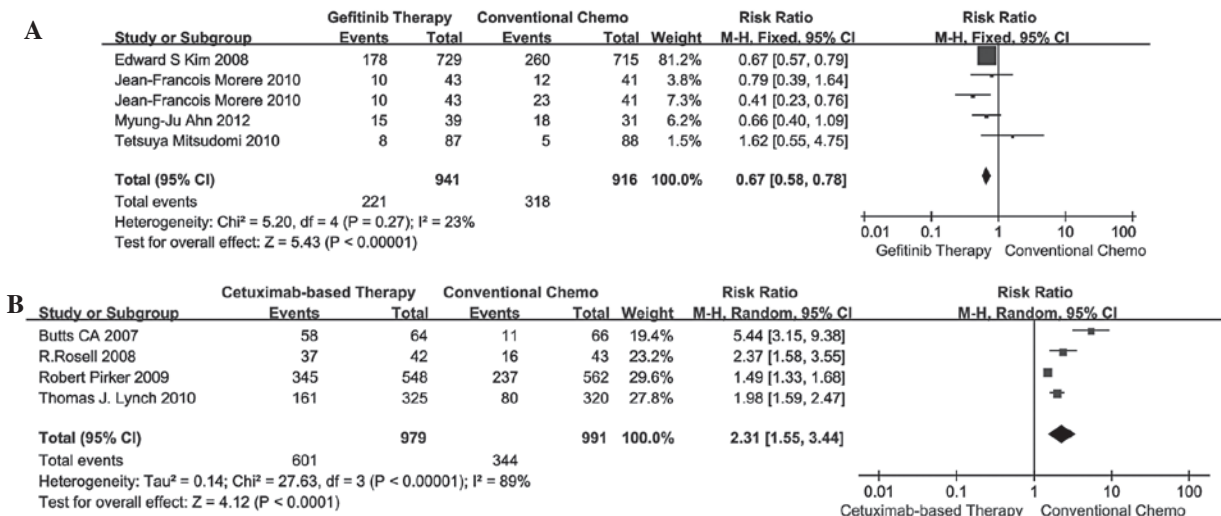


Figure 3. Meta-analysis of the risk ratio (RR) for (A) gefitinib therapy vs. conventional chemotherapy and (B) cetuximab-based therapy vs. conventional chemotherapy in terms of grade 3/4 adverse events (3/4 AEs). (A) Summary data and RR of gefitinib therapy vs. conventional chemotherapy in terms of 3/4 AEs. (B) Summary data and RR of cetuximab-based therapy vs. conventional chemotherapy in terms of 3/4 AEs. Chemo, chemotherapy; CI, confidence interval.

indirect comparison was associated with significantly more bias compared to direct comparisons, while Song *et al* (27) reached

the opposite conclusion with 3 case studies. Another study by Song *et al* (28) further confirmed the reliability of the results of

indirect comparison. Indirect comparison remains a reasonable option in the absence of direct comparison of two drugs and a number of medical journals, such as JAMA, Lancet and BMJ have accepted the findings of indirect comparison (12).

However, our results must be interpreted with caution, as there were certain limitations to our study. Although each of the 8 included studies was considered to be of high quality, the total number of articles was insufficient to draw a credible conclusion. The sample size of included trials was also insufficient for a funnel plot to detect publication bias. Due to the lack or inconformity of patient selection regarding details such as gender, age, smoking history and race, subgroup analyses were not feasible. The analyses also revealed some heterogeneity within the study results, such as safety data of cetuximab-based therapy. One must also consider the limitation on methodology of indirect comparisons and the lack of unpublished or ongoing RCTs.

Despite all the limitations, our results may contribute to a better understanding of gefitinib and cetuximab-based therapies in patients with advanced NSCLC. Based on the present meta-analysis and indirect comparisons, we concluded that cetuximab-based therapy may be associated with a more significant improvement in OS compared to gefitinib therapy, while gefitinib was superior in terms of safety, with a lower incidence of grade 3/4 AEs. There were no significant differences between gefitinib and cetuximab-based therapies in terms of ORR, 1-year survival rate and PFS in patients with advanced NSCLC. Further studies are required to confirm our findings and evaluate the cost-effectiveness of the two therapies, in order to provide a better reference for clinical practice.

## Acknowledgements

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