

Original Article

Erlotinib versus chemotherapy (docetaxel/pemetrexed) as second-line therapy in advanced non-small cell lung cancer: a meta-analysis

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Abstract: Background: The meta-analysis aimed to compare the efficacy and safety of erlotinib versus (vs.) chemotherapy (docetaxel/pemetrexed) as second-line therapy in advanced non-small cell lung cancer (NSCLC). Methods: Literature search was completed in databases of PubMed, Embase and Ovid-Medline up to October 20, 2015; and randomized controlled trials (RCTs) met with predefined criteria were selected. Outcomes such as progression-free survival (PFS), overall survival (OS), objective response rate (ORR) and grade 3-4 toxicity between the erlotinib and chemotherapy were evaluated. Risk ratio (RR) and hazard ratio (HR) with their corresponding 95% confidence intervals (CI) were used to calculate the pooled results. Rev.Man5.2 software was utilized for the meta-analysis. Results: A total of 7 articles (including 900 patients receiving erlotinib and 919 patients receiving pemetrexed/docetaxel) were included in this meta-analysis. There was no significant difference between erlotinib and pemetrexed/docetaxel on PFS and OS, as well as ORR. Moreover, the total RR of the rash, anemia, neutropenia and alopecia were 15.74 (95% CI: 4.94-50.19, $P < 0.001$), 0.34 (95% CI: 0.17-0.66, $P = 0.002$), 0.02 (95% CI: 0.01-0.06, $P < 0.001$) and 0.05 (95% CI: 0.01-0.40, $P = 0.004$), respectively. Conclusions: There was no significant difference of the efficacy and safety between erlotinib vs. chemotherapy as the second-line therapy in advanced NSCLC. However, erlotinib might decrease the risk of anemia, neutropenia and alopecia, and increase the risk of rash, compared with the chemotherapy.

Keywords: Advanced non-small cell lung cancer, second-line therapy, erlotinib, docetaxel/pemetrexed, meta-analysis

Introduction

Lung cancer is one of the most common cancers in the world, and it approximately accounts for 18% of total cancer deaths globally [1]. In 2012, nearly 1,590,000 persons are reported to die from the disease worldwide [2]. Mortality rate of lung cancer is different between male and female. It varies from 0.7 to 120.0 per 100,000 persons among differently aged women [3], and is predicted to be 36 among men [4]. Although incidence of lung cancer has decreased in the past decade, 1,054,393 individuals (569,366 men and 485,027 women) have suffered from invasive lung cancer in the USA [5]. Reportedly, the 5-year survive rate of newly diagnosed lung cancer cases is approximately 15% [6]. Non-small-cell lung cancer (NSCLC) is any type of epithelial lung cancer

other than small cell lung carcinoma, accounting for about 85% of lung cancers, and most patients are diagnosed at an advanced stage [7].

Although NSCLC patients have received standard first-line chemotherapy, most of them would progress ultimately and need subsequent therapy [7]. Application of anticancer agents in these situations is deemed as "second-line therapy". Currently, the established agents in the second-line setting for advanced NSCLC treatment include two cytotoxic agents (docetaxel and pemetrexed) and two epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) (erlotinib and gefitinib) [8]. TKIs can cause high response rates among individuals with oncogenic kinase-driven malignancies, such as EGFR-mutated NSCLC [9].

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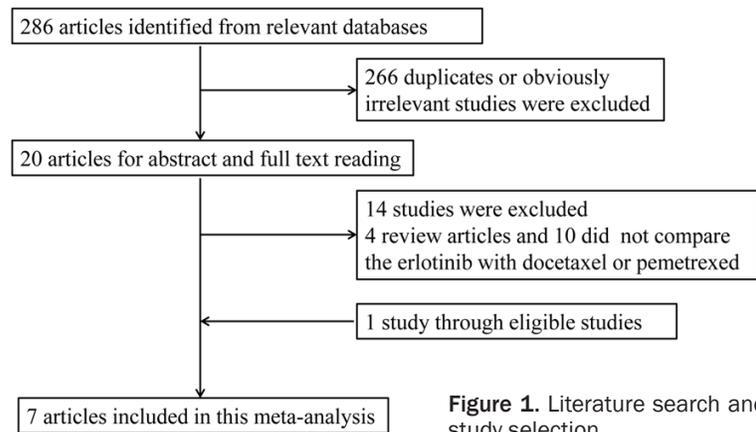


Figure 1. Literature search and study selection.

After the application of TKIs, treatment response of this chemo-resistant malignancy is approximately 80%, and for the 20% individuals with poor responses, the possible reason is that a deletion of polymorphism in *BIM* gene may affect the TKI sensitivity [9].

The EGFR signaling pathway is crucial for regulating tumorigenesis and cell survival, and *EGFR* gene may be overexpressed in NSCLC development [10, 11]. Activation of EGFR gene mutations that encode the tyrosine kinase domain is highly responsive to EGFR-TKIs [12, 13]. A previous meta-analysis indicated that progression-free survival (PFS) and response rates were improved in patients with EGFR mutation who receive EGFR-TKIs, compared with chemotherapy [14]. Lee and co-workers also suggest that EGFR-TKIs therapy can delay disease progression in NSCLC patients with EGFR mutation [15]. However, most NSCLC patients have wild-type EGFR. Indeed, the overall EGFR mutation rate is only 16.7% in unselected patients [16], and about 10% of Western patients and almost 50% of Asian patients are found with the activating mutations [17]. Therefore, it remains uncertain whether EGFR-TKIs would still be of benefit in EGFR wild-type NSCLC patients.

A study demonstrates erlotinib provides no significant benefit in EGFR wild-type patients [18], while other studies indicate that EGFR-TKIs are inferior to chemotherapy in the second-line setting in EGFR wild-type NSCLC [19-21]. However, in Zhao's meta-analysis, chemotherapy significantly improves PFS, compared with EGFR-TKIs, and is considered as a second-line treatment in advanced NSCLC with

wild-type EGFR [22]. In addition, a recent meta-analysis indicates that administration of erlotinib is remarkably related to an increased risk of all-grade diarrhea, stomatitis and high-grade diarrhea, for advanced NSCLC treatment [23]. Therefore, the selection of EGFR-TKIs or chemotherapy in the second-line treatment for the NSCLC is still inconsistent.

In the present work, we conducted a meta-analysis of re-

cently published randomized controlled trials (RCTs) to compare the efficacy and safety between EGFR-TKI, erlotinib, and docetaxel/pemetrexed for the management of advanced NSCLC patients, aiming to find the optimal second-line therapy for NSCLC.

Materials and methods

Search strategy

A systematic literature search was conducted in databases such as PubMed, Embase and Ovid-Medline up to October 20, 2015, to identify relevant articles published in English. The following keywords were used for the literature search: “non-small-cell lung cancer” OR “NSCLC” AND “erlotinib” AND “pemetrexed” OR “docetaxel” AND “randomized controlled trial” OR “RCT”. Meanwhile, manual bibliographic search was further performed for additional studies, and the included articles of previous meta-analyses were also reviewed.

Study selection

Studies included in the present meta-analysis should meet the following criteria: (1) the study was a randomized controlled trial (RCT); (2) the patient was diagnosed with advanced NSCLC, and defined as inoperable locally advanced (stage IIIB) or metastatic or recurrent disease (stage IV); (3) the experimental group was NSCLC patients received erlotinib administration and the control group was those received docetaxel/pemetrexed administration; and (4) the clinical outcomes were mentioned such as PFS, overall survival (OS), objective response rate (ORR) and toxicity (grade 3-4 toxicity). On

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Table 1. Characteristics of studies included in the meta-analysis

Study	Study location	Study data	Line of treatment	Stage	Diagnosis	Treatment	N	Median age (years)	Males (%)	Smoking status	EGFR mutation analysis	Histology (squamous)	EGFR WT patients	Follow-up Median month
Lee 2013	33 study centres in 8 countries (Korea, et al)	2007.12-2010.07	Second	IIIA, IIIB, IV	Histological or cytological	Erlotinib	82	53.9	34.1	Never smokers	Real-time PCR method	0	EGFR unselected	18.0
						Pemetrexed	80	55.9	43.8	Never smokers		0	EGFR unselected	18.0
Karampeazis 2013	9 centers	2006.01-2010.04	Second or third	IIIB, IV	NA	Erlotinib	166	65.0	81.3	74.7% active/ex-smokers	Bidirectional Automatic sequencing	39	EGFR unselected	29.0
						Pemetrexed	166	66.0	83.1	77.1% active/ex-smokers		36	EGFR unselected	27.3
Li 2014	China	2008.12-2012.05	Second	IIIB, IV, Recurrent	Histological	Erlotinib	61	54.3	65.6	75.4% current and former smokers	ARMS	NA	61	14.7
						Pemetrexed	62	55.1	62.9	72.6% current and former smokers		NA	62	14.7
Kawaguchi 2014	Japan	2009.08-2012.07	Second or third	IIIB or IV	Pathologically or histologically	Erlotinib	150	68.0	72.0	74.0% ever smokers	Highly sensitive PCR-based method	29	109	8.9
						Docetaxel	151	67.0	70.9	75.8% ever smoker		32	90	8.9
Garassino 2013	Italy	2007.10-2012.03	Second	NA	NA	Erlotinib	109	66.0	71.0	83.0% current and former smokers	Sanger sequencing + RFLP	31	109	33.0
						Docetaxel	110	67.0	73.0	73.0% current and former smokers		23	110	33.0
Gregorc 2014	Italy	2008.02-2012.04	Second	IIIB or IV	Histological or cytological	Erlotinib	134	66	74	84% current and former smokers	NA	31	79	32.4
						Pemetrexed + Docetaxel	74+55	64	71	87% current and former smokers		16	84	32.4
Ciuleanu 2012	77 sites in 24 countries	2006.04-2010.02	Second	IIB or IV	Histologically	Erlotinib	203	59	79	85% current and former smokers	PCR-based method	77	75	27.9
						Pemetrexed + Docetaxel	105+116	59	72	80% current and former smokers		77	74	24.8

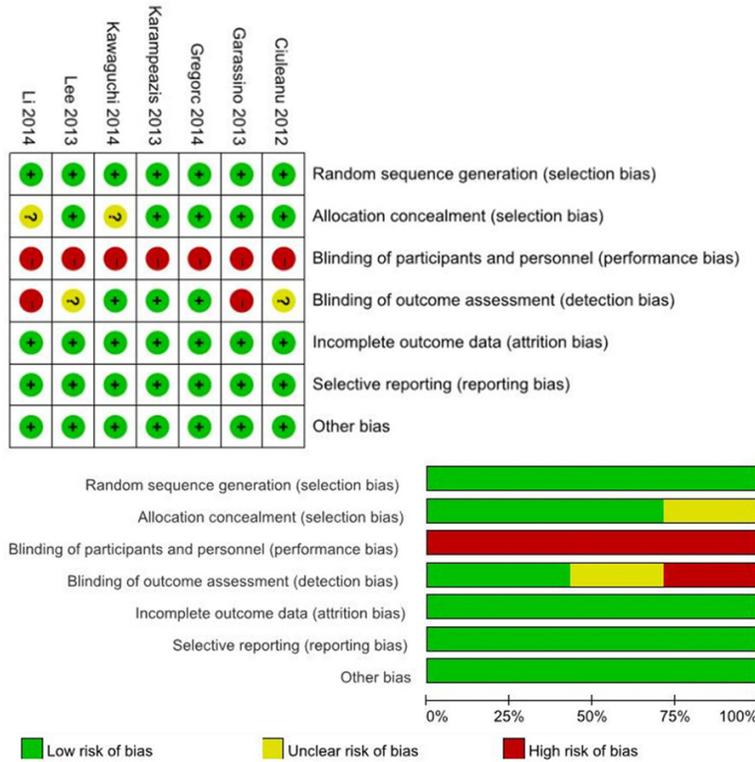


Figure 2. Outcomes of the quality assessment of the included randomized controlled trials.

the other hand, retrospective studies, non-randomized controlled clinical studies, reviews, animal studies, and studies did not provide sufficient data were excluded. In addition, if multiple studies were published in different journals based on the same study population or the same dataset, only the recent one with the most complete study was included.

Data extraction and quality assessment

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta analyses statement (PRISMA) [24], two investigators independently extracted the following data from each study with a predefined information table: first author’s name, publication year, line of treatment, sample size, duration of follow up, relevant baseline data, method of EGFR mutation analysis, and relevant data to calculate the effect size. The risk of bias of included studies was assessed by two investigators using the Cochrane risk of bias assessment tool [25]. Any discrepancy was resolved by discussion with a third investigator.

Statistical analysis

The PFS, OS and ORR in the erlotinib group were compared with the chemotherapy (docetaxel/pemetrexed) group. The risk ratio (RR) and 95% confidence interval (CI) was used as the effect size to calculate the pooled ORR and the toxicities using the Mantel Haenszel method [26], while the hazard ratio (HR) and its corresponding 95% CI was the effect size to evaluate the pooled PFS and OS using the Inverse Variance method [27]. The heterogeneity across studies was examined by the Cochran’s Q statistic and the I^2 statistic [28]. The fixed-effects model was selected for the homogeneous outcomes ($P \geq 0.05$ and $I^2 < 50\%$) and the random-effects model was applied for heterogeneous outcomes ($P < 0.05$ or $I^2 \geq 50\%$). Subgroup analyses

stratified by different chemotherapy agents (docetaxel/pemetrexed/docetaxel + pemetrexed) and different EGFR type (EGFR wild type/EGFR unselected) were used to assess the impacts on all the outcomes. Additionally, for the OS outcome, subgroup analyses stratified by sex, Eastern Cooperative Oncology Group (ECOG) performance status, smoking status and histology were also performed. The above analyses were implemented with the Review Manger 5.2 software (Cochrane Library Software, Oxford, UK), and a P value less than 0.05 was considered to be statistically significant. All P values and 95% CIs were two-sided.

Results

Literature retrieval

The process of study selection is shown in **Figure 1**. By the preliminary search, a total of 286 potentially relevant articles were screened out, 266 of which were excluded since they were duplicates or obviously irrelevant. For the remaining studies, 14 of them were excluded for they did not meet the inclusion criteria (4

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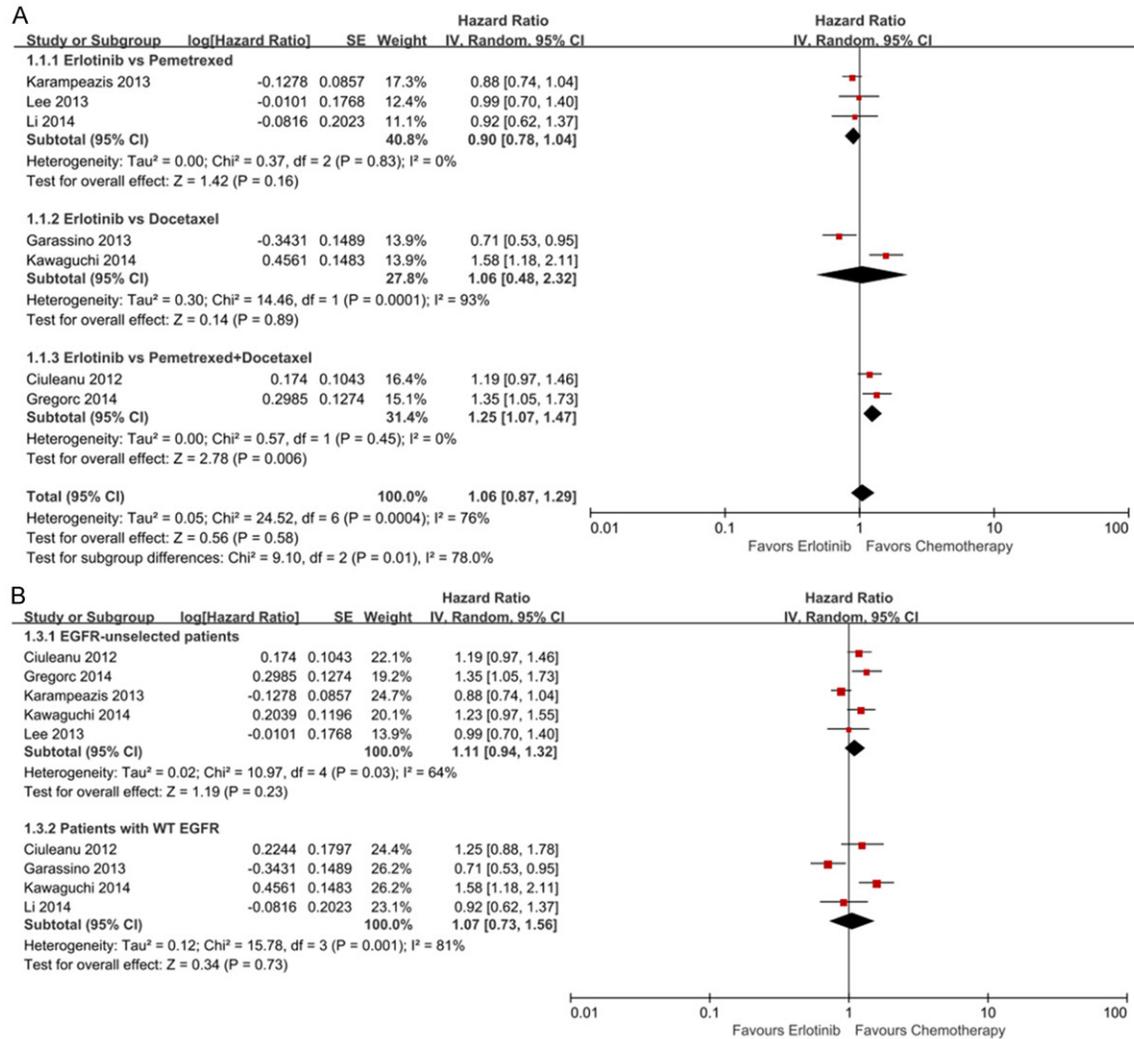


Figure 3. Forest plots for hazard ratio of erlotinib versus chemotherapy (docetaxel/pemetrexed) in progression-free survival (PFS) in advanced non-small cell lung cancer (NSCLC). A. The total estimate and the subgroup analysis stratified by different chemotherapy agents; B. The subgroup analysis stratified by different EGFR types. Squares represent the effect size for the hazard ratio of PFS among advanced NSCLC patients with erlotinib versus chemotherapy. Size of the squares is study-specific weight. Horizontal lines represent 95% confidence intervals (CI). The diamond shape represents the pooled estimates within each analysis.

were review articles and 10 did not compare erlotinib with docetaxel or pemetrexed). Moreover, an additional study was included from the reference list of the eligible studies. Therefore, a total of 7 RCTs were finally included in the present meta-analysis [21, 29-34].

Characteristics of included studies

The baseline characteristics of the included studies are presented in **Table 1**. It was revealed that all of them were published in recent 3 years and focused on the role of erlotinib as second-line or third-line treatment for patients

with NSCLC. The 7 studies were consisted of a total of 1819 patients (including 900 patients received erlotinib and 919 patients received pemetrexed or docetaxel). Three trials compared erlotinib to pemetrexed [29, 31, 32], two trials compared erlotinib to docetaxel [21, 30], and the other two trials compared erlotinib to chemotherapies involving pemetrexed and docetaxel [33, 34]. Patients with only advanced EGFR wild type lung cancer cases were reported in two studies [21, 32], and patients in two studies were EGFR-unselected [29, 31], while patients with both EGFR wild type and EGFR-unselected were reported in three studies [30,

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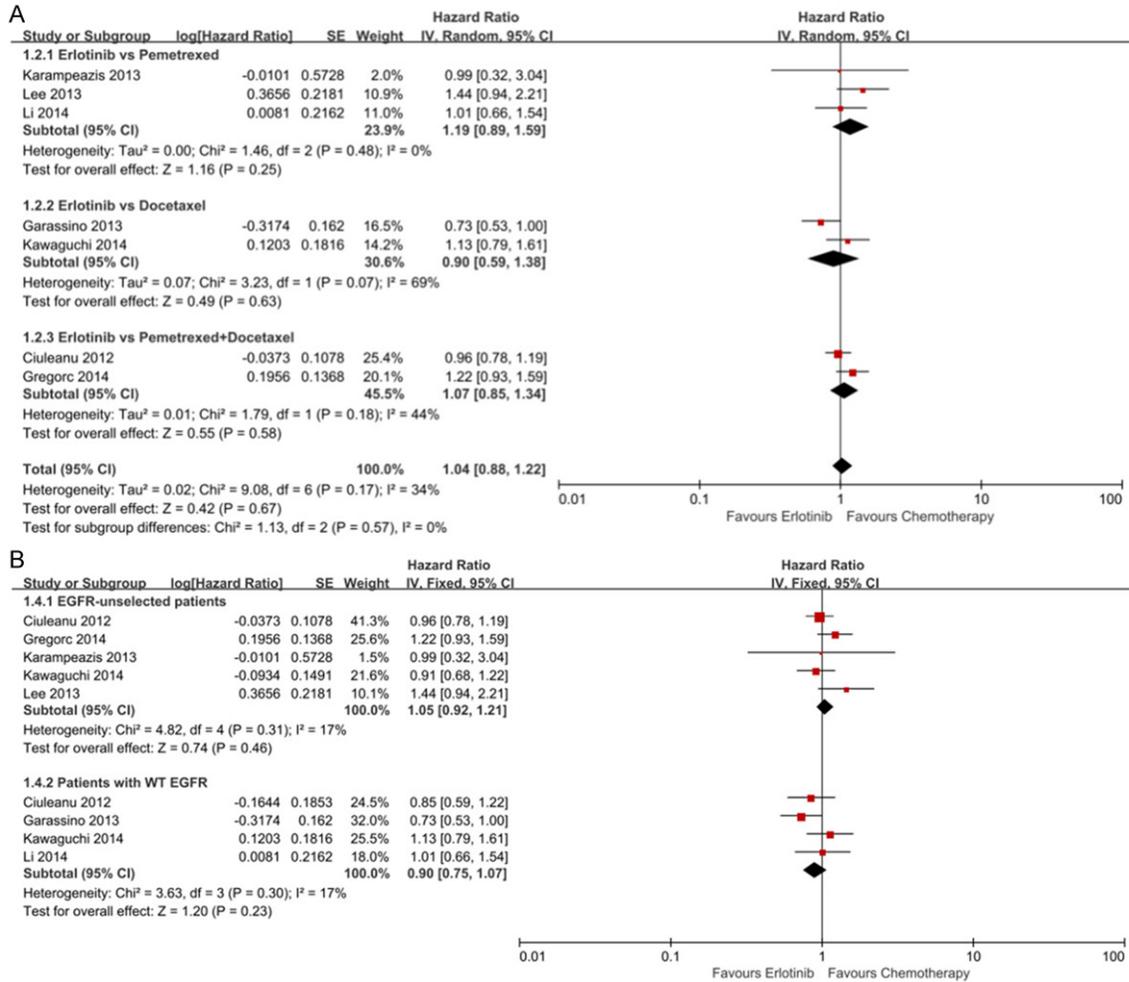


Figure 4. Forest plots for hazard ratio of erlotinib versus chemotherapy (docetaxel/pemetrexed) in overall survival (OS) in advanced non-small cell lung cancer (NSCLC). A. The total estimate and the subgroup analysis stratified by different chemotherapy agents; B. The subgroup analysis stratified by different EGFR types. Squares represent the effect size for the hazard ratio of OS among advanced NSCLC patients with erlotinib versus chemotherapy. Size of the squares is study-specific weight. Horizontal lines represent 95% confidence intervals (CI). The diamond shape represents the pooled estimates within each analysis.

33, 34]. In addition, the risk of bias assessment of the selected studies is presented in **Figure 2**. All studies had a low risk of bias on each bias item except the performance bias. Moreover, the studies carried out by Garassino [21] and Li [32] also had a high risk of detection bias. Overall, the included studies had a favorable quality and were suitable to perform the meta-analysis.

Comparison of the effects on PFS between erlotinib and chemotherapy

As shown in the forest plots in **Figure 3**, the random-effects model was applied for almost all the HR estimates due to substantial hetero-

geneity ($P < 0.05$, $I^2 > 50\%$) among studies, except for two comparisons (erlotinib vs. pemetrexed and erlotinib vs. pemetrexed + docetaxel), which presented significant homogeneity ($P > 0.05$, $I^2 < 50\%$) and thus used fixed-effects model. The total HR (erlotinib vs. pemetrexed + docetaxel) of 1.06 (95% CI: 0.87-1.29, $P = 0.58$) indicated there was no significant difference of PFS between erlotinib and chemotherapy treatments (**Figure 3A**). When stratified by different chemotherapy types, the pooled estimates showed there was no significant differences on PFS between erlotinib and pemetrexed or docetaxel (erlotinib vs. pemetrexed: HR = 0.90, 95% CI: 0.78-1.04, $P = 0.16$; erlotinib vs. docetaxel: HR = 1.06, 95% CI: 0.48-2.32, $P =$

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Table 2. Subgroup analysis of overall survival (OS) between Erlotinib and chemotherapy (docetaxel/pemetrexed)

Groups	No. of studies	Erlotinib vs. chemotherapy (docetaxel/pemetrexed)			
		HR (95% CI)	P_A	I^2 (%)	P_H
Sex					
Men	3	0.8972 [0.7436; 1.0825]	0.2574	0	0.4413
Women	3	0.8965 [0.6526; 1.2315]	0.5000	44.7	0.1638
ECOG performance status					
0 or 1	3	0.8871 [0.7422; 1.0602]	0.1878	0	0.6822
2	3	0.9754 [0.5418; 1.7560]	0.9339	55.7	0.1049
Smoking status					
Never smoker	3	0.7451 [0.5097; 1.0893]	0.1289	0	0.6727
Past smoker	2	0.9650 [0.7487; 1.2439]	0.7834	0	0.4268
Present smoker	2	0.9247 [0.7733; 1.1059]	0.3912	0	0.4523
Histology					
Squamous cell	2	0.8698 [0.6421; 1.1784]	0.368	0	0.8989
Adenocarcinoma	2	0.8047 [0.5717; 1.1326]	0.2128	55.2	0.1353
Other NSCLC	2	1.5403 [0.9172; 2.5868]	0.1024	0	0.5095

ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval; P_A , P value for test of the association; P_H , P value for between-study heterogeneity; NSCLC, non-small cell lung cancer.

0.89; **Figure 3A**). In addition, similar results were observed in the subgroup analyses stratified by EGFR status. The pooled HR of EGFR-unselected patients and patients with wild type EGFR were 1.11 (95% CI: 0.94-1.32, $P = 0.23$) and 1.07 (95% CI: 0.73-1.56, $P = 0.73$), respectively, all without statistical significance (**Figure 3B**).

Comparison of the effects on OS between erlotinib and chemotherapy

The outcome of OS was shown in **Figure 4**. No significant heterogeneity ($P > 0.05$, $I^2 < 50\%$) was identified among all the included studies, so the fixed effects model was applied to calculate the pooled results. However, in the comparison of erlotinib with docetaxel, a significant heterogeneity was detected ($I^2 > 50\%$), thus the random effects model was used. As a result, erlotinib did not show any significant difference on OS, compared with the pemetrexed + docetaxel combination therapy (HR = 1.04, 95% CI: 0.88-1.22, $P = 0.67$, **Figure 4A**). Moreover, no significant difference was observed when stratified by chemotherapy agents (erlotinib vs. docetaxel: HR = 0.90, 95% CI: 0.59-1.38, $P = 0.63$; erlotinib vs. pemetrexed: HR = 1.19, 95% CI: 0.89-1.59, $P = 0.25$; erlotinib vs. docetaxel + pemetrexed: HR = 1.07, 95% CI: 0.85-1.34, $P = 0.58$, **Figure 4A**) or EGFR status (EGFR-unselected: HR = 1.05, 95% CI: 0.92-1.21, $P =$

0.46; wild type EGFR: HR = 0.90, 95% CI: 0.75-1.07, $P = 0.23$, **Figure 4B**). Furthermore, there did not detect any significant association when stratified by sex, ECOG performance status, smoking status and histology ($P > 0.05$, **Table 2**).

Comparison of the effects on ORR between erlotinib and chemotherapy

The analysis of the ORR was presented in **Figure 5**. There was significant heterogeneity ($P < 0.001$, $I^2 > 50\%$) across the included studies, thus the random effects model was applied for the overall analysis; but the fixed-effects model was utilized in the comparison of erlotinib vs. pemetrexed and erlotinib vs. pemetrexed + docetaxel due to a lack of remarkable heterogeneity ($P > 0.05$, $I^2 = 0$). No significant differences were observed from the total estimate on ORR between erlotinib and chemotherapies (RR = 0.88, 95% CI: 0.46-1.70, $P = 0.71$). The pooled RRs of erlotinib vs. pemetrexed, and erlotinib vs. docetaxel + pemetrexed were 1.72 (95% CI: 0.71-4.20, $P = 0.23$) and 1.00 (95% CI: 0.60-1.68, $P = 1.00$), respectively, which also showed a comparable effect between erlotinib and the two chemotherapies. Similar results were also observed in the subgroup analysis stratified by different EGFR status (EGFR-unselected: RR = 1.14, 95% CI: 0.73-1.78, $P = 0.56$; wild type EGFR: RR = 0.53, 95%

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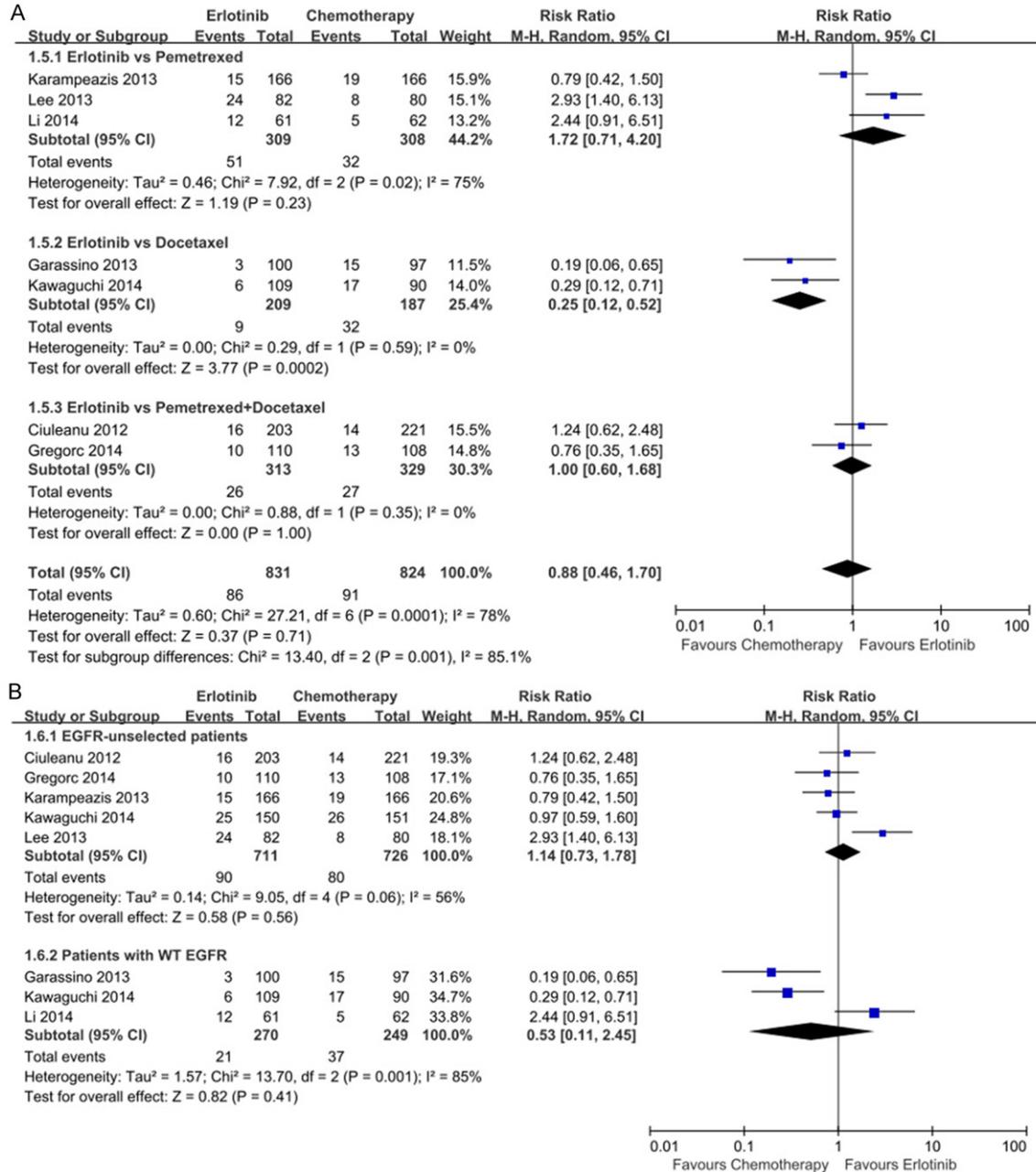


Figure 5. Forest plots for risk ratio of erlotinib versus chemotherapy (docetaxel/pemetrexed) in objective response rate (ORR) in advanced non-small cell lung cancer (NSCLC). A. The total estimate and the subgroup analysis stratified by different chemotherapy agents. B. The subgroup analysis stratified by different EGFR types. Squares represent the effect size for the risk ratio of ORR among advanced NSCLC patients with erlotinib versus chemotherapy. Size of the squares is study-specific weight. Horizontal lines represent 95% confidence intervals (CI). The diamond shape represents the pooled estimates within each analysis.

CI: 0.11-2.45, P = 0.41). However, the pooled analysis of two studies [21, 30] demonstrated a significantly lower ORR for erlotinib compared to docetaxel (RR = 0.25, 95% CI: 0.12-0.52, P<0.001) under a fixed-effects model (P = 0.59, I² = 0%).

Comparison of the effects on toxicities between erlotinib and chemotherapy

The analyses of toxicities were shown in **Table 3**. Compared with chemotherapy, erlotinib resulted in significantly higher grade 3-4 toxicities

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Table 3. Comparison of grade 3-4 toxicities between erlotinib and chemotherapy

Grade 3-4 toxicity	Included trials	RR (95% CI)	P value	Heterogeneity
Rash	5	15.74 (4.94-50.19)	<0.001	P = 0.95, I ² = 0%
Diarrhea	7	2.25 (0.99-5.12)	0.05	P = 0.77, I ² = 0%
Vomiting/Nausea	6	0.92 (0.42-2.04)	0.84	P = 0.53, I ² = 0%
Fatigue/asthenia disorder	6	0.69 (0.44-1.09)	0.11	P = 0.31, I ² = 17%
Anemia	5	0.34 (0.17-0.66)	0.002	P = 0.37, I ² = 7%
Neutropenia	6	0.02 (0.01-0.06)	<0.001	P = 0.44, I ² = 0%
Alopecia	4	0.05 (0.01-0.40)	0.004	P = 0.21, I ² = 36%

RR, risk ratio; CI: confidence interval.

such as rash (RR = 15.74, 95% CI: 4.94-50.19, P<0.001). Besides, patients treated with erlotinib also revealed a remarkably increased risk in diarrhea (RR = 2.25, 95% CI: 0.99-5.12, P = 0.05). However, erlotinib achieved a significantly decreased risk in anemia (RR = 0.34, 95% CI: 0.17-0.66, P = 0.002), neutropenia (RR = 0.02, 95% CI: 0.01-0.06, P<0.001) and alopecia (RR = 0.05, 95% CI: 0.01-0.40, P = 0.004). In addition, no significant difference was found between the two treatments in respects of vomiting/nausea and fatigue/asthenia disorder (P<0.05).

Discussion

After the failure of first-line chemotherapy, docetaxel, pemetrexed, or erlotinib is acceptable as the second- or third- line therapy for patients with advanced NSCLC [35, 36]. Recent studies about second-line treatment indicate that chemotherapy (docetaxel or pemetrexed) is superior to EGFR-TKIs on PFS for EGFR wild type NSCLC [19, 20, 37]. However, our meta-analysis combined 1819 patients (including 900 patients received erlotinib and 919 patients received docetaxel/pemetrexed) in 7 RCTs published in recent three years, and demonstrated that erlotinib presented no significant differences in outcomes of PFS, OS and ORR compared to the docetaxel/pemetrexed for the second- or third-line treatment of advanced NSCLC patients, especially of the EGFR-unselected patients and patients with wide type EGFR.

A recent meta-analysis suggests that chemotherapy is significantly superior to EGFR-TKI in terms of PFS as second-line treatment for the NSCLC [22]. However, in that meta-analysis, only three trials were included in the comparison of erlotinib with chemotherapy. Gregorc

and co-workers' study also shows chemotherapy is more effective than EGFR-TKIs for the management of EGFR wild type patients [34]. Whilst, in their meta-analysis, only two trails compare the effectiveness of erlotinib with pemetrexed/docetaxel. Consistent with this result, another meta-analysis also finds that chemotherapy significantly prolongs PFS in second-line or subsequent therapy for wild type EGFR NSCLC [15]. However, only two trails involving erlotinib vs. chemotherapy are included in their study [15]. Gao and his colleagues also demonstrate that chemotherapy is more advantageous than EGFR-TKIs in PFS for EGFR wild type patients, while the meta-analysis is presented in part at the 2013 American Society of Clinical Oncology annual meeting and only includes three trials [38]. In regardless of the small numbers of the included trails, the above meta-analyses all indicate that chemotherapy has an improvement for EGFR wild type patients compared with EGFR-TKIs, which is inconsistent with our results. It might be due to that the above meta-analyses all recruit the EGFR wild type patients who have non-activating EGFR gene mutations, and this might result in the failure of tyrosine kinase encoding and response to EGFR-TKIs.

Our study also evaluated the toxicities between erlotinib and docetaxel/pemetrexed, in addition to the estimations on PFS, OS and ORR. The total results suggested that the administration of erlotinib caused a significantly decreased risk in anemia, neutropenia and alopecia, compared with the chemotherapy, but resulted in an increased risk of rash and diarrhea. Moreover, no significant difference was found between the erlotinib and docetaxel/pemetrexed in respects of vomiting/nausea and fatigue/asthenia disorder. Inconsistent with our findings, Gregorc's meta-analysis sug-

gests that only the risk of rash is significantly increased, while fatigue/asthenia disorder, leukopenia and thrombocytopenia are decreased significantly with the EGFR-TKIs administration [34]. The different results between the two meta-analyses might be due to that Gregorc's article includes researches not only related to erlotinib but also related to gefitinib.

To the best of our knowledge, this study is the first meta-analysis with a focus on the assessments between erlotinib and chemotherapy as second-line treatment for the advanced NSCLC. We made our best efforts to retrieve seven related articles and found no significant difference between erlotinib and docetaxel/pemetrexed for the second- or third-line treatment of advanced NSCLC patients. However, the results should be interpreted cautiously as all the included RCTs had performance (blinding of participants and personnel) bias.

In addition, several limitations should be discussed in this meta-analysis. First of all, the sample size was still small that only seven RCTs were analyzed in this study, of which two articles involving the comparison between erlotinib and docetaxel, and three articles concerning the comparison between erlotinib and pemetrexed were included.

The small number of the included studies might cause several deviations to the results. Secondly, there were significantly heterogeneities on the assessment of PFS and ORR, even in the subgroup analyses, which might distort the results as heterogeneity is one of the major concerns in meta-analysis for the validity [39]. Thirdly, the data about EGFR mutation status were limited. Although the EGFR mutation rate is only 16.7% in unselected patients [16], the patients with activating EGFR gene mutations are highly responsive to EGFR-TKIs, and that will significantly prolong the PFS [12-14]. Therefore, it's better to collect and analyze the EGFR mutation data to obtain a more comprehensive result. Additionally, different methods for the EGFR mutation detection will also make a difference on the final outcomes, which was not mentioned in the present work. Last but not the least, several trials were not 100% second-line setting studies [29, 30], which might be another confounding factor for the significant heterogeneity. Therefore, more large-scale RCTs are needed to evaluate the best treat-

ment in the second-line setting for advanced NSCLC.

In conclusion, we found a comparable result between erlotinib and docetaxel/pemetrexed on the PFS, OS and ORR for the second-line treatment of advanced NSCLC patients. Meanwhile, the administration of erlotinib might lead to a decreased risk of anemia, neutropenia and alopecia; but an increased risk of rash and diarrhea, compared with the chemotherapy.

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Disclosure of conflict of interest

None.

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