

EGFR-TKIs versus taxanes agents in therapy for nonsmall-cell lung cancer patients

A PRISMA-compliant systematic review with meta-analysis and meta-regression

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Abstract

Background: Currently, the nonsmall-cell lung cancer (NSCLC) is a worldwide disease, which has very poor influence on life quality, whereas the therapeutic effects of drugs for it are not satisfactory. The aim of our PRISMA-compliant systematic review and meta-analysis was to compare the efficacy and safety of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) with Taxanes in patients with lung tumors.

Methods: We collected randomized controlled trials (RCTs) of EGFR-TKIs (gefitinib, erlotinib) versus Taxanes (docetaxel, paclitaxel) for the treatment of NSCLC by searching PubMed, EMbase, and the Cochrane library databases until April, 2016. The extracted data on progression-free survival (PFS), progression-free survival rate (PFSR), overall survival (OS), overall survival rate (OSR), objective response rate (ORR), disease control rate (DCR), quality of life (QoL), and adverse event rates (AEs) were pooled. Disease-relevant outcomes were evaluated using RevMan 5.3.5 software and STATA 13.0 software.

Results: We systematically searched 26 RCTs involving 11,676 patients. The results showed that EGFR-TKIs could significantly prolong PFS (hazard ratio [HR] = 0.78, 95% confidence interval [CI]: 0.66–0.92) and PFSR (risk ratio [RR] = 2.10, 95% CI: 1.17–3.77), and improve ORR (RR = 1.62, 95% CI: 1.38–1.91) and QoL. EGFR-TKIs had similar therapeutic effects to taxanes with respect to OS (HR = 1.00, 95% CI: 0.95–1.05) and OSR (RR = 1.03, 95% CI: 0.94–1.14). Furthermore, there were no significant differences between them in DCR (RR = 0.95, 95% CI: 0.88–1.03). Finally, EGFR-TKIs were superior to taxanes in most of all grades or grade \geq 3 AEs.

Conclusion: In the efficacy and safety evaluation, EGFR-TKIs had an advantage in the treatment of NSCLC, especially for patients with EGFR mutation-positive. The project was prospectively registered with PROSPERO database of systematic reviews, with number CRD42016038700.

Abbreviations: AE = adverse event, CI = confidence interval, DCR = disease control rate, EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor, FACT-L = Functional Assessment of Cancer Therapy-Lung, HR = hazard ratio, LCS = Lung Cancer Subscale, NOS = Newcastle-Ottawa Scale, NSCLC = nonsmall-cell lung cancer, OR = odds ratio, ORR = objective response rate, OS = overall survival, OSR = overall survival rate, PFS = progression-free survival, PFSR = progression-free survival rate, QoL = quality of life, RCT = randomized controlled trial, RR = risk ratio, TOI = Trial Outcome Index.

Keywords: EGFR-TKIs, meta-analysis, meta-regression, randomized controlled trials, taxanes

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1. Introduction

Carcinoma of lungs have become the first killer among all cancers, and is the leading cause of cancer-related mortality across the world, with a 5-year survival of less than 15%.^[1,2] Nonsmall-cell lung cancer (NSCLC) accounts for nearly 80% to 85% among all cases of lung cancers, locally advanced NSCLC 25% to 30% of all cases and metastatic diseases 40% to 50% of all cases.^[3,4] In the last decade, the therapeutic method for these patients consisted of 1st-line chemotherapy that can significantly improve the curative effects, such as gemcitabine, taxanes combining with platinum, and pemetrexed. However, the response rates are modest and after standard 1st-line therapy, several patients relapse of the malady, hence patients with NSCLC demand 2nd-line chemotherapy after 1st-line chemotherapy.^[5]

Currently, it is safe to say that NSCLC patients benefit from taxanes agents, such as paclitaxel and docetaxel, which can be seen as representative of the new generation of anticarcinogen with a unique mechanism: they play a role in the microtubule and tubulin system, combine with free tubulin and promote tubulin assembly into stable microtubules, and inhibit their depolymerization. Therefore, they prevent the division of a large number of cells, leading to cell death.^[6,7] Among paclitaxel plus carboplatin as 1st-line treatment in advanced NSCLC.^[8] Apart from paclitaxel, docetaxel is paclitaxel in the process of structural transformation synthesized paclitaxel derivatives, which has high bioavailability and small side effects. Docetaxel is approved as 1st-line therapy in combination with cisplatin, as single-agent 2nd-line therapy, or as single-agent maintenance therapy for patients with advanced NSCLC in numerous countries.^[9,10]

To date, epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) as molecular targeted therapeutical drugs have aroused people's attention, therein gefitinib and erlotinib have secured approvals for the treatment of advanced NSCLC, especially for those with sensitizing EGFR mutations.^[11] Nevertheless, different mutations may result in different structural changes, thereby affecting subsequent clinical outcomes.^[12] EGFR-TKIs play a role in tumor suppression by blocking the signal transduction of tumor cells, including inhibition of tumor cell proliferation, acceleration of apoptosis, and antiangiogenesis.^[13] Compared with other traditional medicines, gefitinib and erlotinib can prolong progression-free survival (PFS) in EGFR mutation-positive patients, and can be administered easily (orally). A phase 2B open-label randomized controlled trial has shown that gefitinib exhibits good tolerability and antitumor activities in NSCLC.^[14]

Based on these, we performed a meta-analysis and metaregression to explore the efficacy and safety of these medications for NSCLC patients, which could dedicate to make evidencebased clinical decisions for the treatment of pulmonary cancer.

2. Method

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.^[15] The project was prospectively registered with PROSPERO database of systematic reviews, number CRD42016038700.^[16]

2.1. Data sources and search strategy

We systematically searched 3 search engines: PubMed, EMbase, and the Cochrane library from inception to April 2016. The search strategy included keywords and MeSH terms related to therapy using EGFR-TKIs and taxanes. Clinical trials were in any languages with patients presenting with NSCLC (see details in Table S1, http://links.lww.com/MD/B469). We also scrutinized the reference list of relevant publications for additional studies.

2.2. Inclusion criteria

The relevant literature was selected carefully had to meet the following 4 criteria: all patients were diagnosed with NSCLC; the treatment arm were given EGFR-TKIs for therapy; while the control arm were given taxanes for cure; measurable outcomes were reported; and randomized controlled trials (RCTs). Ethical approval was not necessary, because of meta-analysis is a type of secondary statistics study, not directly associated with the subjects.

2.3. Data extraction

Two investigators (AN and ZYS) read the references and extracted the data independently. If we had any disagreements, we asked the 3rd investigator (LQ or ZQC). Every eligible study included the following information: the first author, publication year, trial design, sample size, age, gender, performance status, clinical phase, EGFR status, disease status, intervention, outcome assessment time, the main outcomes, risk of bias, and Newcastle-Ottawa Scale (NOS) score. The main outcomes were as follows: PFS, progression-free survival rate (PFSR), overall survival (OS), overall survival rate (OSR), objective response rate (ORR), disease control rate (DCR), quality of life (QoL), and adverse events (AEs).

2.4. Study quality assessment

The Cochrane Collaboration tool was used to evaluate the quality of these studies.^[17] We assessed the following 7 items of risk of bias: random sequence (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. Low risk, high risk, and unclear risk were classified in all studies. The NOS^[18,19] as recommended by the Cochrane Non-Randomized Studies Methods Working Group, our meta-analysis also used NOS to assess the quality of the included RCTs. NOS using the following criteria label as "yes," or "no": Is the case definition adequate? Representativeness of the cases? Selection of Controls? Definition of Controls? Comparability of cases and controls? (0-2) Ascertainment of exposure? (0-2) Same method of ascertainment for cases and controls? and nonresponse rate? We excluded some studies which score less than 5 score.

2.5. Statistical analysis

The hazard ratio (HR), risk ratio (RR), and odds ratio (OR) with 95% confidence interval (CI) were used in eligible study. If studies did not have significant heterogeneity (P > 0.10, $I^2 < 50\%$), fixed-effects model was calculated. By contrast, random-effects model was employed. Furthermore, using subgroup analysis for the possible causes of sources of heterogeneity factors. The results of the meta-regression with the *P* value less than 0.05 means that the factors could cause significant impact to overall. Funnel plot was produced to assess publication bias. All statistical analyses were conducted with Review Manager 5.3.5 statistical software (Cochrane Collaboration) and STATA 13.0 software (StataCorp, College Station).

3. Results

3.1. Article selection and risks of bias

After searching the PubMed, EMbase, and the Cochrane library, we identified 633 articles, based on title and abstract screening, and obtained as full texts records. A total of 26 studies were included (Fig. 1).

We evaluated the risks of bias of all articles by the Cochrane Collaboration's tool and NOS scale, the required data can be evaluated as acceptable quality. The detail of quality assessment was shown in Table 1, Table S2, http://links.lww.com/MD/B469 and Fig. S1, http://links.lww.com/MD/B469.

3.2. Characteristics of included studies

The detailed characteristics of 26 studies were presented in Table 1. All the studies involved 11,676 patients, among which 5836 patients who received gefitinib/erlotinib were used as the treatment group and 5840 patients who received docetaxel/ paclitaxel as the control group. Nine studies^[20–28] compared



gefitinib versus docetaxel. Five studies^[29–33] compared erlotinib versus docetaxel. Eleven studies^[34–44] compared gefitinib versus paclitaxel. One studies^[45] compared erlotinib versus paclitaxel. Twenty-five studies^[20–26,28–45] were randomized. Nineteen studies^[22,24,27–41,43,44] included EGFR status, for example, EGFR mutation, EGFR wild-type, EGFR protein expression, and EGFR gene copy number. Taxanes combine with platinum and taxanes alone were used in 14 studies^[27,30,34–45] and 12 studies^[20–26,28,29,31–33] respectively. Three studies^[20,26,45] were classified by phase II clinical trials, and 19 studies^[21–25,27–30,32–38,41–43] were classified by phase III. Thirteen studies^[20,21,25,27,29–35,37,45] were designed as multicenter and 12 studies^[20–24,28,36,38–44] were designed as single center.

3.3. Outcome evaluation and meta-analysis

3.3.1. Progression-free survival (PFS), progression-free survival rate (PFSR). Twenty-one studies^[20-22,24-27,29-36,38-42,45] were finally included for analysis, which included 9096 patients, and 1 study^[44] was excluded due to irrelevant data. According to different drug types, the studies could be divided into 4 groups. There was significant heterogeneity between the included studies $(P < 0.00001, I^2 = 93\%)$ and subgroup $(P < 0.0001, I^2 = 88.2\%)$. Therefore, random-effect model was used for analysis. Comparing paclitaxel, gefitinib can significantly prolong PFS in patients (HR=0.50, 95% CI: 0.38-0.66). There was no statistically significant difference in gefitinib versus docetaxel (HR=0.97, 95% CI: 0.89–1.07), erlotinib versus docetaxel (HR = 1.02, 95% CI: 0.72-1.44), and erlotinib versus paclitaxel (HR = 1.45, 95%CI: 0.98–2.15). In general, the PFS was significantly longer in the EGFR-TKIs group than taxanes groups in patients with NSCLC (HR=0.78, 95% CI: 0.66-0.92). Then, 5 studies^[20,24,25,33] reported 6-month PFSR (RR=0.97, 95% CI: 0.67-1.39), no significant difference was detected between the 4 treatment arms in patients. Five studies^[25,27,28,33,34] reported 1-year PFSR (RR = 4.97, 95% CI: 2.75–8.98) and only 1 study^[28] reported 2-year PFSR (RR=19, 95% CI: 1.12–322.62), we can know EGFR-TKIs can significantly prolong 1-year/2-year PFSR in patients. Overall, EGFR-TKIs were superior to taxanes in patients with NSCLC (RR=2.10, 95% CI: 1.17–3.77) (Fig. 2).

3.3.2. Overall survival (OS), overall survival rate (OSR). Sixteen studies^[20-22,24-27,29,31-34,36,41,42,45] including 8539 patients were finally included for OS analysis. Because of not relevant data, 1 study^[44] was not included finally. No significant heterogeneity was presented in studies (P=0.13, $I^2=29\%$). Therefore, we used fixed-effects model for analysis. Gefitinib produced longer OS than paclitaxel (HR=0.90, 95% CI: 0.82-0.99). No significant differences were observed in gefitinib (HR = 1.03, 95% CI: 0.96–1.11) or erlotinib (HR = 1.05, 95% CI: 0.92-1.20) versus docetaxel. Erlotinib was inferior to paclitaxel in OS (HR = 1.73, 95% CI: 1.09-2.74). In summary, there was only a nonsignificant trend toward improved OS for the EGFR-TKIs over taxanes groups (HR = 1.00, 95% CI: 0.95–1.05). From Fig. 3B, we can get that EGFR-TKIs cannot significantly prolong 6-month/1-year OSR in patients (RR=0.65, 95% CI: 0.17-2.55; RR = 0.97, 95% CI: 0.89-1.07), but it can significantly prolong 2-year OSR in patients (RR=1.21, 95% CI:1.08-1.36). Overall, in terms of survival rate, EGFR-TKIs had equally therapy value to taxanes (RR = 1.03, 95% CI: 0.94-1.14) (Fig. 3).

3.3.3. Objective response rate (ORR). A total of 8469 patients were enrolled on these 17 studies $^{[20-22,24,25,27,28,31,32,34-36,38, 39,414445]}$

^{39,41,44,45]} (21 analyses) for ORR analysis. Significant heterogeneity was existed in included studies (P < 0.00001, $I^2 = 68\%$). Whether docetaxel (RR = 1.85, 95% CI: 1.48–2.32) or paclitaxel (RR = 1.63, 95% CI: 1.34–1.97), gefitinib can improve patient's ORR. There was no significant difference between erlotinib versus docetaxel (RR=0.41, 95% CI: 0.11–1.54) and erlotinib versus paclitaxel (RR=0.33, 95% CI: 0.07–1.54). Overall, EGFR-TKIs produced higher ORR than Taxanes in patients with NSCLC (RR=1.62, 95% CI: 1.38–1.91) (Fig. 4A).

3.3.4. Disease control rate (DCR). Twelve studies^[20–22,25–29, 31,32,35,45] (16 analyses) were identified, covering a total of 5218 subjects for DCR analysis. Significant heterogeneity among studies (P=0.0007, $I^2=61\%$). Except the result of erlotinib versus paclitaxel (RR=0.7, 95% CI: 0.58–0.84) indicated that paclitaxel can increase DCR, no significant differences were observed in additional three therapy groups (Fig. 4B).

3.3.5. Quality of life (QoL). We used Functional Assessment of Cancer Therapy-Lung (FACT-L), Trial Outcome Index (TOI), and Lung Cancer Subscale (LCS) to assess the QoL. The results of FACT-L analysis (RR=1.21, 95% CI: 1.06–1.38), LCS analysis (RR=1.09, 95% CI: 0.96–1.23), and TOI analysis (RR=1.52, 95% CI: 1.27–1.81) showed that EGFR-TKIs group had better QoL than taxanes groups (Fig. 5).

3.3.6. Adverse event rates (AEs). The OR and 95% CI for common AEs were shown in Table 2. Comparing taxanes, EGFR-TKIs led to a lower rate in hematologic toxicity, alopecia, myalgia, pyrexia, and gastrointestinal reaction, except diarrhea (all grades OR = 1.92, 95% CI: 1.55–2.39; grade \geq 3 OR = 1.70, 95% CI: 1.18–2.47). Meanwhile, rash was more common in the EGFR-TKIs groups (all grades OR = 4.62, 95% CI: 3.46–6.17; grade \geq 3 OR = 4.60, 95% CI: 2.90–7.32). There was a similar incidence of constipation and pyrexia in grade \geq 3.

First author/		Sample		Gender	performance	Smoking	Clinical			Interv	ention	Outcome		Risk	NOS
publication year Cufer 2006 ⁽²⁰⁾	Multilateral (European, South American,	68:73	Age T:63.0 (34–85); C:59.5 (29–83)	(M:F) 98:43	status T:0/1/2:13/30/25; C:0/1/2: 11/41/	rate, % T:67.6; C:67.1	= =	NA NA	UISEASE Stage	Treatment arm 250 mg/d gefitinib orally	Control arm 75mg/m ² docetaxel i.v.	assessment time 3wk	ULUDINES	of blas	7
kim 2008 ^[21]	Middle Eastern countries) Multilateral (Furone	733-733	T-61 (27-84)- C-60	945-512	21 T-0/1/2/3/not	T-70.8- C-70.5	=	MA	T-IIIR/IV-183/388-C	250 ma/d nefitinih	75 mn/m ² docetavel	Evenu 3 wk Evenu 6	TOOMER	Hich	~
	Asia, North, et al)		(20-84)		428/86/0/1; C:0/ 1/22/3/nd 1/22/3/nd recorded:181/ 463/84/0/5		=	ŝ	IIB/N:211/383;	orally genuine	.v.	WK	000000T	-	_
Maruyama 2008 ⁽²²⁾	Single center (Japan)	245:244	T:≤ 64: 138 ≥65: 107; C: ≤64: 135 ≥65: 109	302: 187	T:0/1/2:85/149/11; C:0/1/2: 93/141/ 10	T:71.0; C:64.3	≡	EGFR mutation;EGFR FISH;EGFR protein expression	T:IIIB/IV:47/159;C:IIIB/ N:50/150;	250 mg/d gefitinib orally	60 mg/m ² ; docetaxel; i.v.	Every 4wk for the first 24wk, every 8wk thereafter	123460	High	œ
Sekine 2009 ^[23]	Single center (Japan)	245:244	NA	NA	NA	NA	≡	NA	IIIB or IV	250 mg/d gefitinib	60 mg/m ² docetaxel	Every 4wk until 12 wk	9	High	7
Douillard 2010 ^[24]	Single center (Canada)	733:733	NA	954:512	0 or 1/2:1296/170;	79.7	=	EGFR copy number; EGFR protein expression;EGFR mutation; KRAS	NA	250 mg/d gefitinib orally	75mg/m ² docetaxel i.v.	NA	(123)	Unclear	œ
Lee 2010 ^[25]	Multilateral (6 in Koreal	82:79	T:57 (21–74) C:58	100:61	T:0/1/2:2/74/6; C:0/ 1/2:2/71/6	T:63.4; C:54.4	≡	NA	IIIB or IV	250 mg/d gefitinib	75 mg/m ² docetaxel	3wk, every 6wk	123456	High	7
Morèrea 2010 ⁽²⁶⁾	NA	43:42	T:70 (45-79); C:71	71:14	T:2/3:30/13; C:2/3: 28/14	T:95.3; C:85.7	=	NA	T:IIIB/IV:7/36;C:IIIB/ N-6/36	250 mg/d gefitinib	75 mg/m ² docetaxel	Every 6wk,every 9 wk	1246	High	80
Mitsudomi 2010 ⁽²⁷⁾	Multicenter (36 in Japan)	86:86	T:64 (34–74); C:64 (41–75)	53:119	T:0/1:56/30; C:0/1: 52/34	T:29.1; C:33.7	=	EGFR mutation (Exon 19 deletion/ 185.881	T:IIIB/N:10/41;C:IIIB/ N:9/41;	250 mg/d gefitinib orally	cisplatin 80 mg/m ² i.v. plus docetaxel 60 mo/m ²	Every 2mo <1 year	12346	High	2
Yamamoto 2010 ^[28]	Single center (Japan)	245:244	T:≤ 64: 138 ≥65: 107; C: ≤64: 35 ×65: 100	302: 187	T:0/1/2:85/149/11; C:0/1/2: 93/141/ 10	T:71.0; C:64.3	≡	EGFR mutation;EGFR FISH;EGFR protein	T:IIIB/IV:47/159;C:IIIB/ N:50/150;	250 mg/d gefitinib orally	60 mg/m ² ; docetaxel; i.v.	Every 4wk for the first 24wk, every 8wk thereafter	34	High	œ
Ciuleanu 2012 ^[29]	Multicenter (77 sites in 24 countries)	203:211	T:59 (36–80); C:59 (22–79)	321:103	T:0/1/2:29/135/39; C:0/1/2: 23/152/ A6	T:85C:80	=	EGFR mutation;EGFR wild	T:IIIB/IV:41/162;C:IIIB/ N:51/170;	150 mg/d erlotinib orally	75 mg/m ² docetaxel i.v.	Every 3wk until 48 wk, every 12wk	12450	Unclear	7
Rosell 2012 ^[30]	Multicenter (42 hospitals in France, Italy, and Snain)	86:87	T:65 (24–82); C:65 (29–82)	47:126	T:0/1/2:127/47/12; C:0/1/2: 30/45/ 12	T:34; C:28	=	EGFR mutations	T:N3/IIIA/IIIB/IV:1/1/6/ 78;C:N3/IIA/IIIB/ N:0/0/5/82;	150 mg/d erlotinib orally	75mg/m ² cisplatin plus 75mg/m ² docetaxel	Every 6wk	10	High	00
Garassino 2013 ⁽³¹⁾	Multicenter (52 Italian	109:110	T:66 (40-81); C:67	150:69	T:0/1/2:152/48/9; C-0/1/2- 53/50/7	T:83; C:73	M	wild-type EGFR	NA	150 mg/d erlotinib	75 mg/m ² docetaxel	Every 9wk/cycle	12346	High	ø
Gregorc 2014 ^[32]	Multicenter (14 centers in Italy)	134:129	T:66 (33–85); C:64 (39–77)	190:73	T:0/1/2:173/53/8; C:0/1/2: 65/56/8	T:57; C:58	=	EGFR mutation;EGFR wild;KRAS mutation;not available	T:IIIB/W/not available:12/121/ 1;C:IIIB/W/not available:17/170/ 2-	150 mg/d erlotinib orally	75 mg/m ² docetaxel i.v.	4wk,8wk	12346	High	œ
Kawaguchi 2014 ^[33]	Multicenter (Japan)	150:151	T:68 (37–82); C:67 (31–85)	215:86	T:0/1/2:177/67/6; C:0/1/2: 78/67/6	T:74; C:75.8	=	EGFR mutation;EGFR wild;not available	T:IIIB/IV:30/120;C:IIIB/ N:29/122;	150 mg/d erlotinib orally	60 mg/m ² docetaxel i.v.	Every mo for the first 4mo, every 2mo	120	High	2
Mak 2009 ^[34]	Multicenter (China, Indonesia,Japan, Malaysia, et al)	609:608	T:57 (24-84); C:57 (25-84)	252:965	T:0/1/2:157/391/61; C:0/1/2: 161/ 382/65	T:6.3; C:6.4	≡	EGFR mutation (Exon 19 deletion/Exon 21 L858R/Exon 20 T790M/ multiplemutation/	T:IIIB/IV:160/459;C: IIIB/IV:144/463	250 mg/d gefitinib orally	Paciltaxel 200 mg/m ² I.v. and carboplatin	Every 6 wk	(12)(3)(3)(3)(3)(3)(3)(3)(3)(3)(3)(3)(3)(3)	High	2
Maemondo 2010 ^[35]	Multilateral (43 in Japan)	114:114	T:63.9 \pm 7.7 (43–75); C:62.6 \pm 8.9	83:145	T:0/1/2:54/59/1; C:0/ 1/2:57/55/2	T:34.2; C:42.1	=	EGFR mutation (Exon 19 deletion/ 18688)	T:IIIB/IV:15/88;C:IIIB/ N:21/84;	250 mg/d gefitinib orally	Paclitaxel 200 mg/m ² i.v. and	Every 2mo	1346	Unclear	7
Fukuoka 2011 ^[36]	Single center (Asia)	609:608	< 65 (899) >65 (318)	252:965	0 or 1:1091	6.3	≡	EGFR mutation;EGFR gene copy number;EGFR protein expression	Adenocarcinoma; IIIB or IV	250 mg/d gefitinib orally	Paclitaxel 200 mg/m ² i.v. and carboplatin	NA	133	High	ŝ
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Table 1

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/inthor/		Comulo		Condor	oonomaajaan	Cmoking	Clinical			retri	vention	Outcome		N N	907
L aution year	Trial design	size (T:C)	Age	(H:F)	status	siliukiliy rate, %	phase	EGFR status	Disease stage	Treatment arm	Control arm	assessment time	Outcomes	of bias so	COLE
ngprasert 2011 ^[37]	Multicenter (China, Indonesia,Japan,	590:561	<65 (899) ≧65 (304)	244:907	T:0,1/2:535/55; C:0,1/2:508/53	T:6.3; C:6.6	=	EGFR mutation positive/negative	IIIB/N	250 mg/d gefitinib orally	Paclitaxel 200 mg/m ² i.v. and	1,3,6,9,12,15,18wk	2	High	9
o 2012 ^[38]	Malaysia, et al) Single center (Japan)	114:119	<65 (121) >65 (112)	29:204	0 or 1/2:223/10	0.0	≡	EGFR mutation (cfDNA or Tumor)	IIIB/ IV:73/160	250 mg/d gefitinib orally	carboplatin paclitaxel 200 mg/m ² i.v. and	NA	(1)	Unclear	ŝ
umi 2012 ^[39]	Single center (Japan)	72:76	T:63.0 (43–75); C:62.2 (35–74)	53:95	T:0/1/2:40/32/0; C:0/ 1/2:43/32/1	T:29; C:39	NA	EGFR mutation (Exon 19 deletion/	T:IIIB/IV:10/52;C:IIIB/ IV:15/52;	250 mg/d gefitinib orally	carboplatin paclitaxel 200 mg/m ² i.v. and	NA	(136	high	œ
duyn 2012 ^[40]	Single center (Netherland)	NA	NA	NA	NA	NA	NA	EGFR mutation	IIIB or IV	250 mg/d gefitinib orally	Paclitaxel 200 mg/m ² i.v. and	NA	Θ	Unclear	9
ong WU 2012 ^[41]	Single center (China)	184:188	<65 (307) >65 (65)	80:292	0 or 1/2:307/356;	2.4	≡	EGFR mutation;EGFR gene copy number;EGFR	Adenocarcinoma; IIIB or IV	250 mg/d gefitinib orally	carboplatin Paclitaxel 200 mg/m ² i.v. and carboplatin	Every 6 wk	(12350)	Unclear	2
ue 2013 ^[42]	Single center (Japan)	114:114	NA	NA	NA	NA	=	protein expression	NA	250 mg/d gefitinib orally	Paclitaxel 200 mg/m ² i.v. and	NA	(1)	Unclear	~
ong Wu 2013 ⁽⁴³⁾	Single center (Asia)	102:124	<65 (167) >65 (59)	54:172	T:0 or 1/2:96/6; C:0 or 1/2: 115/9	T:5.9; C:8.1	≡	EGFR mutation	Adenocarcinoma; IIIB or IV	250 mg/d gefitinib orally	carboplatin carboplatin/paclitaxel 200 mg/m ² i.v.	Every 6 wk,4 mo	9	Unclear	00
tanabe 2014 ^[44]	Single center (Japan)	114:111	65 (35–75)	82:143	0/1/2:110/112/3	38.2	NA	EGFR mutations (exon19 deletion, L858R, G719X,	IIIB/N:34/171	250 mg/d gefitinib orally	and carboplatin Paclitaxel 200 mg/m ² i.v. and carboplatin	Every 2 mo	(123)	Unclear	~
1baum 2008 ⁽⁴⁵⁾	Multilateral; (14 study sites)	52:51	≧70:48; <70:55	51:52	2	T:never/past6/ 46;C:never/ past4/47	=	and Loo Iu) NA	T:IIB/IV:7/45;C:IIB/ IV:7/44	Erlotinib 150 mg/d orally	Paclitaxel 200 mg/m ² i.v. and carboplatin	Every cycle	12346	Unclear	~
D: PFS. @: 0S.	CORR. C. DCR	2 B 00	and C AF rates. Al	E=adverse	s event. C=control ar	rm. DCB = diseas	e control	rate F=female M=	= male mo = month	VA — not annlicable N	AOS = Newcastle-Ottav	wa Scale NSCLC – no	nsmall-cell lund cancer	ORB = obiec	~tive

response rate, OS = overall survival, PFS= progression-free survival, OoL = quality of file, T = treatment arm, wE = week.

5

Study or Subgroup	log[Hazard Rat	io]	SE	Weight	IV. Random, 95% CI	IV. Random. 95% CI	
1.1.1 gefitinib vs doce	etaxel						
Cufer 2006	-0.06187	54 0.1978	85481	4.2%	0.94 [0.64, 1.39]		
Douillard 2010	0.039220	71 0.06	60736	5.3%	1.04 [0.92, 1.17]	-	
Kim 2008	0.039220	71 0.06	0736	5.3%	1.04 [0.92, 1.17]	-	
Lee 2010	-0.316081	55 0.1600	00813	4.5%	0.73 (0.53, 1.00)		
Manuyama 2008	-0.105360	52 0.1127	71244	5.0%	0.90 10.72 1 121		
Alterational 2010	0.000000	C4 0.047/	1000	E 40/	0.0210.84 1.011	-	
Mitsudomi 2010	-0.083381	0.0470	11020	3.470	0.92 [0.84, 1.01]		
Morerea 2010	0.398776	12 0.2271	1053	3.9%	1.49 [0.95, 2.33]		
Subtotal (95% CI)	0.01. Chil - 11.00		- 0.00	33.6%	0.97 [0.89, 1.07]	T	
Test for overall effect:	Z = 0.57 (P = 0.57)) (df = 6 (P	= 0.09	i); I* = 46%	•		
1.1.2 gefitinib vs pacl	litaxel						
Fukuoka 2011	-0.301105	09 0.0684	13469	5.3%	0.74 10.65, 0.851		
Gato 2012	0 371063	68 0 1550	8703	4 6%	0.69 (0.51, 0.94)		
Incure 2012	.1 133203	73 0 157	6181	4 6%	0 32 10 24 0 441		
House 2012	4 20203	0 0 4500	Data	4.070	0.32 [0.24, 0.44]		
Maemondo 2010	-1.20397	28 0.1560	90858	4.0%	0.30 [0.22, 0.41]		
Mok 2009	-0.301105	09 0.0684	13469	5.3%	0.74 [0.65, 0.85]		
OIZUMI 2012	-1.20397	28 0.1588	30858	4.6%	0.30 [0.22, 0.41]		
Verduyn 2012	-0.843970	07 0.113	32478	5.0%	0.43 [0.34, 0.54]		
Yi-Long WU 2012	-0.235722	33 0.1244	8626	4.9%	0.79 [0.62, 1.01]		
Subtotal (95% CI)				38.6%	0.50 [0.38, 0.66]	-	
Heterogeneity: Tau ² =	0.14; Chi ² = 86.72	. df = 7 (P	< 0.00	001); I ² =	92%		
Test for overall effect:	Z = 4.93 (P < 0.00	001)		1.000			
1.1.3 erlotinib vs doc	etaxel						
Ciuleanu 2012	0 173053	31 0 1041	1011	5.0%	1.19 (0.97 1.461		
Comenine 2012	0.170000	07 0 1404	0000	4 704	1 44 14 05 4 901		
Garassino 2013	0.34358	0.148	0420	9.170	1.41 [1.05, 1.89]		
Gregorc 2014	0.23901	0.1256	3176	4.9%	1.27 [0.99, 1.62]		
Kawaguchi 2014	0.198850	86 0.1195	6993	4.9%	1.22 [0.97, 1.54]	-	
Rosell 2012	-0.994252	27 0.1964	15618	4.2%	0.37 [0.25, 0.54]		
Subtotal (95% CI)				23.6%	1.02 [0.72, 1.44]	-	
Heterogeneity: Tau ² =	0.14; Chi ² = 36.03	df = 4 (P	< 0.00	(001); I ² =	89%		
Test for overall effect:	Z = 0.09 (P = 0.92)					
1.1.4 erlotinib vs pac	litaxel						
Lilenbaum 2008	0.371563	56 0.2004	2616	4.1%	1.45 [0.98, 2.15]		
Subtotal (95% CI)				4.1%	1 45 10 98 2 151		
and the second					then format mital		
Heterogeneity: Not app	plicable						
Heterogeneity: Not app Test for overall effect:	plicable Z = 1.85 (P = 0.06)					
Heterogeneity: Not app Test for overall effect: . Total (95% CI)	plicable Z = 1.85 (P = 0.06)		100.0%	0.78 [0.66, 0.92]	•	
Heterogeneity: Not app Test for overall effect: . Total (95% CI) Heterogeneity: Tau? =	2 = 1.85 (P = 0.06 0.13: Chi ² = 260.1) 9. df = 20.	(P < 0	100.0% 00001): P	0.78 [0.66, 0.92]	•	
Heterogeneity: Not app Test for overall effect: . Total (95% CI) Heterogeneity: Tau ² =	plicable Z = 1.85 (P = 0.06 0.13; Chi ² = 269.1 Z = 3.03 (P = 0.07) 9. df = 20	(P < 0.	100.0% 00001); P	0.78 [0.66, 0.92]	02 0.5 1 2	
Heterogeneity: Not app Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for subgroup diffe	plicable Z = 1.85 (P = 0.06 0.13; Chi ² = 269.1 Z = 3.03 (P = 0.00 prences: Chi ² = 25) 9, df = 20 2) 53. df = 3	(P < 0.	100.0% 00001); P	0.78 [0.66, 0.92] = 93% = 88.2%	0.2 0.5 1 2 Favours EGFR-TKI Favours Taxa	anes
Heterogeneity: Not app Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect. Test for subgroup diffe	plicable Z = 1.85 (P = 0.06 0.13; Chi ² = 269.1 Z = 3.03 (P = 0.00 mences: Chi ² = 25 Experimental) 9, df = 20 2) 53. df = 3 Contro	(P < 0. (P < 0.	100.0% 00001); P 0001); P =	0.78 [0.66, 0.92] = 93% = 88.2% Risk Ratio	0.2 0.5 1 2 Favours EGFR-TKI Favours Taxa Risk Ratio	anes
Heterogeneity: Not app Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for suboroup diffe Study or Subgroup	Dicable Z = 1.85 (P = 0.06 0.13; Chi ² = 269.1 Z = 3.03 (P = 0.00 rences: Chi ² = 25 Experimental Events Total) 9, df = 20 2) 53. df = 3 Contro Events	(P < 0. (P < 0. ol Total	100.0% 00001); P 0001), P Weight	0.78 [0.66, 0.92] = 93% - 88.2% Risk Ratio M-H. Random, 95% C	0.2 0.5 1 2 Favours EGFR-TKI Favours Taxa Risk Ratio M-H. Random. 95% CI	anes
Heterogeneity: Not app Test for overall effect. Total (95% CI) Heterogeneity: Tau ² = Test for overall effect. Test for subaroup diffe Study or Subgroup 1.7.1 6-month PFS su	Dicable Z = 1.85 (P = 0.06 0.13; Chi ² = 269.1 Z = 3.03 (P = 0.00 rences: Chi ² = 25 Experimental Events Total rvival rate) 9, df = 20 2) 53. df = 3 Contro Events	(P < 0) (P < 0) ol Total	100.0% 00001); P 0001): P = Weight	0.78 [0.66, 0.92] = 93% BR 2% Risk Ratio M-H, Random, 95% C	0.2 0.5 1 2 Favours EGFR-TKI Favours Taxa Risk Ratio M-H, Random, 95% CI	anes
Heterogeneity: Not app Test for overall effect: . Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for suboroup diffe Study or Subgroup 1.7.1 6-month PFS su Garassino 2013	Dicable Z = 1.85 (P = 0.06 0.13; Chi ² = 269.1 Z = 3.03 (P = 0.00 rences: Chi ² = 25 Experimental Events Total Irvival rate 18 109) 9, df = 20 2) 53. df = 3 Contro Events 30	(P < 0. (P < 0.) I <u>Total</u> 110	100.0% 00001); P 0001). P = Weight 11.4%	0.78 [0.66, 0.92] = 93% 88.2% Risk Ratio <u>M-H. Random. 95% C</u> 0.61 [0.36, 1.02]	0.2 0.5 1 2 Favours EGFR-TKI Favours Taxa Risk Ratio M-H, Random, 95% Cl	anes
Heterogeneity: Not app Test for overall effect: . Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for subdroun diffe Study or Subgroup 1.7.1 6-month PFS su Garassino 2013 Kim 2008	Dicable Z = 1.85 (P = 0.06 0.13; Chi ² = 269.1 Z = 3.03 (P = 0.00 rences: Chi ² = 25 Experimental Events Total rivival rate 18 109 125 659) 9, df = 20 2) 53. df = 3 Contro Events 30 118	(P < 0. (P < 0.)I Total 110 657	100.0% 00001): P 00011. P Weight 11.4% 12.3%	0.78 [0.66, 0.92] = 93% = 88.2% Risk Ratio M-H. Random, 95% C 0.61 [0.36, 1.02] 1.06 [0.84, 1.33]	0.2 0.5 1 2 Favours EGFR-TKI Favours Taxa Risk Ratio M-H. Random. 95% Cl	anes
Heterogeneity: Not app Test for overall effect: . Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: . Test for subgroup 1.7.1 6-month PFS su Garassino 2013 Kim 2008 Lee 2010	Dicable Z = 1.85 (P = 0.06 0.13; Chi ² = 269.1 Z = 3.03 (P = 0.00 rences: Chi ² = 25 Experimental Events Total Invival rate 18 109 125 659 26 82	9, df = 20 (2) 53. df = 3 (Contro Events 30 118 10	(P < 0. (P < 0.)I Total 110 657 79	100.0% 00001); I ² 0001). I ² = Weight 11.4% 12.3% 10.8%	0.78 [0.66, 0.92] = 93% 88.2% Risk Ratio M-H. Random. 95% C 0.61 [0.36, 1.02] 1.06 [0.84, 1.33] 2.50 [1.26, 4.85]	0.2 0.5 1 2 Favours EGFR-TKI Favours Taxa Risk Ratio I M-H. Random, 95% CI	anes
Heterogeneity: Not app Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for subgroup 1.7.1 6-month PFS su Garassino 2013 Kim 2008 Lee 2010 Moritrea 2010	Dicable Z = 1.85 (P = 0.06 0.13; Chi ^p = 269.1 Z = 3.03 (P = 0.00 rences: Chi ^p = 25 Experimental Events Total rivival rate 18 109 125 659 26 622 1 42	9, df = 20 2) 53. df = 3 Contro Events 30 118 10 7	(P < 0. (P < 0.)I Total 110 657 79 41	100.0% 00001); I ² 00011. I ² = Weight 11.4% 12.3% 10.8%	0.78 [0.66, 0.92] = 93% BB 2% Risk Ratio M-H. Random. 95% C 0.61 [0.36, 1.02] 1.06 [0.84, 1.33] 2.50 [1.29, 4.85] 0.14 [0.02, 1.09]	0.2 0.5 1 2 Favours EGFR-TKI Favours Taxa Risk Ratio M-H. Random, 95% Cl	anes
Heterogeneity: Not apy Test for overall effect: . Total (95% CI) Heterogeneity: Tau? = Fast for overall effect: . Test for subaroun diffe Study or Subgroup 	Dicable Z = 1.85 (P = 0.06 0.13; Chi ² = 269, 1 Z = 3.03 (P = 0.00 rences: Chi ² = 25 Experimental Events Total rivial rate 18 109 125 659 26 62 1 43 0 4 100	9, df = 20 2) 53. df = 3 Contro Events 30 118 10 7	(P < 0. (P < 0. I I I I I I 657 79 41	100.0% 00001); i ² 00011. i ² = Weight 11.4% 12.3% 10.8% 4.9%	0.78 [0.66, 0.92] = 93% Risk Ratio M-H. Random, 95% C 0.61 [0.36, 1.02] 1.06 [0.84, 1.33] 2.50 [1.29, 4.85] 0.14 [0.02, 1.06] 0.98 [0.27, 1.07]	0.2 0.5 1 2 Favours EGFR-TKI Favours Taxa Risk Ratio I M-H. Random, 95% CI	anes
Heterogeneity: Not apy Test for overail effect: . Total (95% CI) Heterogeneity: Tau ² = Test for overail effect: . Test for subaroun diffe Study or Subgroup I.7.1 6-month PFS su Garassino 2013 Kim 2008 .ee 2010 Morèrea 2010 Yi-Long WU 2012 Exelected (75 C C)	Dicable Z = 1.85 (P = 0.06 0.13; Chi ² = 269, 1 Z = 3.03 (P = 0.00 rences: Chi ² = 26 Experimental Events Total rivival rate 18 109 125 659 26 62 1 43 94 184	9, df = 20 2) 53. df = 3 Contro Events 30 118 10 7 109	(P < 0. (P < 0.)1 110 657 79 41 188 1025	100.0% 00001); P 00011; P 00001; P 0000; P 0000; P 0000; P 0000; P 0000; P 0000; P 000; P 00; P 0; P	0.78 [0.66, 0.92] = 93% BB 2% Risk Ratio M-H. Random. 95% C 0.61 [0.36, 1.02] 1.06 [0.84, 1.33] 2.50 [1.24, 8.65] 0.14 [0.02, 1.06] 0.88 [0.73, 1.06]	0.2 0.5 1 2 Favours EGFR-TKI Favours Taxi Risk Ratio M-H. Random, 95% CI	anes
Heterogeneity: Not apy Test for overall effect: . Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: . Fest for suberoun diffe Study or Subbroup 1.7.1 6-month PFS su Garassino 2013 Kim 2008 Lee 2010 Morèrea 2010 Yi-Long WU 2012 Subtotal (95% CI)	plicable Z = 1.85 (P = 0.06 0.13; Chi ² = 269; 1 Z = 3.03 (P = 0.00 rennes: Chi ² = 25 Experimental Events Total rivival rate 18 109 125 659 26 82 1 43 94 184 1077 201	9, df = 20 2) 53. df = 3 Contro Events 30 118 10 7 109	(P < 0. (P < 0.)1 110 657 79 41 188 1075	100.0% 00001); i* 00011; i* Weight 11.4% 12.3% 10.8% 4.9% 12.4% 51.8%	0.78 [0.66, 0.92] = 03% BB 2% Risk Ratio M-H, Random, 95% C 0.61 [0.36, 1.02] 1.06 [0.84, 1.33] 2.50 [1.29, 4.85] 0.14 [0.02, 1.06] 0.88 [0.73, 1.06] 0.97 [0.67, 1.39]	0.2 0.5 1 2 Favours EGFR-TKI Favours Taxa Risk Ratio M-H. Random, 95% Cl	anes
Heterogeneity: Not apy Test for overail effect: Total (95% CI) Heterogeneity: Tau ² = Test for overail effect: Test for suboroup diffe Study or Suboroup diffe Study or Suboroup Otto Garrassino 2013 Kim 2008 Lee 2010 Morierea 2010 Yi-Long WU 2012 Subtotal (95% CI) Total events	plicable Z = 1.85 (P = 0.06 0.13; Chi ² = 269.1 Z = 3.03 (P = 0.00 rences: Chi ² = 25 Experimental Events Total rvival rate 18 109 125 659 26 82 1 43 94 184 107 264	9, df = 20 2) 53. df = 3 Contro Events 30 118 10 7 109 274	(P < 0. (P < 0.) 110 657 79 41 188 1075	100.0% 00001); P 00011; P 11.4% 12.3% 10.8% 4.9% 12.4% 51.8%	0.78 [0.66, 0.92] = 93% 88.2% Risk Ratio M-H. Random. 95% C 0.61 [0.36, 1.02] 1.06 [0.84, 1.33] 2.50 [1.29, 4.85] 0.14 [0.02, 1.06] 0.88 [0.73, 1.06] 0.97 [0.67, 1.39]	0.2 0.5 1 2 Favours EGFR-TKI Favours Taxa Risk Ratio M-H, Random, 95% CI	anes
Heterogeneity: Not apy Test for overail effect: . Total (95% CI) Heterogeneity: Tau ² = Test for overail effect: . Test for suboroup diffe Study or Subgroup arrassino 2013 Kim 2008 Lee 2010 Morèrea 2010 Worèrea 2010 Vi-Long WU 2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overail effect: .	Dicable Z = 1.85 (P = 0.06 0.13; Chi ² = 269.1 Z = 3.03 (P = 0.00 rences: Chi ² = 25 Experimental Events: Total rivival rate 18 109 125 659 26 62 1 43 94 184 184 00 10, Chi ² = 16.12 2 - 0.18 (P = 0.86	9, df = 20 2) 53, df = 3 Contro Events 30 118 10 7 109 274 df = 4 (P	(P < 0. (P < 0.) 110 657 79 41 188 1075 = 0.003	100.0% 00001); I ² 00011; I ² = <u>Weight</u> 11.4% 12.3% 10.8% 4.9% 12.4% 51.8%	0.78 [0.66, 0.92] = 93% 88.2% Risk Ratio M-H. Random. 95% C 0.61 [0.36, 1.02] 1.06 [0.84, 1.33] 2.50 [1.29, 4.85] 0.14 [0.02, 1.06] 0.88 [0.73, 1.06] 0.97 [0.67, 1.39]	0.2 0.5 1 2 Favours EGFR-TKI Favours Taxa Risk Ratio M-H. Random. 95% CI	anes
Heterogeneity: Not apy Test for overail effect: Total (95% CI) Heterogeneity: Tau ² = Test for overail effect: Test for subaroup diffe Study or Subgroup 1.7.1 6-month PFS su Garassino 2013 Kim 2008 Lee 2010 Morèrea 2010 Yi-Long WU 2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overail effect: 1.7.2 1-year PES event	plicable Z = 1.85 (P = 0.06 0.13; Chi ² = 269.1 Z = 3.03 (P = 0.00 rences: Chi ² = 25 Experimental Events Total rvival rate 18 109 125 659 26 82 1 43 94 184 194 184 107 264 0.10; Chi ² = 16.12 Z = 0.18 (P = 0.86 ival rate) 9, df = 20 2) 53. df = 3 Contro Events 30 118 10 7 109 274 df = 4 (P	(P < 0. (P < 0.) 110 657 79 41 188 1075 = 0.002	100.0% 00001); I ² 00011; I ² = <u>Weight</u> 11.4% 12.3% 10.8% 12.4% 51.8%	0.78 [0.66, 0.92] = 93% 88.2% Risk Ratio M-H. Random. 95% C 0.61 [0.36, 1.02] 1.06 [0.84, 3.33] 2.50 [1.04, 4.03] 0.44 [0.02, 1.06] 0.88 [0.73, 1.06] 0.97 [0.67, 1.39]	0.2 0.5 1 2 Favours EGFR-TKI Favours Taxa Risk Ratio M-H. Random, 95% CI	anes
Heterogeneity: Not app Test for overall effect: : Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for subaroun diffe Study or Subgroup 17.7 16 -month PFS su Garassino 2013 Kim 2008 Lee 2010 Morèrea 2010 Yi-Long WU 2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: : 17.7 1-year PFS surv memo 2015	Dicable Z = 1.85 (P = 0.06 0.13; Chi ² = 269, 1 Z = 3.03 (P = 0.00 remose: Chi ² = 25 Experimental rivival rate 18 109 125 659 26 82 1 43 94 184 1077 264 0.10; Chi ² = 16, 12 Z = 0, 18 (P = 0.86 rivial rate 50 100 100 100 100 100 100 100 100 100 1	9, df = 20 2) 53, df = 3 Contro Events 30 118 10 7 109 274 df = 4 (P	(P < 0. (P < 0. 110 657 79 41 188 1075 = 0.003	100.0% 00001); I ² 00011; I ² 11.4% 12.3% 10.8% 4.9% 12.4% 51.8% 3); I ² = 759	0.78 [0.66, 0.92] = 93% BB 2% Risk Ratio M-H. Random .95% C 0.61 [0.36, 1.02] 1.06 [0.84, 1.33] 2.50 [1.29, 4.85] 0.14 [0.02, 1.06] 0.88 [0.73, 1.06] 0.97 [0.67, 1.39]	0.2 0.5 1 2 Favours EGFR-TKI Favours Taxa Risk Ratio M-H. Random, 95% Cl	anes
Heterogeneity: Not apy Test for overail effect: Total (95% CI) Heterogeneity: Tau ² = Test for overail effect: Test for subaroup diffe Study or Subgroup 1.7.1 6-month PFS su Garassino 2013 Kim 2008 Lee 2010 Morèrea 2010 Yi-Long WU 2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overail effect: 1.7.2 1-year PFS surv Inoue 2012	Dicable Z = 1.85 (P = 0.06 0.13; Chi ² = 269.1 Z = 3.03 (P = 0.00 rennes: Chi ² = 25 Experimental Events Total rivial rate 18 109 125 659 26 82 1 43 94 184 1077 264 10.0; Chi ² = 16.12 Z = 0.18 (P = 0.86 ival rate 50 114	9, df = 20 2) 53. df = 3 Contro Events 30 118 10 7 109 274 df = 4 (P	(P < 0) (P < 0	100.0% 00001); P 00011; P 11.4% 12.3% 10.8% 4.9% 51.8% 3); P = 759 9.7%	0.78 [0.66, 0.92] = 93% Risk Ratio M-H. Random. 95% C 0.61 [0.36, 1.02] 1.06 [0.84, 1.33] 2.50 [129, 4.85] 0.14 [0.02, 1.06] 0.88 [0.73, 1.06] 0.97 [0.67, 1.39] %	0.2 0.5 1 2 Favours EGFR-TKI Favours Taxa Risk Ratio M-H. Random, 95% Cl	anes
Heterogeneity: Not apy Test for overall effect: . Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Trest for subdroun diffe Study or Subgroup 1.7.1 6-month PFS su Garassino 2013 Kim 2008 Lee 2010 Moritrea 2010 Yi-Long WU 2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: . 1.7.2 1-year PFS surv Inoue 2012 Maemondo 2010	Dicable Z = 1.85 (P = 0.06 0.13; Chi ² = 269, 1 Z = 3.03 (P = 0.00 rences: Chi ² = 269, 1 Experimental Events Total rvival rate 18 109 125 659 26 82 1 43 94 184 107 264 2 1 43 94 184 107 264 2 0.18 (P = 0.86 ival rate 50 114 48 114	9, df = 20 2) 53. df = 3 Contro Events 30 118 10 7 109 274 df = 4 (P 5 4	(P < 0. (P < 0.) 110 657 79 41 188 1075 = 0.002 114 114	100.0% 00001); P 00011; P 11.4% 12.3% 10.8% 4.9% 12.4% 51.8% 3); P = 759 9.7% 9.2%	0.78 [0.66, 0.92] = 93% = 88.2% Risk Ratio M-H. Random .95% C 0.61 [0.36, 1.02] 1.06 [0.44, 1.33] 2.50 [1.29, 4.65] 0.14 [0.02, 1.06] 0.88 [0.73, 1.06] 0.97 [0.67, 1.39] %	0.2 0.5 1 2 Favours EGFR-TKI Favours Taxa Risk Ratio M-H. Random, 95% Cl	anes
Heterogeneity: Not apy Test for overall effect: . Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: . Test for subaroun diffe Study of Subgroup 1.7.1 6-month PFS su Garassino 2013 Kim 2008 Lee 2010 Morèrea 2010 Yi-Long WU 2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: . 1.7.2 1-year PFS surv inoue 2012 Maemondo 2010 Mok 2009	$\begin{array}{l} \text{plicable} \\ \text{Z} = 1.85 \ (\text{P} = 0.06 \\ \text{0.13}, \ \text{Chi}^{\text{P}} = 269, 1 \\ \text{Z} = 3.03 \ (\text{P} = 0.00 \\ \text{remces}, \ \text{Chi}^{\text{P}} = 25, \\ \text{Experimental} \\ \text{Events}, \ \text{Total} \\ \text{rvival rate} \\ 18 109 \\ 125 659 \\ 26 82 \\ 1 43 \\ 94 184 \\ 1077 \\ 264 \\ 0.10, \ \text{Chi}^{\text{P}} = 16, 12 \\ \text{Z} = 0.18 \ (\text{P} = 0.86 \\ \text{ival rate} \\ 50 114 \\ 48 114 \\ 152 669 \end{array}$	9, df = 20 2) 53, df = 3 Contro Events 30 118 10 7 109 274 df = 4 (P 5 4 4	(P < 0. (P < 0. 10 110 657 79 41 1075 = 0.003 114 114 608	100.0% 00001); i ² 00011; i ² 11.4% 12.3% 10.8% 4.9% 12.4% 51.8% 3); i ² = 759 9.7% 9.2% 12.1%	0.78 [0.66, 0.92] = 93% Risk Ratio M-H. Random. 95% C 0.61 [0.36, 1.02] 1.06 [0.84, 1.33] 2.50 [124, 8.55] 0.14 [0.02, 1.06] 0.88 [0.73, 1.06] 0.88 [0.73, 1.06] 0.97 [0.67, 1.39] %	0.2 0.5 2 Favours EGFR-TKI Favours Taxa Risk Ratio M-H. Random. 95% Cl	anes
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Heterogeneity: Not apy Test for overall effect: Total (95% CI) Heterogeneity: Tau ² = Test for overall effect: Test for overall effect: Test for suboroup diffe Study or Subgroup 1.7.1 6-month PFS sup Garassino 2013 Kim 2008 Lee 2010 Morierea 2010 Yi-Long WU 2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 2 1.7.2 1-year PFS surv Incue 2012 Maemondo 2010 Mok 2009 Morierea 2010 Yi-Long WU 2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 2 1.7.3 2-yesr PFS surv Maemondo 2010 Subtotal (95% CI) Total events	$\begin{array}{c} \text{plicable} \\ \text{Z} = 1.85 \ (\text{P} = 0.06 \\ \text{0.13; } \text{Ch}^{\text{P}} = 269.1 \\ \text{Z} = 3.03 \ (\text{P} = 0.06 \\ \text{rences: } \text{Ch}^{\text{P}} = 258 \\ \text{Experimental} \\ \text{Events} \text{Total} \\ \text{revents} \text{Total} \\ \text{18} 109 \\ 125 659 \\ 26 82 \\ 1 43 \\ 94 184 \\ 1077 \\ 264 \\ 1077 \\ 1077 \\ 264 \\ 1077 \\ 1077 \\ 264 \\ 1077 \\ 264 \\ 1077 \\ 10$	9, df = 20 2) 53, df = 3 Contro Events 30 118 10 7 109 274 df = 4 (P 4 4 1 15 66 df = 4 (P 001) 0 0 0	(P < 0) (P < 0) 100 657 79 118 1075 = 0.000 114 114 1065 = 0.02 114 114	100.0% 00001); P 00011; P 11.4% 12.3% 10.8% 10.8% 12.4% 51.8% 3); P = 759 9.7% 9.7% 12.1% 12.1% 12.1% 12.1% 12.1% 12.1% 12.1% 12.1% 2.7% 12.1% 12.1% 2.7% 12.1% 2.7% 12.1% 2.3% 3.2% 3.2%	0.78 [0.66, 0.92] = 93% Risk Ratio M-H. Random. 95% C 0.61 [0.36, 1.02] 1.06 [0.84, 1.33] 2.50 [129, 4.85] 0.14 [0.02, 1.06] 0.88 [0.73, 1.06] 0.88 [0.73, 1.06] 0.97 [0.67, 1.39] % 10.00 [4.14, 24, 15] 12.00 [4.7, 32.18] 3.70 [2.67, 5.13] 0.32 [0.19, 5.63] 4.97 [2.75, 8.98] 19.00 [1.12, 322.62]	0.2 0.5 2 Favours EGFR-TKI Favours Taxa Risk Ratio M-H. Random. 95% Cl	anes
Heterogeneity: Not apy Test for overail effect: Total (95% CI) Heterogeneity: Tau ² = Test for overail effect: Test for subdroup diffe Study or Subgroup 1.7.1 6-month PFS sup Garassino 2013 Kim 2008 Lee 2010 Moritrea 2010 Yi-Long WU 2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overail effect: : Maemondo 2010 Mok 2009 Moritrea 2010 Yi-Long WU 2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overail effect: : 1.7.3 2-yesr PFS surv Maemondo 2010 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Total events Heterogeneity: Tau ² = Total events Heterogeneity: Tau ² = Total events Heterogeneity: Not apy	plicable Z = 1.85 (P = 0.06 0.13; Chi ² = 269, 1 Z = 3.03 (P = 0.06 Experimental Events Total rvival rate 18 109 125 659 26 62 1 43 94 184 1077 264 0.0; Chi ² = 16.12 Z = 0.18 (P = 0.86 1077 264 0.0; Chi ² = 16.12 Z = 0.18 (P = 0.86 114 152 609 0 43 48 114 152 609 0 43 48 104 298 0.26; Chi ² = 12.34 Z = 5.32 (P < 0.00 rival rate 9 114 114 9) 9. df = 20 2) 53. df = 3 Controc Events 30 118 10 7 109 274 df = 4 (P 4 4 1 1 5 df = 4 (P 4 4 1 1 5 df = 4 (P 0 0 0 0 0 0 0 0 0 0 0 0 0	(P < 0) (P < 0) 100 110 657 79 41 188 1075 = 0.00: 114 118 1065 = 0.02; 114 114 114	100.0% 00001); * 00011, * = Weight 11.4% 12.3% 10.8% 4.9% 12.4% 51.8% 3; * = 75? 9.7% 9.2% 12.1% 11.3% 45.0%); * = 68% 3.2% 3.2%	0.78 [0.66, 0.92] = 93% Risk Ratio M-H. Random, 95% C 0.61 [0.36, 1.02] 1.06 [0.84, 1.33] 2.50 [129, 4.85] 0.41 [0.02, 1.06] 0.88 [0.73, 1.06] 0.97 [0.67, 1.39] % 10.00 [4.14, 24, 15] 12.00 [4.7, 32, 18] 3.70 [2.67, 513] 0.32 [0.01, 7.59] 3.27 [1.90, 5.63] 4.97 [2.75, 8.98] 19.00 [1.12, 322,62] 19.00 [1.12, 322,62]	0.2 0.5 1 2 Favours EGFR-TKI Favours Taxa Risk Ratio M-H. Random, 95% Cl	anes
Heterogeneity: Not apy Test for overail effect: Total (95% CI) Heterogeneity: Tau ² = Test for overail effect: Test for subaroun diffe Study or Subgroup 1.7.1 6-month PFS sup Garrassino 2013 Kim 2008 Lee 2010 Moritrea 2010 Yi-Long WU 2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overail effect: 1 Naciona 2012 Maemondo 2010 Mok 2009 Moritrea 2010 Yi-Long WU 2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overail effect: 1 1.7.3 2-yesr PFS surv Maemondo 2010 Subtotal (95% CI) Total events Heterogeneity: Not app Test for overail effect: 1	$\begin{array}{l} \text{plicable} \\ \text{Z} = 1.85 \ (\text{P} = 0.06 \\ \text{0.13; } \text{Ch}^{\text{P}} = 269, 1 \\ \text{Z} = 3.03 \ (\text{P} = 0.06 \\ \text{erences: Chi^{\text{P}}} = 269, 1 \\ \text{Z} = 3.03 \ (\text{P} = 0.06 \\ \text{erences: Chi^{\text{P}}} = 16, 10 \\ \text{125} \ 659 \\ 26 \ 62 \\ 1 \ 43 \\ 94 \ 184 \\ 1077 \\ 264 \\ 1077 \\ 107 \\ $) 9. df = 20 2) 53. df = 3 Contro Events 30 118 10 7 109 274 df = 4 (P 5 4 4 1 1 5 df = 4 (P 0 0 0 0 0 0	(P < 0) (P < 0) 110 657 79 41 188 1075 = 0.000 114 114 1065 = 0.022 114 114	100.0% 00001); ² 00011; ² 11.4% 12.3% 10.8% 4.9% 12.4% 51.8% 3; ² = 75? 9.7% 9.2% 12.1% 12.3% 12.3% 13.% 2.7% 11.3% 45.0%); ² = 68% 3.2% 3.2%	0.78 [0.66, 0.92] = 93% Risk Ratio M-H. Random .95% C 0.61 [0.36, 1.02] 1.06 [0.44, 1.33] 2.50 [1.29, 4.65] 0.14 [0.02, 1.06] 0.88 [0.73, 1.06] 0.97 [0.67, 1.39] % 10.00 [4.14, 24, 15] 12.00 [4.47, 32, 18] 3.70 [2.67, 5.13] 0.22 [0.01, 7.59] 3.27 [1.90, 5.63] 4.97 [2.75, 8.98] 19.00 [1.12, 322.62]	0.2 0.5 1 2 Favours EGFR-TKI Favours Taxa Risk Ratio M-H. Random, 95% Cl	anes
Heterogeneity: Not apy Test for overail effect: . Total (95% CI) Heterogeneity: Tau ² = Test for overail effect: Test for subaroun diffe Study or Subgroup 1.7.1 6-month PFS su Garassino 2013 Kim 2008 Lee 2010 Moritrea 2010 Yi-Long WU 2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overail effect: . 1.7.2 1-year PFS surv Inoue 2012 Makemondo 2010 Mok 2009 Moritrea 2010 Yi-Long WU 2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overail effect: . 1.7.3 2-year PFS surv Inoue 2010 Yi-Long WU 2012 Subtotal (95% CI) Total events Heterogeneity: Not app Test for overail effect: . Total (95% CI)	$\begin{array}{l} \text{plicable} \\ \text{Z} = 1.85 \ (\text{P} = 0.06 \\ \text{U} = 3.03 \ (\text{P} = 0.06 \\ \text{removes: } Chi^2 = 255 \\ \text{Experimental} \\ \text{revival rate} \\ 18 \ 109 \\ 125 \ 659 \\ 26 \ 82 \\ 1 \ 43 \\ 94 \ 184 \\ 1077 \\ 264 \\ 0.10; \ Chi^2 = 16.12 \\ \text{Z} = 0.18 \ (\text{P} = 0.86 \\ 1017 \\ 264 \\ 102 \\ \text{Z} = 0.18 \ (\text{P} = 0.86 \\ 104 \\ 105 \\ 103 \\ 48 \ 184 \\ 106 \\ 286 \\ 0.26; \ Chi^2 = 12.34 \\ 114 \\ 9 \\ 114 \\ 114 \\ 9 \\ 0lcable \\ \text{Z} = 2.04 \ (\text{P} = 0.04 \\ 2255 \\ \end{array}$	9, df = 20 2) 53, df = 3 Contro Events 30 118 109 274 df = 4 (P 5 4 41 15 66 df = 4 (P 001) 0 0	(P < 0) (P < 0) Total 110 657 79 41 188 1075 = 0.002 114 118 1065 = 0.022 114 114 114 114	100.0% 00001); P 00011; P 11.4% 12.4% 12.4% 12.4% 12.4% 3); P = 759 9.7% 9.7% 9.2% 12.1% 2.7% 11.3% 45.0% ; P = 68% 3.2% 100.0%	0.78 [0.66, 0.92] = 03% BR 2% Risk Ratio M.H. Random .95% C 0.61 [0.36, 102] 1.06 [0.84, 1.33] 2.50 [1.29, 4.85] 0.14 [0.02, 1.06] 0.88 [0.73, 1.06] 0.97 [0.67, 1.39] % 10.00 [4.14, 24, 15] 12.00 [4.47, 32, 18] 3.70 [2.67, 5.13] 0.32 [0.10, 5.63] 4.97 [2.75, 8.98] 19.00 [1.12, 322.62] 2.10 [1.17, 3.77]	0.2 0.5 2 Favours EGFR-TKI Favours Taxa Risk Ratio M-H. Random, 95% Cl	anes
Heterogeneity: Not apy Test for overall effect: : Total (95% CI) Test for suboroup diffe Eest for overall effect: : Test for suboroup diffe Study or Subgroup I.7.1 6-month PFS sup Garrassino 2013 Kim 2008 Lee 2010 Morèrea 2010 Worèrea 2010 Worèrea 2010 Vi-Long WU 2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: : I.7.2 1-year PFS surv Maemondo 2010 Wok 2009 Morèrea 2010 Ci-Long WU 2012 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: : I.7.3 2-yesr PFS surv Maemondo 2010 Subtotal (95% CI) Total events Heterogeneity: Not app Test for overall effect: : Total (95% CI) Total events	$\begin{array}{c} \text{plicable} \\ \text{Z} = 1.85 \ (\text{P} = 0.06 \\ \text{0.13; } \text{Ch}^{\text{P}} = 269, 1 \\ \text{Z} = 3.03 \ (\text{P} = 0.06 \\ \text{rences: Ch}^{\text{P}} = 269, 1 \\ \text{Z} = 3.03 \ (\text{P} = 0.06 \\ \text{rences: Ch}^{\text{P}} = 269, 1 \\ \text{R} = 100 \\ \text{rences: Ch}^{\text{P}} = 26, 1 \\ \text{R} = 100 \\ 125 \ 659 \\ 26 \ 82 \\ 1 \ 43 \\ 94 \ 184 \\ 107 \\ 264 \\ 1077 \\ 264 \\ 275 \\ 100$	9, df = 20 2) 53, df = 3 Contro Events 30 118 10 7 109 274 df = 4 (P 4 4 1 1 5 df = 4 (P 0 0 0 0 0 0 0	(P < 0) (P < 0) 110 657 79 41 188 1075 = 0.002 114 118 1065 = 0.022 114 114 114 2254	100.0% 100.0% 10001); i ² 00011; i ² 11.4% 12.3% 10.8% 4.9% 12.4% 51.8% 3; i ² = 75% 9.2% 12.1% 11.3% 45.0% 1; i ² = 68% 3.2% 3.2% 100.0%	0.78 [0.66, 0.92] = 93% Risk Ratio M-H. Random. 95% C 0.61 [0.36, 1.02] 1.06 [0.84, 1.33] 2.50 [129, 4.85] 0.14 [0.02, 1.06] 0.88 [0.73, 1.06] 0.88 [0.73, 1.06] 0.97 [0.67, 1.39] % 10.00 [4.14, 24.15] 12.00 [4.7, 32.18] 3.70 [2.67, 5.13] 0.32 [0.01, 7.59] 3.27 [1.90, 5.63] 4.97 [2.75, 8.98] 19.00 [1.12, 322.62] 19.00 [1.12, 322.62]	0.2 0.5 2 Favours EGFR-TKI Favours Taxa Risk Ratio M-H, Random, 95% Cl	anes

Figure 2. Forest plot of comparison for PFS (A) and PFSR (B) between EGFR-TKIs and taxanes in NSCLC. EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor, NSCLC = nonsmall-cell lung cancer, PFS = progression-free survival, PFSR = progression-free survival rate.

3.4. Subgroup analyses and meta-regression

Table 3 presented a summary of subgroup meta-analyses and meta-regression performed. EGFR status, platinum in control arm, clinical phase of trials, and trial design may have resulted in significant and substantial heterogeneity in our analysis; therefore, the study can be divided into 4 subgroups.

PFS: the 1st subgroup was performed on EGFR status, which result showed that comparing taxanes, EGFR-TKIs can significantly prolong PFS in patients with EGFR mutation (HR = 0.57,

95% CI: 0.43–0.76), EGFR mutation-positive (HR = 0.42, 95% CI: 0.27–0.65), and unknown EGFR mutation (HR = 0.68, 95% CI: 0.58–0.80). But EGFR-TKIs were inferior to taxanes in EGFR wild-type patients (HR = 1.32, 95% CI: 1.11–1.57) and EGFR mutation-negative (HR = 1.59, 95% CI: 0.50–5.02). There was no significant difference in EGFR copy number and EGFR protein expression. The 2nd subgroup grouped by platinum in control arm, the results demonstrated that EGFR-TKIs had an advantage over taxanes plus platinum (HR = 0.42,

	log[Haz	ard Ratio]		SE	Weight	IV. Fixed. 95% CI	IV. Fixed. 95% CI
2.1.1 gefitinib vs do	cetaxel					and the second second second	
Cufer 2006	-0	03045921	0.232	90986	1.3%	0.97 [0.61, 1.53]	
Douillard 2010	0	00995033	0.060	30326	19.8%	1.01 [0.90, 1.14]	+
Kim 2008	0	01980263	0.061	11793	19.3%	1.02 10.90 1.151	+
Lee 2010	-0	13926207	0.178	89559	2.3%	0.87 10.61 1.241	
Manuyama 2008	0	11332868	0 115	56277	5.4%	1.12 (0.89, 1.40)	
Mitsudomi 2010	0	40347508	0 300	21878	0.5%	1 64 10 75 3 581	
Mariana 2010	0	49347390	0.399	20022	1 40/	1.04 [0.75, 5.50]	
Morerea 2010	0	3/190390	0.230	39833	1.4%	1.45 [0.92, 2.28]	
Subtotal (95% CI)					50.0%	1.03 [0.36, 1.11]	T
Test for overall effect	z = 5.17, dt = 0.82 (t)	P = 0.52 P = 0.41); 1* = 0	170			
2 1 2 nefitinih vs na	clitavel						
Eukuoka 2011	A	10525052	0.005	10404	17 00/	0.0010 70 1.021	
Pukuuka 2011	~	10000000	0.000	22264	0.50/	0.90 [0.79, 1.02]	
Mak 2000		00431069	0.004	22222	0 10/	0.03 [0.03, 1.24]	
NICK 2009	-0	09431000	0.094	22322	0.176	0.91 [0.76, 1.09]	
Subtotal (95% CI)	-0	08338161	0.120	33533	32.5%	0.92 [0.73, 1.16]	•
Heterogeneity: Chi2 :	= 0.04, df =	3 (P = 1.00): 1 ² = 0	1%		the former and	
Test for overall effect	t: Z = 2.13 (P = 0.03)					
2.1.3 erlotinib vs do	ocetaxel						
Ciuleanu 2012		-0.040822	0,107	75884	6.2%	0.96 (0.78, 1.19)	
Garassino 2013	0	31481074	0 162	39205	27%	1 37 (1 00 1 88)	
Gradore 2013	0	13102826	0.102	33016	4 00/	1 14 (0 88 1 48)	
Gregore 2014	0	00424000	0.134	33910	4.076	0.01 (0.66, 1.46)	
Subtotal (05% Ch	-0	09431068	0.149	1055	16 200	1.05 (0.02 1.22)	-
unitotal (95% CI)	4.07	0.0.000		00/	10.270	1.05 [0.52, 1.20]	
neterogeneity: Chi2	= 4.67, df =	3 (P = 0.20); I= 3	10%			
rest for overall effect	. 2 = 0.76 (= 0.45)					
2.1.4 erlotinib vs pa	clitaxel						
Lilenbaum 2008	0	54812141	0.234	21528	1.3%	1.73 [1.09, 2.74]	
Subtotal (95% CI)					1.3%	1.73 [1.09, 2.74]	
Heterogeneity: Not a	pplicable						
Test for overall effect	L Z = 2.34 (P = 0.02					
							1
Total (95% CI)					100.0%	1.00 [0.95, 1.05]	•
Total (95% CI) Heterogeneity: Chi ² :	= 21.15, df =	15 (P = 0.	13); 2 =	= 29%	100.0%	1.00 [0.95, 1.05]	05 07 1 15 2
Total (95% CI) Heterogeneity: Chi ² Test for overall effect	= 21.15, df = t: Z = 0.06 (15 (P = 0. P = 0.96)	13); l² =	= 29%	100.0%	1.00 [0.95, 1.05]	0.5 0.7 1 1.5 2 Favoure EGER-TKI Favoure Taxanes
Total (95% CI) Heterogeneity: Chi ² Test for overall effect Test for subgroup dif	= 21.15, df = t: Z = 0.06 (ferences: C	15 (P = 0. P = 0.96) hi ² = 11.28	13); l ² =	= 29% (P = 0	100.0%	1.00 [0.95, 1.05]	0.5 0.7 1 1.5 2 Favours EGFR-TKI Favours Taxanes
Total (95% CI) Heterogeneity: Chi ² Test for overall effec Test for suboroup dif	= 21.15, df = t: Z = 0.06 (ferences: C Experime	= 15 (P = 0. P = 0.96) hi ² = 11.28	13); l ² = . df = 3 Control	= 29% (P = 0	100.0% 1011. i ^z = 7	1.00 [0.95, 1.05]	0.5 0.7 1 1.5 2 Favours EGFR-TKI Favours Taxanes
Total (95% CI) Heterogeneity: Chi ² Test for overall effec Test for suboroup dif	= 21.15, df = t: Z = 0.06 (ferences: C Experime Events	= 15 (P = 0. P = 0.96) hi ² = 11.28 ental for the second	13); ² = . df = 3 Control	= 29% (P = 0 I Total	100.0% 1.011. 1² = 7 Weight	1.00 [0.95, 1.05]	0.5 0.7 1 1.5 2 Favours EGFR-TKI Favours Taxanes Risk Ratio M-H. Random, 95% Cl
Total (95% CI) Heterogeneity: Chi ² a Test for overall effect Test for suboroup dif Study or Subgroup 2.6.1.6-month surviv	= 21.15, df = t: Z = 0.06 (ferences: C Experime Events cal rate	= 15 (P = 0. P = 0.96) hi ² = 11.28 ental <u>total Ev</u>	13); ² = . df = 3 Control	= 29% (P = 0 I Total	100.0% 1.01). I ² = 7 <u>Weight</u>	1.00 [0.95, 1.05]	0.5 0.7 1 1.5 2 Favours EGFR-TKI Favours Taxanes Risk Ratio <u>M-H. Random. 95% Cl</u>
Total (95% CI) Heterogeneity: Chi ² Test for overall effect Test for suboroup dif Study or Subgroup 2.6.1 6-month surviv Cutor 2006	= 21.15, df = t: Z = 0.06 (ferences: C Experime Events val rate	15 (P = 0. P = 0.96) hi ² = 11.28 ental Total Ev	13); ² = . df = 3 Control rents 1	= 29% (P = 0 I Total	100.0% 1.01). I ² = 7 <u>Weight 1</u>	1.00 [0.95, 1.05]	0.5 0.7 1 1.5 2 Favours EGFR-TKI Favours Taxanes Risk Ratio M-H. Random, 95% Cl
Total (95% CI) Heterogeneity: Chi ² a Test for overall effect Test for subgroup dif Study or Subgroup 2.6.1 6-month surviv Cufer 2006	= 21.15, df = t: Z = 0.06 (ferences: C Experime Events val rate 45	15 (P = 0. P = 0.96) hi ² = 11.28 ental Total Ev 68	13); l ² = . df = 3 Control rents_1	= 29% (P = 0 I Total 1 73	100.0% 1.01). I ² = 7 <u>Weight 1</u> 7.8%	1.00 [0.95, 1.05] 3.4% Risk Ratio M-H. Random, 95% CI 1.18 [0.90, 1.53] 0.23 (0.92, 0.90)	0.5 0.7 1 1.5 2 Favours EGFR-TKI Favours Taxanes Risk Ratio M-H. Random. 95% Cl
Total (95% CI) Heterogeneity: Chi ² 1 Test for overall effect Test for subaroup dif Study or Subaroup 26.1 6-month surviv Cufer 2006 Morièrea 2010 Subarol (95% CI)	= 21.15, df = t: Z = 0.06 (ferences: C Experime Events val rate 45 5	15 (P = 0. P = 0.96) hi ² = 11.28 ental 6 Total Ev 68 43	13); l ² = df = 3 Control rents 1 41 15	= 29% (P = 0 I Total 1 73 41	100.0% 1.01). I ² = 7 <u>Weight 1</u> 7.8% 1.1%	1.00 [0.95, 1.05] 3.4% Risk Ratio M-H. Random, 95% CI 1.18 [0.90, 1.53] 0.32 [0.13, 0.80] 0.65 [0.17, 2.55]	0.5 0.7 1 1.5 2 Favours EGFR-TKI Favours Taxanes Risk Ratio M-H. Random. 95% Cl
Total (95% CI) Heterogeneity: Chi ² 1 Test for overall effect Test for subaroun dif Study or Subgroup 2.6.1 6-month surviv Cufer 2006 Morierea 2010 Subtotal (95% CI)	= 21.15, df = t: Z = 0.06 (ferences: C Experime Events val rate 45 5	15 (P = 0. P = 0.96) hi ² = 11.28 ental 6 Total Ev 68 43 111	13); l ² = df = 3 Control rents 1 41 15 56	= 29% (P = 0 [[[[[[]]]]]]]]]]]]]	100.0% 1.011. I ² = 7 <u>Weight 1</u> 7.8% 1.1% 8.9%	1.00 [0.95, 1.05] 3.4% Risk Ratio M-H. Random, 95% CI 1.18 [0.90, 1.53] 0.32 [0.13, 0.80] 0.65 [0.17, 2.55]	0.5 0.7 1 1.5 2 Favours EGFR-TKI Favours Taxanes Risk Ratio M-H. Random, 95% Cl
Total (95% CI) Heterogeneity: Chi ² a Test for overall effect Test for subaroun dif Study or Subgroup 2.6.1 6-month surviv Cufer 2006 Morierea 2010 Subtotal (95% CI) Total events	= 21.15, df = t: Z = 0.06 (ferences: C Experime Events ral rate 45 5	ental (P = 0.96) hi ² = 11.28 ental (<u>Total Ev</u> 68 43 111	13); l ² = df = 3 Control rents 1 41 15 56	= 29% (P = 0 [[[[[[]]]]]]]]]]]]]	100.0% 1.011. I ² = 7 Weight I 7.8% 1.1% 8.9%	1.00 [0.95, 1.05] 3.4% Risk Ratio M-H. Random, 95% CI 1.18 [0.90, 1.53] 0.32 [0.13, 0.80] 0.65 [0.17, 2.55]	0.5 0.7 1 1.5 2 Favours EGFR-TKI Favours Taxanes Risk Ratio M-H. Random. 95% Cl
Total (95% CI) Heterogeneity: Chi ² = Test for overall effect Test for subgroup 2.6.1 6-month surviv Cufer 2006 Morèrea 2010 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect	= 21.15, df = t: Z = 0.06 (ferences: C Experime Events val rate 45 5 50 = 0.86; Chi ² : Z = 0.61 (P	$15 (P = 0.96)$ $P = 0.96)$ $h^{p} = 11.28$ $Total = Ev$ 68 43 111 $= 8.21, df = = 0.54)$	13); l ² = df = 3 Control ents 1 41 15 56 1 (P = (= 29% (P = 0 I Total 1 73 41 114 0.004);	100.0% 1.011. I ² = 7 <u>Weight 1</u> 7.8% 1.1% 8.9% I ² = 88%	1.00 [0.95, 1.05] 3.4% Risk Ratio M.H. Random, 95% Cl 1.18 [0.90, 1.53] 0.32 [0.13, 0.80] 0.65 [0.17, 2.55]	0.5 0.7 1 1.5 2 Favours EGFR-TKI Favours Taxanes Risk Ratio M-H. Random. 95% Cl
Total (95% CI) Heterogeneity: Chi ² a Test for overall effect Test for subgroup 2.6.1 6-month surviv Cufer 2006 Morèrea 2010 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 2.6.2 d une survivil	= 21.15, df = t: Z = 0.06 (i ferences: C Experim: Events val rate 45 5 50 c 0.86; Ch ^p : Z = 0.61 (P	15 (P = 0. P = 0.96) hi ² = 11.28 ental 0 Total Ev 68 43 111 = 8.21, df = = 0.54)	13); l ² = df = 3 Control ents 1 41 15 56 1 (P = (= 29% (P = 0 I Total 1 73 41 114 0.004);	100.0% 1.011. I ² = 7 <u>7.8%</u> 1.1% 8.9% I ² = 88%	1.00 [0.95, 1.05] 3.4% Risk Ratio M-H. Random, 95% CI 1.18 [0.90, 1.53] 0.32 [0.13, 0.80] 0.65 [0.17, 2.55]	0.5 0.7 1 1.5 2 Favours EGFR-TKI Favours Taxanes Risk Ratio M-H. Random, 95% Cl
Total (95% CI) Heterogeneity: Chi ^p a Test for overall effect Test for suboroun dif Study or Subproun Cufer 2006 Morierea 2010 Subtotal (95% CI) Total events Heterogeneity: Tau ^p a Test for overall effect 2.6.2 1-year survival	= 21.15, df = t: Z = 0.06 (ferences: C Experime Events val rate 45 5 5 0.86; Chi ² : Z = 0.61 (P rate	15 (P = 0. P = 0.96) hi ² = 11.28 ental Total Ev 68 43 111 = 8.21, df = = 0.54)	13); l ² = df = 3 Control ents 1 41 15 56 1 (P = (= 29% (P = 0 I Total 1 114 0.004);	100.0% .011. I ² = 7 <u>Weight 1</u> 7.8% 1.1% 8.9% I ² = 88%	1.00 [0.95, 1.05] 3.4% Risk Ratio <u>M-H. Random, 95% C1</u> 1.18 [0.90, 1.53] 0.32 [0.13, 0.80] 0.65 [0.17, 2.55]	0.5 0.7 1 1.5 2 Favours EGFR-TKI Favours Taxanes Risk Ratio M-H. Random. 95% Cl
Total (95% CI) Heterogeneity: Chi ² 1 Test for overall effect Test for subaroun dif Study or Subgroup. 2.6.1 6-month survio Cufer 2006 Morèrea 2010 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 2.6.2 1-year survival Fukuoka 2011 Comming Cuip	= 21.15, df = t: Z = 0.06 (ferences: C Experime Events ral rate 45 50 0.86; Chi ² - Z = 0.61 (P rate 400	e 15 (P = 0. P = 0.96) hi ² = 11.28 ental Total Ev 68 43 111 = 8.21, df = = 0.54) 609 400	13); l ² = df = 3 Control ents 1 41 15 56 1 (P = (= 29% (P = 0 (Total 1) 73 41 114 0.004); 608	100.0% 1.011. ² = 7 Weight 1 7.8% 1.1% 8.9% ² = 88% 16.0% 5.2%	1.00 [0.95, 1.05] 3.4% Risk Ratio M-H. Random, 95% CI 1.18 [0.90, 1.53] 0.32 [0.13, 0.80] 0.65 [0.17, 2.55] 1.10 [1.01, 1.20] 0.09 [0.97, 1.15]	0.5 0.7 1 1.5 2 Favours EGFR-TKI Favours Taxanes Risk Ratio M-H. Random, 95% Cl
Total (95% CI) Heterogeneity: Chi ² = Test for overall effect Test for subgroup 2.6.1 6-month surviv Cufer 2006 Morèrea 2010 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 2.6.2 1-year survival Evikuoka 2011 Garassino 2013 Isomo 2013	= 21.15, df = t: Z = 0.06 (ferences: C Experime Events ral rate 45 5 5 0.86; Ch ² Z = 0.61 (P rate 400 35	68 609 609 609 609 100 609 100 609 100 609 100 609 100 609 100 609 100 609 100 609 100 609 100 609 100 609 100 609 100 600 600 600 600 600 600 600	13); l ² = df = 3 Control ents 1 41 15 56 1 (P = (364 44	= 29% (P = 0 I Total 1 114 0.004); 608 110	100.0% .011. I ² = 7 <u>Weight 1</u> 7.8% 1.1% 8.9% I ² = 88% 16.0% 5.3% 5.4%	1.00 [0.95, 1.05] 3.4% Risk Ratio M.H. Random, 95% CI 1.18 [0.90, 1.53] 0.32 [0.13, 0.80] 0.65 [0.17, 2.55] 1.10 [1.01, 1.20] 0.80 [0.56, 1.15] 0.080 [0.56, 1.15]	0.5 0.7 1 1.5 2 Favours EGFR-TKI Favours Taxanes Risk Ratio M-H. Random, 95% CI
Total (95% CI) Heterogeneity: Chi ² a Test for overall effect Test for suboroun dif Study or Suboroun dif Cufer 2006 Morièrea 2010 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 2.6.2 1-year survival Fukuoka 2011 Garassino 2013 Inoue 2012	= 21.15, df = t: Z = 0.06 (ferences: C Experime Val rate 45 5 50 = 0.86; Chi ² + Z = 0.61 (P rate 400 35 97 97	15 (P = 0.96) hi ² = 11.28 ental for Total Ev 68 43 111 = 8.21, df = = 0.54) 609 109 114 200	13); l ² = df = 3 Control ents 1 41 15 56 1 (P = (364 44 99	= 29% (P = 0 I Total 1 114 0.004); 608 110 114	100.0% 1011. ² = 7 Weight 7.8% 1.1% 8.9% ² = 88% 16.0% 5.3% 15.1%	1.00 [0.95, 1.05] 3.4% Risk Ratio M-H. Random, 95% CI 1.18 [0.90, 1.53] 0.32 [0.13, 0.80] 0.65 [0.17, 2.55] 1.10 [1.01, 1.20] 0.80 [0.56, 1.15] 0.88 [0.88, 1.09] 0.98 [0.88, 1.09]	0.5 0.7 1 1.5 2 Favours EGFR-TKI Favours Taxanes Risk Ratio M-H. Random. 95% Cl
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Total (95% CI) Heterogeneity: Chi ² a Test for overall effect Test for suboroup dif Study or Suboroup 2.6.1 6-month surviv Cufer 2006 Morèrea 2010 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 2.6.2 1-year survival Fukuóka 2011 Garassino 2013 Inoue 2012 Kim 2008 Maruyama 2008	= 21.15, df = t: Z = 0.06 (ferences: C Experime Ferences: C Experime 45 5 50 0.86; Chi ² : Z = 0.61 (P rate 400 35 97 231 117 2	 15 (P = 0.96) P = 0.96) hi² = 11.28 ental 68 43 111 8.21, df = 8.21, df = 0.54) 609 109 114 723 245 43 	13); ² = df = 3 Control tents 1 15 56 1 (P = (364 44 99 131 5	<pre>= 29% (P = 0 I Total 1 73 41 114 0.0004); 608 110 114 41 41 41</pre>	100.0% .011. I ² = 7 .011. I ² = 7 .1% .1% 8.9% .1% 8.9% .1% .1% .1% .1% .1% .1% .1% .1	1.00 [0.95, 1.05] 3.4% Risk Ratio M.H. Random, 95% CI 1.18 [0.90, 1.53] 0.32 [0.13, 0.80] 0.65 [0.17, 2.55] 1.10 [1.01, 1.20] 0.80 [0.56, 1.15] 0.96 [0.88, 1.09] 0.94 [0.81, 1.09] 0.94 [0.75, 1.06] 0.38 [0.08, 1.86]	0.5 0.7 1 1.5 2 Favours EGFR-TKI Favours Taxanes Risk Ratio M-H. Random. 95% Cl
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Total (95% CI) Heterogeneity: Chi ² s Test for overall effect Test for suboroun dif Study or Suboroun dif Cufer 2006 Morèrea 2010 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect 2.6.2 1-year survival Fukuoka 2011 Garassino 2013 Inoue 2012 Kim 2008 Maruyama 2008 Morèrea 2010 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect	= 21.15, df = t: Z = 0.06 (ferences: C Experime ral rate 45 5 50 0.86; Chi ² : Z = 0.61 (P rate 400 35 97 231 17 17 2 882 e 0.01; Chi ² : Z = 0.55 (P	 15 (P = 0.96) P = 0.96) hi² = 11.28 ental 68 43 111 8.21, df = 0.54) 609 109 114 723 43 1843 e 9.96, df = 0.58) 	13); ² = df = 3 Control ents 1 15 56 1 (P = (364 44 99 241 131 5 1 884 5 (P = (= 29% (P = 0 I Total I 73 41 114 0.004); 110 114 710 244 41 1827 0.08); I	100.0% .011. I ² = 7 .011. I ² = 7 .1% .1% .1% .1% .1% .1% .1% .1%	1.00 [0.95, 1.05] 3.4% Risk Ratio M-H. Random, 95% CI 1.18 [0.90, 1.53] 0.32 [0.13, 0.80] 0.65 [0.17, 2.55] 1.10 [1.01, 1.20] 0.80 [0.56, 1.15] 0.96 [0.88, 1.09] 0.94 [0.81, 1.09] 0.98 [0.75, 1.06] 0.38 [0.88, 1.86] 0.97 [0.89, 1.07]	0.5 0.7 1 1.5 2 Favours EGFR-TKI Favours Taxanes
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Total (95% CI) Heterogeneity: Chi ^p a Test for overall effect Test for suboroun dif Study or Suboroun dif Cufer 2006 Morièrea 2010 Subtotal (95% CI) Total events Heterogeneity: Tau ^p a Test for overall effect 2.6.2 1-year survival Fukuoka 2011 Garassino 2013 Inoue 2012 Kim 2008 Morièrea 2010 Subtotal (95% CI) Total events Heterogeneity: Tau ^p a Test for overall effect 2.6.3 2-year survival Fukuoka 2011 Fukuoka 2011 Fukuoka 2011 Fukuoka 2011 Fukuoka 2011	= 21.15, df = t: Z = 0.06 (ferences: C Experime val rate 45 5 50 0.86; Ch ² 2 2 = 0.61 (P rate 400 35 97 231 117 2 882 e 0.01; Ch ² 2 = 0.55 (P rate 2 = 0.55 (P) rate 2 = 0.55 (P) ra	$\begin{array}{c} 15 \ (P=0.)\\ P=0.96)\\ h ^{2}=11.28\\ ental\\ \hline Total Ev\\ 68\\ 43\\ 111\\ e8.21, df=\\ e0.54)\\ \hline 609\\ 109\\ 114\\ 723\\ 245\\ 43\\ 1843\\ e9.96, df=\\ e0.58)\\ \hline 609\\ 114 \end{array}$	13): ² = df = 3 Control eents 1 15 56 1 (P = (364 44 99 91 364 44 93 5 1 364 5 (P = (183 61	= 29% (P = 0 1 73 41 114 0.004); 608 110 114 710 241 1827 608; 1 14	100.0% .011. I ² = 7 Weight 1 7.8% 1.1% 8.9% I ² = 88% 16.0% 5.3% 15.1% 12.9% 0.4% 61.3% I ² = 50% 12.3% 9.0%	1.00 [0.95, 1.05] 3.4% Risk Ratio M-H. Random, 95% CI 1.18 [0.90, 1.53] 0.32 [0.13, 0.80] 0.65 [0.17, 2.55] 1.10 [1.01, 1.20] 0.80 [0.56, 1.15] 0.98 [0.88, 1.09] 0.94 [0.81, 1.09] 0.94 [0.81, 1.09] 0.94 [0.81, 1.09] 0.98 [0.75, 1.06] 0.38 [0.08, 1.86] 0.97 [0.89, 1.07] 1.24 [1.06, 1.45] 1.08 [0.86, 1.36]	0.5 0.7 1 1.5 2 Favours EGFR-TKI Favours Taxanes
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Figure 3. Forest plot of comparison for overall survival (A) and overall survival rate (B) between EGFR-TKIs and taxanes in NSCLC. EGFR-TKI=epidermal growth factor receptor tyrosine kinase inhibitor, NSCLC=nonsmall-cell lung cancer, OS=overall survival, OSR=overall survival rate.

95% CI: 0.27–0.65) and no advantage over taxanes alone (HR = 1.09, 95% CI: 0.98–1.20) in PFS. According to clinical phase of trials, the 3rd subgroup analysis result showed that the superiority of EGFR-TKIs over taxanes in phase III trials (HR=0.77, 95% CI: 0.66–0.90). No difference was detected between 2 arms in phase II trials. The last subgroup under trial design, multicenter studies, and single center studies presented that the significant improvement of PFS was found in the EGFR-

TKIs group compared with the taxanes groups (HR = 0.76, 95% CI: 0.64-0.89).

OS: As opposed to taxanes, EGFR-TKIs had a tendency to extend OS in patients with EGFR mutation (HR = 0.72, 95% CI: 0.40–1.29), EGFR mutation-positive (HR = 0.93, 95% CI: 0.74–1.18), and unknown EGFR mutation (HR = 0.75, 95% CI: 0.67–0.84); however, patients with EGFR mutation-negative (HR = 1.25, 95% CI: 0.97–1.61) was opposite. There were

A

B

itudy or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% CI	M-H. Random, 95% Cl
1.1 gelitinib vs doo	etaxel			-		0.0710 10 0.000	
Juner 2006		60	10	13	2.0%	0.97 [0.42, 2.23]	
Cim 2008	60	650	50	657	8.0%	1 20 10 84 1 711	+
ee 2010	23	82	6	79	2.6%	3 69 [1 59, 8 59]	
Aaruyama 2008	45	200	24	187	5.1%	1.75 [1.11, 2.76]	
Mitsudomi 2010	36	58	15	59	4.9%	2.44 [1.51, 3.95]	
ramamoto a 2010	28	182	8	173	3.0%	3.33 [1.56, 7.10]	
ramamoto b 2010	40	173	18	170	4.6%	2.18 [1.31, 3.65]	
ramamoto c 2010	42	160	21	160	4.9%	2.00 [1.24, 3.22]	
ramamoto d 2010	45	151	24	150	5.2%	1.86 [1.20, 2.89]	
ramamoto e 2010	33	172	11	156	3.6%	2.72 [1.42, 5.20]	
Cotal events	421	2004	237	2021	40.078	1.00 [1.40, 1.04]	
teteropeneity: Tau ² #	0.07 Ch?	= 21.02	af = 10 (P=0.0	2) P = 521		
lest for overall effect.	Z = 5.35 (P	< 0.000	01)				
1.1.2 osfilinih va nac	literel						
Sakuraka 2011	53	200	44	108	6.1%	1 10 10 84 1 691	+
Soto 2012	81	114	56	119	7.4%	1.51 [1.21, 1.89]	-
Aaemondo 2010	84	114	35	114	6.7%	2.40 [1.78, 3.23]	-
Aok 2009	262	609	196	608	8.0%	1.33 [1.15, 1.55]	-
DIZUMI 2012	53	72	23	76	5.9%	2.43 [1.68, 3.52]	-
Watanabe 2014	36	114	22	111	5.1%	1.59 [1.00, 2.53]	
ri-Long WU 2012	82	184	56	188	6.9%	1.50 [1.14, 1.96]	1
Subtidual (95% CI)		1407	422	1414	40.1%	1.63 [1.34, 1.97]	×.
teterogeneity: Taul =	0.04 Ch	= 20.29	432 df = 6 (P	- 0.00	2): 1* = 704		
lest for overall effect.	Z = 4.96 (P	< 0.000	(10			2	
A 2 estatistic or d	at seat						
a senotihib vs doc	etaxel	100			1.07	0.10.00.00.0.00	
Generation 2013	10	134	10	120	2.8%	0.74 (0.34, 1.67)	
Subtotal (95% CD	10	234	13	226	4 3%	0.41 [0.11. 1.54]	-
fotal events	13		28			and for the stand	
feterogeneity: Tau ^a =	0.65; Ch	= 3.41, d	1 = 1 (P	0.06)	P = 71%		
fest for overall effect.	Z = 1.32 (P	= 0.19)					
A destation of the	-						
1.1.4 eriotinib vs pac	intaxel	-	-				
Subtotal (95% CH	2	52	6	51	1.0%	0.33 [0.07, 1.54]	
Intal events	2	24		-	1.4.4	area farant stad	
and a second	plicable						
teterogeneity. Not ap							
feterogeneity: Not ap fest for overall effect.	Z=1.41 (P	= 0.16)					
Test for overall effect.	Z = 1.41 (P	4257		4242	100.05	1.0711.30 1.011	
reterogeneity: Not ap lest for overall effect: lotal (95% CI)	Z = 1.41 (P	4257	202	4212	100.0%	1.62 [1.38, 1.91]	•
reterogeneity: Not ap l'est for overall effect. l'otal (95% CI) l'otal events interrogeneity: Toul a	Z = 1.41 (P	4257	703	4212 P = 0.0	100.0%	1.62 [1.38, 1.91]	•
reterogeneity: Not ap l'est for overall effect: l'otal (95% CI) l'otal events reterogeneity: Tau ² s l'est for overall effect	Z = 1.41 (P 1087 0.08; Chi ^p Z = 5.87 (P	4257 = 62.27. < 0.000	703 df = 20 (01)	4212 P < 0.0	100.0% 0001); I ² =	1.62 [1.38, 1.91] 68% 0.0	• 1 0.1 1 10
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Figure 4. Forest plot of comparison for objective response rate (A) and disease control rate (B) between EGFR-TKIs and taxanes in NSCLC. EGFR-TKI= epidermal growth factor receptor tyrosine kinase inhibitor, NSCLC=nonsmall-cell lung cancer.

similar treatment effects between them in patients with EGFR wild-type, EGFR copy number, and EGFR protein expression. Six studies were grouped into taxanes plus platinum and 10 studies were grouped into taxanes alone, the result displayed no significant difference between EGFR-TKIs and taxanes in OS (HR = 1.00, 95% CI: 0.95–1.05). According to clinical phase of trials, which result showed there was no OS benefit for EGFR-TKIs over taxanes (HR = 0.99, 95% CI: 0.94–1.04). Multicenter had 10 studies and an additional 5 studies were single center, the overall result showed EGFR-TKIs had no significant difference in OS in NSCLC patients (HR = 0.97, 95% CI: 0.90–1.04).

ORR: The results indicated that there was benefit for EGFR-TKIs over taxanes in NSCLC patients with EGFR mutation (HR = 1.26, 95% CI: 0.92-1.71) and EGFR mutation-positive (HR = 1.49, 95% CI: 1.21-1.83), but patients with EGFR mutation-negative (HR = 0.05, 95% CI: 0.01-0.35) and EGFR wild-type (HR = 0.68, 95% CI: 0.28-1.66) were converse. EGFR-TKIs had equally therapy value to taxanes in EGFR copy number and EGFR protein expression patients. According to platinum in control arm (RR = 1.62, 95% CI: 1.38-1.91), clinical phase of trials (RR = 1.63, 95% CI: 1.39-1.91), and trial design (RR = 1.62, 95% CI: 1.38-1.91), we can make a conclusion that EGFR-TKIs had sustained clinical improvements over taxanes for patients in ORR.

DCR: After 3 subgroup analyses, the conclusion demonstrated whether paclitaxel or docetaxel, EGFR-TKIs cannot significantly improve DCR in NSCLC patients, the detail data were showed in Table 3.

We also did meta-regression to find the source of heterogeneity. We found that grouping by platinum in control arm revealed differences in outcomes of PFS and DCR with *P* value less than 0.05. Moreover, EGFR status might have influenced heterogeneity in PFS (P=0.039). Besides, grouping by clinical phase of trials, differences could be found in OS (P=0.036).

3.5. Publication bias

We did the funnel plot according to PFS, OS, ORR, and DCR was shown in Fig. 6. The funnel plot showed asymmetry among our included studies, which proved the existence of publication bias.

4. Discussion

We carried out this meta-analysis to compare PFS, PFSR, OS, OSR, ORR, DCR, QoL, and AEs between EGFR-TKIs and taxanes. EGFR-TKIs can significantly prolong PFS and PFSR after therapy. The therapeutic effects of EGFR-TKIs were similar to taxanes in OS. Furthermore, taxanes were inferior to EGFR-TKIs in ORR. There was no significant difference between EGFR-TKIs and taxanes in DCR, while taxanes had a tendency to improve DCR. We found whether in FACT-L, LCS, or TOI, the results showed EGFR-TKIs surpassed taxanes in QoL with NSCLC patients. We found that comparing taxanes, NSCLC patients with EGFR mutation, EGFR mutation-positive, and unknown EGFR mutation can benefit from EGFR-TKIs on PFS, OS, and ORR. However, they cannot get beneficial treatment, who with EGFR wild-type and EGFR mutation-negative. There was no significant difference in EGFR copy number and EGFR protein expression. Thus, EGFR-TKIs are more suitable for patients with EGFR mutations and EGFR mutation-positive. Li et al^[46] made a relevant study, they also found that EGFR-TKIs were more efficient in EGFR mutations patients.

As per the analysis of heterogeneity, we did meta-regression and detail subgroup with EGFR status, platinum in control arm, clinical phase of trials, and trial design. First after EGFR status subgroup analyses, although the results showed PFS and ORR were different to drug groups, they had same tendency with drug groups. EGFR status on the effect of OS had difference on drug groups; hence, EGFR status might cause heterogeneity. Besides, we used platinum in control arm, clinical phase of trials, and trial design were operated in different groups, the results of PFS, OS, ORR, and DCR were equivalent to drug groups. However, analysis by meta-regression was found that platinum in control arm and clinical phase of trials were same to lead to heterogeneity, the detail results were showed in Table 3. Subsequent analysis will be confirmed. In fact, small sample size may be one of the causes of heterogeneity.

There are also published meta-analysis, such as that by Zhao et $al^{[3]}$ who compared the therapeutic values of gefitinib versus



Figure 5. Forest plot of comparison for Functional Assessment of Cancer Therapy-Lung (A), Lung Cancer Subscale (B), and Trial Outcome Index (C) between EGFR-TKIs and taxanes in NSCLC. EGFR-TKI=epidermal growth factor receptor tyrosine kinase inhibitor, NSCLC=nonsmall-cell lung cancer.

docetaxel, while we included more studies and outcomes. In fact, incorporating more clinical outcomes will bring more strong evidences in evaluation of efficacy and safety with NSCLC patients. Furthermore, we expanded the sample size and obtained consistent with their conclusions. To date, there has been no published meta-analysis comparing the efficacy and safety between EGFR-TKIs and taxanes. Pilkington et al^[47] published a systematic review of the clinical effectiveness of 1stline chemotherapy, and they mentioned that, compared with paclitaxel and platinum, gefitinib had a statistically significant improvement in PFS, which was also consistent with the

findings of our study, proving above-described results were trustworthy.

EGFR-TKIs could prolong PFS, improve ORR and QoL, yet they have many side-effects, such as rash and diarrhea.^[48,49] Taxanes also have several AEs: gastrointestinal reaction, alopecia, and hematological toxicity, particularly grade 3/4 leukopenia and neutropenia which tended to be more frequent after treatment with taxanes.^[50,51] In the meta-analysis of this study, except for diarrhea and rash, there was a slightly worse trend toward EGFR-TKIs compared with taxanes. EGFR-TKIs were superior to taxanes in rates of many AEs, such as all Table 2

Summary of all AEs rate.			
Adverse events		All grades	CTC grade ≥ 3
Hematologic toxicity	Neutropenia	0.09 (0.07-0.11)	0.02 (0.01-0.02)
	Anemia	0.29 (0.15-0.57)	0.26 (0.18-0.38)
	Thrombocytopenia	0.27 (0.14-0.56)	0.10 (0.03–0.38)
	Leukopenia	0.13 (0.08-0.20)	0.03 (0.02–0.05)
	Febrile neutropenia	0.13 (0.08-0.23)	0.10 (0.06–0.19)
Gastrointestinal reaction	Diarrhea	1.92 (1.55–2.39)*	1.70 (1.18–2.47)*
	Nausea	0.49 (0.37-0.64)	0.48 (0.29-0.80)
	Vomiting	0.60 (0.43-0.83)	0.43 (0.24–0.76)
	Constipation	0.53 (0.37-0.76)	0.93 (0.51–1.71) [†]
Other	Alopecia	0.12 (0.09-0.16)	0.07 (0.01-0.37)
	Rash	4.62 (3.46–6.17)*	4.60 (2.90–7.32)*
	Myalgia	0.21 (0.15-0.29)	0.24 (0.09-0.64)
	Pyrexia	0.55 (0.44–0.70)	0.40 (0.12-1.40)*

White depicts EGFR-TKIs had significant results in reducing AEs. AE=adverse event, CTC=common toxicity criteria, EGFR-TKI=epidermal growth factor receptor tyrosine kinase inhibitor. * Showed EGFR-TKIs had significant results in increasing AEs. * Depicts nonsignificant results.

Table 3

	HR/RR	Heterogeneity within subgroups	Difference between	P from
	(5570 01)	within Subgroups	Subgroups	incla-regression
PFS				
EGFR status				a aaa*
Overall	0.82 (0.67–1.00)	Yes $(P < 0.00001, P = 86\%)$	Yes (P<0.00001, P=88.1%)	0.039
EGFR Mutation	0.57 (0.43–0.76)	Yes $(P=0.007, F=62\%)$		
EGFR Mutation positive	0.42 (0.27–0.65)	No $(P=0.21, F=37\%)$		
EGFR Mutation negative	1.59 (0.50–5.02)	Yes $(P < 0.00001, F = 95\%)$		
EGFR wild-type	1.32 (1.11–1.57)	No $(P=0.71, P=0\%)$		
unknown EGFR Mutation	0.68 (0.58-0.80)	NA		
EGFR copy number	0.96 (0.69–1.35)	Yes $(P=0.006, I=76\%)$		
EGFR protein expression	0.96 (0.71-1.29)	Yes (P<0.00001, P=86%)		
Platinum in control arm				
Overall	0.78 (0.66-0.92)	Yes (P<0.00001, P=93%)	Yes (P<0.00001, P=95.6%)	0.001*
Taxanes alone	1.09 (0.98-1.20)	Yes ($P=0.03$, $\ell = 52\%$)		
Taxanes plus platinum	0.42 (0.27-0.65)	Yes (P<0.00001, P=94%)		
Clinical phase of trials				
Overall	0.82 (0.71-0.96)	Yes (P<0.00001, P=90%)	Yes ($P=0.005$, $\ell = 87.4\%$)	0.104
Phase III trials	0.77 (0.66-0.90)	Yes (P<0.00001, P=91%)		
Phase II trials	1.25 (0.93-1.69)	No $(P=0.20, l^2=38\%)$		
Trial design				
Overall	0.76 (0.64-0.89)	Yes ($P < 0.00001$, $l^2 = 93\%$)	Yes ($P=0.03$, $l^2=77.9\%$)	0.103
Multicenter	0.89 (0.73-1.08)	Yes (P<0.00001, P=91%)		
Single center	0.60 (0.45-0.81)	Yes ($P < 0.00001$, $l^2 = 94\%$)		
OS				
EGFR status				
Overall	0.91 (0.85-0.98)	No $(P=0.03, l^2=44\%)$	Yes $(P=0.001, P=73.4\%)$	0.748
EGFR Mutation	0.72 (0.40-1.29)	No $(P=0.58, P=0\%)$		
EGFR Mutation positive	0.93 (0.74-1.18)	No $(P=0.35, l^2=0\%)$		
EGFR Mutation negative	1.25 (0.97-1.61)	No $(P=0.56, P=0\%)$		
EGFR wild-type	0.96 (0.80-1.16)	No $(P=0.73, P=0\%)$		
unknown EGFR mutation	0.75 (0.67–0.84)	Yes $(P=0.11, f=61\%)$		
EGFR copy number	1.07 (0.91-1.25)	No $(P=0.56, P=0\%)$		
EGFR protein expression	1.00 (0.80–1.25)	No $(P=1.00, f=0\%)$		
Platinum in control arm				
Overall	1.00 (0.95-1.05)	No $(P=0.13, l^2=29\%)$	No $(P=0.29, l^2=10.3\%)$	0.392
Taxanes alone	1.03 (0.95-1.11)	No $(P=0.58, P=0\%)$		
Taxanes plus platinum	0.97 (0.90-1.05)	No $(P=0.06, \ell=45\%)$		
Clinical phase of trials	· · · · · · · · · · · · · · · · · · ·			
Overall	0.99 (0.94-1.04)	No $(P=0.24, l^2=19\%)$	Yes $(P=0.02, P=81.6\%)$	0.036*
Phase III trials	0.98 (0.92-1.03)	No $(P=0.66, l^2=0\%)$		
Phase II trials	1.34 (1.03-1.75)	No $(P=0.20, f=38\%)$		

Table 3

	HR/RR (95% CI)	Heterogeneity within subgroups	Difference between subgroups	P from meta-regression
Trial design				
Overall	0.97 (0.90-1.04)	No $(P=0.19, P=24\%)$	No $(P=0.31, P=3.7\%)$	0.400
Multicenter	1.02 (0.95-1.10)	No $(P=0.13, l^2=34\%)$		
single center	0.97 (0.90-1.04)	No $(P=0.44, P=0\%)$		
ORR				
EGFR status				
Overall	1.17 (0.87-1.57)	Yes ($P=0.02$, $l^2=51\%$)	Yes ($P=0.01$, $l^2=66.0\%$)	0.089
EGFR Mutation	1.26 (0.92-1.71)	No $(P=0.62, l^2=0\%)$		
EGFR Mutation positive	1.49 (1.21-1.83)	No $(P=0.97, P=0\%)$		
EGFR Mutation negative	0.05 (0.01-0.35)	NA		
EGFR wild-type	0.68 (0.28–1.66)	NA		
EGFR copy number	1.14 (0.49-2.65)	No $(P=0.22, l^2=34\%)$		
EGFR protein expression	1.12 (0.62-2.03)	No $(P=0.33, P=10\%)$		
Platinum in control arm				
Overall	1.62 (1.38-1.91)	Yes ($P < 0.00001$, $l^2 = 68\%$)	No $(P=0.82, l^2=0\%)$	0.887
Taxanes alone	1.58 (1.19–2.11)	Yes $(P=0.0003, P=68\%)$		
Taxanes plus platinum	1.65 (1.35-2.01)	Yes $(P=0.0005, l^2=71\%)$		
Clinical phase of trials				
Overall	1.63 (1.39-1.91)	Yes $(P=0.0002, l^2=63\%)$	Yes $(P=0.08, l^2=67.0\%)$	0.097
Phase III trials	1.68 (1.43–1.96)	Yes $(P=0.0004, l^2=63\%)$		
Phase II trials	0.69 (0.26-1.85)	No $(P=0.23, P=32\%)$		
Trial design				
Overall	1.62 (1.38-1.91)	Yes ($P < 0.00001$, $l^2 = 68\%$)	No $(P=0.19, P=42.6\%)$	0.284
Multicenter	1.31 (0.91-1.89)	Yes $(P < 0.00001, l^2 = 81\%)$		
single center	1.71 (1.47-2.00)	No $(P=0.05, P=44\%)$		
DCR				
Platinum in control arm				
Overall	0.95 (0.88-1.03)	Yes ($P=0.0007$, $l^2=61\%$)	Yes ($P=0.11$, $P=59.9\%$)	0.039*
Taxanes alone	0.93 (0.86-1.00)	No $(P=0.05, l^2=43\%)$		
Taxanes plus platinum	1.08 (0.91-1.29)	Yes $(P=0.06, P=64\%)$		
Clinical phase of trials				
Overall	0.97 (0.90-1.05)	Yes ($P = 0.005$, $l^2 = 55\%$)	No $(P=0.37, P=0\%)$	0.481
Phase III trials	0.98 (0.91-1.06)	Yes $(P=0.009, l^2=56\%)$		
Phase II trials	0.82 (0.55-1.21)	Yes $(P=0.08, l^2=60\%)$		
Trial design	· /	· · · ·		
Overall	0.96 (0.89-1.04)	Yes ($P=0.001$, $\hat{f}=60\%$)	No $(P=0.68, l^2=0\%)$	0.770
Multicenter	0.93 (0.82-1.06)	Yes $(P < 0.0001, P = 78\%)$		
single center	0.96 (0.89-1.04)	No $(P=0.94, l^2=0\%)$		

CI = confidence interval, DCR = disease control rate, EGFR = epidermal growth factor receptor, HR = hazard ratio, NA = not applicable, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, RR = risk ratio.

* Factors could be an important source of heterogeneity.

hematologic toxicity, myalgia, and pyrexia, etc. All of the data were listed in Table 2. It illustrated that the risk of AE rates was not increased when EGFR-TKIs instead of taxanes were applied for the treatment of NSCLC.

Holistic nursing care can improve the curable effects and significantly reduce adverse effects in the treatment of patients with hematological system disorders using high-dose dexamethasone pulse, and it deserves to be promoted to clinic.^[52] Auricular acupressure can significantly reduce the gastrointestinal side effects in lung cancer patients after chemotherapy, and be without any adverse reaction and high compliance.^[53] Meanwhile pantoprazole joint granisetron and methoxychlor Puan and dexamethasone prevent chemotherapy-induced gastrointestinal reactions with better efficacy, adverse reactions are mild, worthy of clinical application.^[54]

Certainly this meta-analysis had several limitations need to be addressed. First most of included trials were allocated in Asian region (Table 1), which may cause the geographical limitations. Besides, due to limited or missing data about current trials, details such as gender, age, smoking, and cancer stage were unable to be analyzed. Moreover, not all of the patients in this study were serious, especially the performance status ≤ 2 , which may be proved that the basic level was mixed. Although anticancer drugs have been used widely in NSCLC, related randomized clinical trials appear to be limited. Furthermore, the different outcome assessment times could lead to the existence of publication bias. Positive results are easy to be published, negative results with several AEs are not likely to be viewed. Finally the quality of included studies were variable, although most of them with acceptable quality, high-quality, well-level, and large-scale double-blind RCTs are needed for further research. Considering the limitations above, further studies were warranted to complete the information and the results of this research must be interpreted with caution.

In terms of PFS, PFSR, ORR, QoL, and AEs, EGFR-TKIs were superior to taxanes in NSCLC patients from the present metaanalysis study, particularly who were with EGFR mutationpositive. There were no differences between EGFR-TKIs and



Figure 6. Funnel plot of comparison for PFS (A), OS (B), objective response rate (C), and disease control rate (D) between gefitinib and taxanes in NSCLC. NSCLC=nonsmall-cell lung cancer, OS=overall survival, PFS=progression-free survival.

taxanes in OS, OSR, and DCR. From a clinical perspective, no matter the efficacy or the toxicity, EGFR-TKIs are significant difference potential and valuable choices in the treatment of NSCLC. Certainly we need more high-quality and large-scale RCTs for further research.

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