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Erlotinib plus tivantinib versus erlotinib alone in patients with previously treated stage IIIb/IV non–small-cell lung cancer

A meta-analysis based on randomized controlled trials

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Abstract

Background: Whether erlotinib plus tivantinib (ET) can achieve better clinical benefits than erlotinib plus placebo (EP) among participants with previously treated advanced non-small-cell lung cancer (NSCLC) is still disputed. We conducted a meta-analysis to evaluate the anticancer efficacy and safety of both regimens.

Materials and methods: We searched for pertinent trials at PubMed, ScienceDirect, The Cochrane Library, Scopus, Ovid MEDLINE, Embase, Web of Science, and Google Scholar. Endpoints mainly included progression-free survival (PFS), overall survival (OS), objective response rate (ORR), disease control rate (DCR), and adverse events (AEs).

Results: We included 1522 patients who previously received ≥1 systemic anti-cancer regimen that included platinum-based chemotherapy. Although ET failed to improve OS (hazard ratio [HR] = 0.91, 95% confidence interval [CI]: 0.75–1.10, $P = .35$), the ET group had better PFS (HR = 0.73, 95% CI: 0.67–0.80, $P < .00001$), higher ORR (HR = 1.50, 95% CI: 1.06–2.12, $P = .02$), and better DCR (HR = 1.38, 95% CI: 1.20–1.59, $P < .00001$). Our subanalysis suggested that the ET group may have had better OS among patients with high Mesenchymal to epithelial transition factor (MET) expression (HR = 0.76, 95% CI: 0.58–0.99, $P = .04$) and good VeriStrat (HR = 0.88, 95% CI: 0.83–0.93, $P < .0001$). AEs were roughly similar except for specific hematological toxicities: more neutropenia and febrile neutropenia were observed in the ET group, both of which should not be overlooked.

Conclusions: ET appears to be superior to EP due to better PFS and higher response rates, especially for patients with high MET expression and good VeriStrat. The greater hematological toxicity in the ET regimen is non-negligible.

Abbreviations: AEs = adverse events, CI = confidence intervals, CR = complete response rate, DCR = disease control rate, EGFR = epidermal growth factor receptor, EP = erlotinib plus placebo, ET = tivantinib plus erlotinib, GRADE = Grades of Recommendations Assessment, Development and Evaluation, HR = hazard ratio, ILD = interstitial lung disease, NSCLC = non-small-cell lung cancer, ORR = objective response rate, OS = overall survival, PD = progressive diseases, PFS = progression-free survival, PR = partial response rate, RCT = randomized controlled trial, RECIST = Response Evaluation Criteria in Solid Tumors, RR = risk ratios, SD = stable disease rate, TKI = tyrosine kinase inhibitor.

Keywords: erlotinib, MET inhibitors, meta-analysis, non-small cell lung cancer, randomized clinical trial, tivantinib

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Novelty and Impact Statements: This meta-analysis compared the anti-tumor effectiveness and toxicity of erlotinib plus tivantinib (ET) and erlotinib plus placebo (EP) for non–small-cell lung cancer (NSCLC). Our analysis suggested: ET group has more clinical benefits than the EP group with better PFS, ORR, and DCR; ET may be more suitable for patients with high-level MET expression; higher rates of neutropenia and febrile neutropenia are found in the ET group.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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1. Introduction

Lung carcinoma is a common malignant tumor with high-level mortality, with 228,150 estimated new cases and 142,670 estimated deaths in America in 2019, and >85% of lung carcinomas were non–small-cell lung cancer (NSCLC).[1–3] Most advanced NSCLC patients have a moderate survival time (only 10–12 months) even after aggressive treatment.[4] Thankfully, the discovery of epidermal growth factor receptor (EGFR) inhibitors made an obvious clinical improvement in the therapy of NSCLC.[5] Nevertheless, some advanced NSCLC patients still have cancer progression and develop resistance to EGFR inhibitors.

The MET receptor is essential for tumor cell migration, invasion, proliferation, inhibition of apoptosis, and metastasis.[6,7] MET amplification is regarded as the crucial mechanism behind resistance to EGFR inhibitors.[8–10] Recently, some preclinical studies have shown that disrupting MET signaling by using a tyrosine kinase inhibitor (TKI) or an antibody might overcome resistance to EGFR inhibitors.[11] As a small-molecule MET inhibitor, tivantinib disrupts downstream intracellular signaling through an ATP-independent binding mechanism and shows antiproliferative activities in many cancer models.[12,13] Therefore, tivantinib plus erlotinib (ET) is a theoretically reasonable regimen for advanced NSCLC patients previously receiving systemic anticancer regimens, and this regimen was researched in some randomized clinical trials (RCTs) with contradictory outcomes. A phase-III RCT demonstrated that the ET group was associated with similar OS (hazard ratio [HR] = 0.831, 95% confidence interval [CI]: 0.556–1.243, $P = .37$) but a tendency toward better progression-free survival (PFS) (HR = 0.707, 95% CI: 0.482–1.037, $P = .08$) in high-MET subpopulations compared with erlotinib plus placebo (EP).[14] However, another phase-III RCT indicated that the ET group had superior PFS (HR = 0.72, 95% CI: 0.52–0.99, $P = .01$) and better overall survival (OS) (HR = 0.70, 95% CI: 0.49–1.01, $P = .03$) in the high-MET subgroups.[15]

To tackle this controversy, we conducted a meta-analysis of pertinent RCTs to compare anti-cancer efficacy and toxicity between ET and EP groups to give the latest evidence-based advice for clinical stage IIIb to IV NSCLC patients who previously had ≥1 systemic anticancer regimen that included platinum-based chemotherapy.

2. Material and methods

The meta-analysis was completed based on PRISMA (Preferred Reporting Items for Systematic Review and Meta-analyses). (Table S1, http://links.lww.com/MD/E418) (Registration information: PROSPERO CRD42018102843). All analyses were based on previous published studies; thus, no ethical approval and patient consent are required.

2.1. Search strategy

All pertinent studies were acquired on June 5, 2019 through the following databases: PubMed, ScienceDirect, The Cochrane Library, Scopus, Web of Science, Embase, Ovid MEDLINE, and Google Scholar. We searched for the following terms: "tivantinib," "erlotinib," and "lung cancer." Table S2, http://links.lww.com/MD/E419 displays the detailed search strategy. The references of enrolled RCTs were searched to obtain potentially eligible studies. All included articles needed to be written in English.

2.2. Selection criteria

Studies fulfilling these criteria were enrolled in accordance with PICOS (Patients, Intervention, comparison, Outcome, Study design): patients: patients with clinical stage IIIb/IV NSCLC (the AJCC 7th edition[16]) who had already received ≥1 systemic anticancer regimen containing platinum-based chemotherapy, with no previous exposure to EGFR inhibitors; intervention and comparison: ET group vs EP group; outcome: PFS, OS, objective response rate (ORR), disease control rate (DCR), and adverse events (AEs); study design: RCT written in English.

Cohort studies, review, meta-analyses, conference papers, case reports, animal trials, and articles with the same patient sources were excluded.

2.3. Data extraction

The data were extracted by 2 investigators (HD and LW) independently to acquire these data: authors, publication time, nation, number of patients, participants' traits (age, race, histological types, pretreatment), anticancer efficacy index (PFS, OS, ORR, DCR), and AEs (any-grade and grade 3 AEs). All discrepancies were resolved by the third investigator (SZ). When analyzing PFS and OS, we adopted the HR regarding the number and time of the event instead of the odds ratio. We obtained HRs and 95% CIs directly when univariate survival analysis was conducted. Otherwise, HRs and 95% CIs were acquired from the Kaplan–Meier curve.[17]

2.4. Quality evaluation

RCT quality was assessed by the 5-point Jadad scale, including 3 major fields: randomization, masking, and accountability of all patients. RCTs having 3 to 5 points were high-quality.[18]

We adopted GRADE (Grading of Recommendations Assessment, Development and Evaluation) to assess the therapeutic strategy and study design of outcomes (survival, response rates, toxicity). GRADE included 4 grades in total (high, medium, low, and very low).[19]

2.5. Statistical analysis

This meta-analysis was conducted using RevMan 5.2 and STATA 12.0. HRs and 95% CIs were adopted when analyzing PFS and OS (HR >1 favored the ET arm; HR <1 favored the EP arm). Risk ratios (RRs) and 95% CIs were adopted when analyzing ORR, DCR (RR >1 favored the EP arm; RR <1 favored the ET arm), and AEs (RR >1 favored the ET arm; RR <1 favored the EP arm). Subanalyses of PFS, OS, and ORR were conducted to determine whether the results differed in light of nation, previous therapy, tivantinib dosage, VeriStrat labels, histology, EGFR, KRAS, or MET. Heterogeneity was appraised using the χ^2 test as well as the I^2 statistic. When $I^2 > 50\%$ or $P < .10$ in the χ^2 test, showing significant heterogeneity, we adopted a random-effect model; otherwise, we adopted a fixed-effect model. We evaluated publication bias using Begg test and Egger tests. $P < .05$ was considered statistically significant.

3. Results

3.1. Search results and study quality assessment

The procedure for selecting RCTs is depicted in Figure 1. Finally, we selected 5 studies[14,15,20–22] comprising 1522 patients who

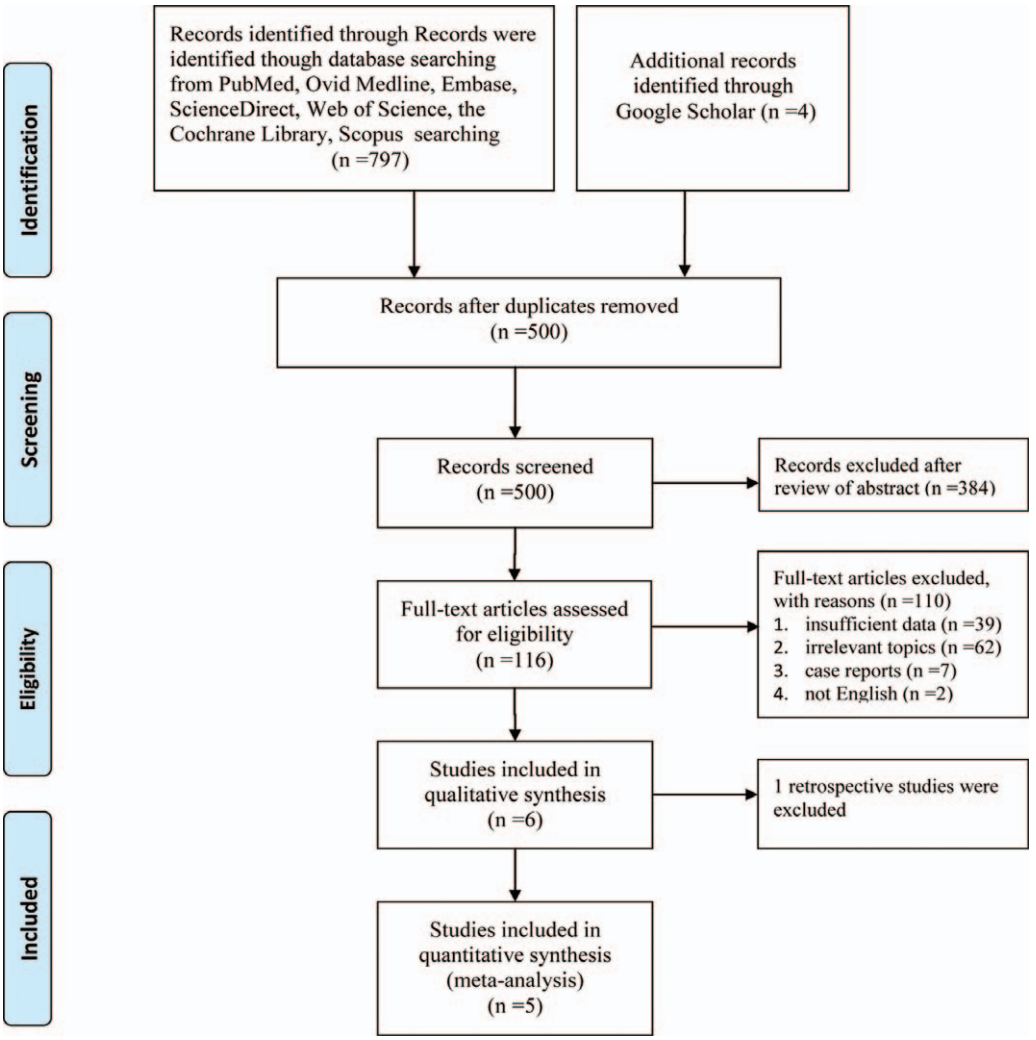

Figure 1. Flow chart of study selection.

previously received ≥1 systemic anticancer regimen that included platinum-based chemotherapy, with no previous treatment with EGFR inhibitors (ET group, 764; EP group, 758), for this meta-analysis. All included studies were RCTs. All included RCTs were of good quality (1 RCT scored 5 points and 2 RCTs scored 4 points using the Jadad scale, Table S3, http://links.lww.com/MD/E420). In fact, 2 included studies[21,22] were 2 subgroups of 1 included RCT.[15] Furthermore, most results were of high/medium quality and some of low quality by GRADE (Table S4, http://links.lww.com/MD/E421). Table 1 shows the basic traits and main appraisal index of the 5 included articles.

3.2. Antitumor effectiveness

We evaluated the anticancer efficacy of ET and EP with respect to PFS, OS, ORR, and DCR.

Three trials reported PFS (heterogeneity: $I^2 = 0\%$, $P = .88$). The ET group had an obviously better PFS compared with the EP group (HR = 0.73, 95% CI: 0.67–0.80, $P < .00001$; Fig. 2A).

Three trials reported OS (heterogeneity: $I^2 = 0\%$, $P = .88$). No apparent difference was detected between the groups (HR = 0.91, 95% CI: 0.75–1.10, $P = .35$; Fig. 2B).

Three trials reported ORR (heterogeneity: $I^2 = 0\%$, $P = .90$). The ET group had a higher ORR than the EP group (RR = 1.50, 95% CI: 1.06–2.12, $P = .02$; Fig. 3A). Two trials reported DCR (heterogeneity: $I^2 = 0\%$, $P = .35$). The ET group had apparently better DCR (RR = 1.38, 95% CI: 1.20–1.59, $P < .00001$; Fig. 3B). In our subanalysis of response rates, 2 RCTs reported a complete response rate (CR), but 1 RCT[14] did not have patients reaching CR, and no obvious difference was detected between the 2 groups (0% vs 2.4%, $P = .29$). Two RCTs reported the partial response rate (PR), and no significant difference was detected (RR = 1.52, 95% CI: 0.77–2.97, $P = .23$; Fig. 3C). Three RCTs reported the stable disease rate (SD), which was higher in the ET group (RR = 1.29, 95% CI: 1.11–1.50, $P = .001$; Fig. 3D).

3.3. AEs

The toxicity of ET and EP based on all grades of AEs as well as on grade ≥3 AEs was compared. Additionally, we conducted subanalyses of the 10 most common toxic events.

Only 1 RCT reporting any-grade AEs showed no apparent difference between the groups (97.5% vs 96.4%, $P = .27$). This

Table 1

Characteristics of all included studies.

	Study	Nation	Previous therapy*	Groups	Patients (n)	Initial dosage		Median age,y	Histology	Tumor stage†		Follow-up (mo)	Design	Score‡
						ET	EP			IIIb	IV			
2011	Sequist et al [20]	North America, Europe	≥1 Chemotherapy regimens	ET vs EP	84/83	E: 50 mg/day T: 360 mg bid	E: 50 mg/day	64.0/62.0	NSCLC	8/11	76/72	14.0/14.0	RCT	4
2015	Yoshioka et al [14]	Japan, Korea, Taiwan	1–2 Systemic anticancer regimens including PBC	ET vs EP	154/153	E: 50 mg/day T: 360 or 240 mg bid	E: 50 mg/day	63.0/63.0	NS	6/9	148/143	11.2/11.2	RCT	4
2015	Scagliotti et al [15]	North America, Europe, Australia	1–2 Systemic anticancer regimens including PBC	ET vs EP	526/522	E: 50 mg/day T: 360 mg bid	E: 50 mg/day	62.0/61.0	NS	22/14	499/501	12.0/12.0	RCT	5
2018	Scagliotti et al[21]§	North America, Europe, Australia	1-2 systemic anticancer regimens including PBC	ET vs EP	56/53	E:50 mg/day T:360 mg bid	E:50 mg/day	59.5/65.0	NS	NA	NA	12.0/12.0	RCT	5
2019	Buttigliero et al[22]§	North America, Europe, Australia	1–2 Systemic anticancer regimens including PBC	ET vs EP	504/492	E:50 mg/day T: 360 mg bid	E:50 mg/day	62.0/61.0	NS	21/13	478/472	12.0/12.0	RCT	5

bid = bisindie, E = erlotinib, EP = erlotinib plus placebo, ET = tivantinib combined with erlotinib, mo = months, NA = not available, NS = nonsquamous lung cancer, NSCLC = non-small-cell lung cancer, PBC = platinum-based chemotherapy, RCT = randomized controlled trail, T = tivantinib.

* Previous therapy included platinum-based chemotherapy but no exposure to EGFR inhibitors.

† Tumor stage was classified according to the AJCC 7th edition.

‡ The quality of RCT was evaluated using the 5-point Jadad scale.

§ The 2 studies were 2 subgroups of 1 RCT.

RCT also reported grade ≥3 AEs, and no obvious difference was detected (41.6% vs 36.6%, $P = .09$).

Quite a few patients with previously treated advanced NSCLC underwent drug discontinuations for various reasons during treatment. The ET group had fewer drug discontinuations than the EP group (HR = 0.96, 95% CI: 0.94–0.99, $P = .004$, Fig. 4A). We analyzed the reasons for dose discontinuations in detail, including progressive diseases and unacceptable AEs. Compared to the EP group, patients in the ET group had a lower incidence of dose discontinuations due to PD (HR = 0.85, 95% CI: 0.79–0.92, $P < .0001$, Fig. 4B). Additionally, ET induced more dose discontinuations due to intolerable AEs (HR = 1.43, 95%: 1.04–1.96, $P = .03$, Fig. 4C) compared with EP.

In the subanalysis of the 10 most common AEs (in order of occurrence rate: skin rash, fatigue/asthenia, diarrhea, anorexia/decreased appetite, nausea, dermatitis acneiform, anemia, neutropenia, febrile neutropenia, and interstitial lung disease [ILD]), the results of any-grade AEs demonstrated no obvious difference between the two arms in the rate of skin rash, fatigue/asthenia, anorexia/decreased appetite, nausea, dermatitis acneiform, anemia, febrile neutropenia, or ILD. For all-grade AEs, the ET group had less diarrhea (RR = 0.85, 95% CI: 0.74–0.98, $P = .02$) but more neutropenia (RR = 6.96, 95% CI: 1.42–33.96, $P = .02$; Table S5, http://links.lww.com/MD/E422) than the EP group. Besides, the results of grade ≥3 AEs suggested that obvious differences were not detected in fatigue/asthenia, anemia, rash, diarrhea, anorexia/decreased appetite, ILD, dermatitis acneiform, or nausea between arms. ET induced more grade ≥3 neutropenia (RR = 22.61, 95% CI: 2.70–189.51, $P = .004$) and grade ≥3 febrile neutropenia (RR = 14.96, 95% CI: 1.71–130.49, $P = .01$; Table S6, http://links.lww.com/MD/E423).

3.4. Subgroup analysis

To determine whether the anti-cancer efficacy of the 2 regimens differed, we estimated the pooled outcomes of PFS, OS, and ORR in light of nation, previous therapy, tivantinib dosage, VeriStrat labels, histology, EGFR, KRAS, and MET (Table 2). Intriguingly,

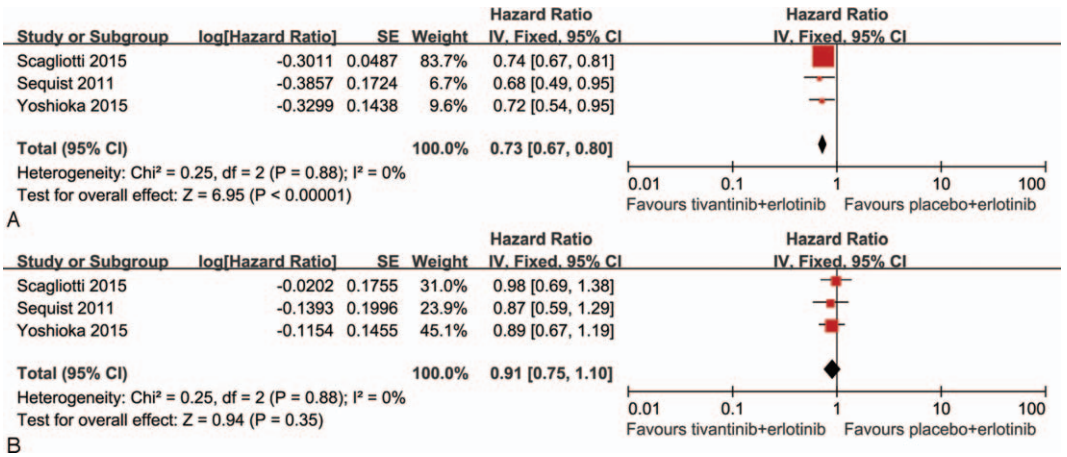

Figure 2. Forest plots of progression-free survival (PFS) (A) and overall survival (OS) (B) associated with tivantinib plus erlotinib (ET) versus erlotinib plus placebo (EP).

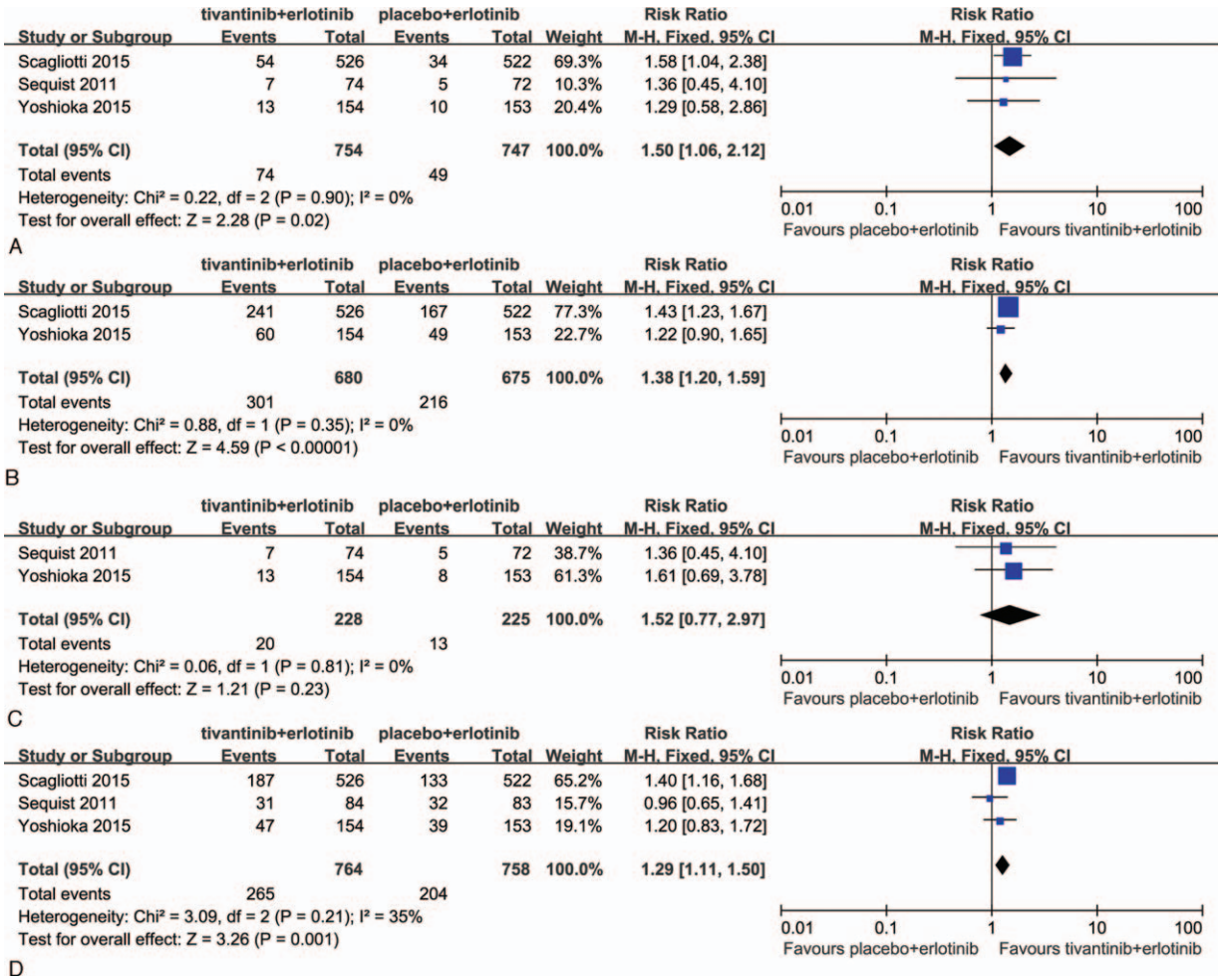

Figure 3. Forest plots of objective response rate (ORR) (A), disease control rate (DCR) (B), partial response rate (PR) (C), and stable disease rate (SD) (D) associated with erlotinib plus placebo (ET) versus erlotinib plus placebo (EP).

the ET group had superior OS among patients with high-level MET (HR = 0.76, 95% CI: 0.58–0.99, $P = .04$) and good VeriStrat (HR = 0.88, 95% CI: 0.83–0.93, $P < .0001$). This positive finding is in line with some recent clinical trials.[15,22]

Compared with the EP group, the ET group did not have an improved PFS among participants with squamous NSCLC (HR = 1.05, 95% CI: 0.56–1.98, $P = .88$), participants harboring wild-type KRAS (HR = 0.82, 95% CI: 0.64–1.07, $P = .14$). or participants with poor VeriStrat (HR = 1.00, 95% CI: 0.98–1.03, $P = 1.00$). In addition, the ET regimen did not have a higher ORR among patients from East Asia (HR = 1.29, 95% CI: 0.58–2.86, $P = .53$), patients who had undergone ≥1 chemotherapy regimens (HR = 1.36, 95% CI: 0.45–4.10, $P = .58$), patients using 240/360 mg of tivantinib (HR = 1.29, 95% CI: 0.58–2.86, $P = .53$), or patients harboring mutant EGFR (HR = 1.40, 95% CI: 0.96–2.03, $P = .08$). These findings may have been caused by the limited number of included RCTs, and some different results may be found if new studies are done. Other results of the subanalysis were all robust.

3.5. Sensitivity Analysis

PFS (Figure S1A, http://links.lww.com/MD/E424), OS (Figure S1B, http://links.lww.com/MD/E424) and ORR (Figure S1C, http://links.lww.com/MD/E424) all showed robust outcomes, with no estimated values going beyond the 95% CIs.

3.6. Publication Bias

We could not find evidence of publication bias in the results of PFS (Begg test, $P = .296$; Egger test, $P = .244$; Figure S2A, http://links.lww.com/MD/E425), OS (Begg test, $P = 1.000$; Egger test, $P = .973$; Figure S2B, http://links.lww.com/MD/E425), or ORR (Begg test, $P = 1.000$; Egger test, $P = .322$; Figure S2C, http://links.lww.com/MD/E425).

4. Discussion

In spite of some advances in therapy, NSCLC remains a major cause of cancer mortality. Some patients using EGFR inhibitors have had unsatisfactory results, such as drug resistance and low response rates. These problems require urgent attention. This meta-analysis compared the anti-cancer efficacy and safety between the ET and EP groups among clinical stage IIIb to IV NSCLC patients who previously had ≥1 systemic anticancer regimen that contained platinum-based therapy but no previous treatment with EGFR inhibitors. Our pooled outcomes showed that ET was associated with some clinical benefits, including

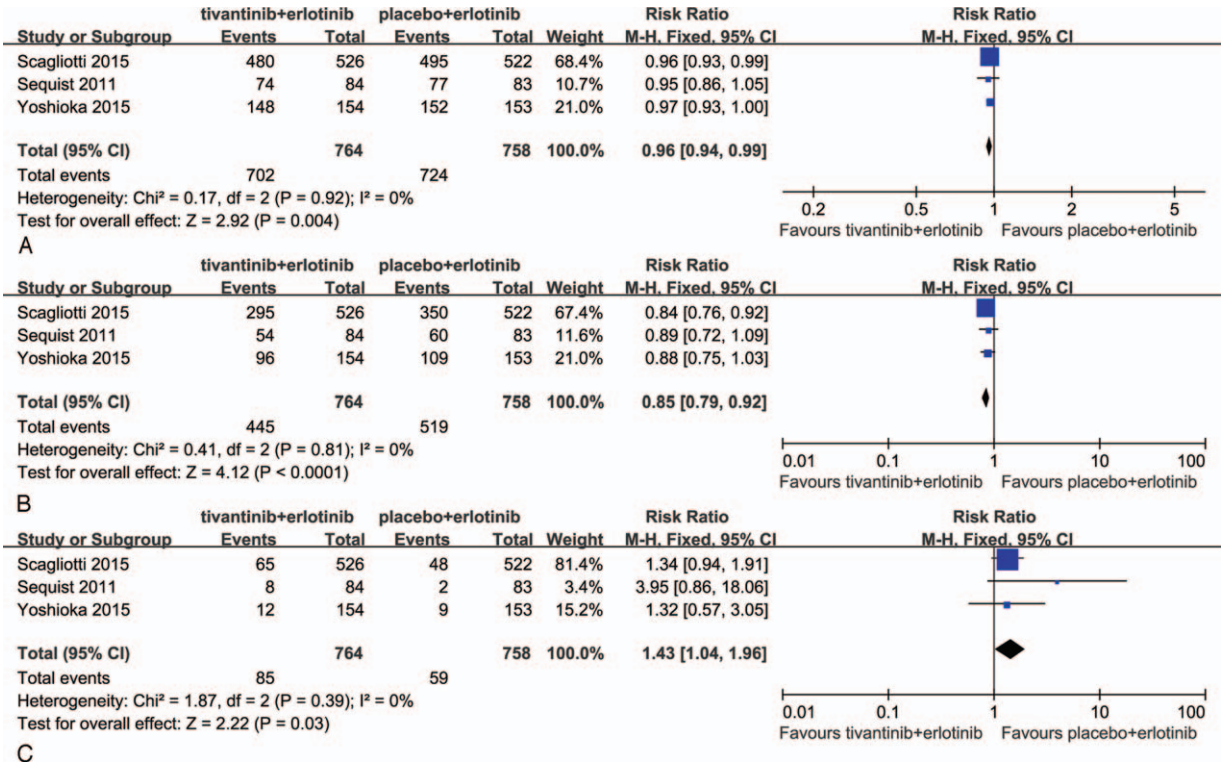

Figure 4. Forest plots of risk ratios (RRs) of dose discontinuations (A), dose discontinuations due to progressive diseases (B) and dose discontinuations due to unacceptable adverse events (AEs) (C) associated with erlotinib plus placebo (ET) versus erlotinib plus placebo (EP).

improved PFS and higher response rates. Regretfully, the ET regimen failed to improve OS. Most common AEs were roughly equivalent, apart from specific hematological AEs (neutropenia, febrile neutropenia). In our subanalysis, the ET regimen was associated with better OS among patients with high-level MET and good VeriStrat.

The survival index is the most crucial point that we ought to take into consideration in regard to the therapeutic efficacy of both groups. Our results indicate that the ET group had a significantly improved PFS but did not have a superior OS among stage IIIb/IV NSCLC patients with ≥1 previous systemic anticancer regimen. A recent multinational double-blind RCT reported that patients in the ET group had an improved PFS, but the ET group failed to achieve the primary endpoint of superior OS among nonsquamous NSCLC patients with previous treatments.[15] Analogously, contrary to expectations, a phase-II RCT of 33 centers demonstrated that the ET regimen did not meet the primary endpoint (better OS) in previously treated advanced NSCLC patients.[20] Gerber et al[23] indicated that the ET regimen did not lead to superior survival compared to conventional chemotherapy of a single agent. Moreover, a single-arm trial of 10 centers found that the ET group did not experience great clinical benefits among NSCLC patients who were resistant to previous EGFR-TKI therapy.[24] Another RCT of 70 patients with advanced papillary renal cell carcinoma also demonstrated that the ET regimen had no superior clinical activities.[25] A recent meta-analysis of 2577participants with NSCLC found that MET TKI plus EGFR inhibitor did not prolong OS compared to EGFR inhibitor plus placebo.[26] There is a possible reason for the failure to improve OS. Some studies indicated that MET amplification during the resistance to EGFR inhibitors mainly occurred among participants harboring EGFR mutations and not among participants harboring wild-type EGFR.[9,27] Participants with EGFR mutations made up only approximately 8.1% of the total participants in our ET group. Therefore, a small proportion could hardly lead to an OS benefit among patients treated with the ET regimen. In conclusion, we admit that although ET did not prolong OS, this regimen had better PFS and higher response rates among patients with previously treated IIIb/IV NSCLC.

Undoubtedly, subanalysis is an indispensable part of evaluating the anticancer efficacy of both groups as well. According to our subanalysis, ET was associated with an improved OS among participants expressing high MET and participants with good VeriStrat. On one hand, some early clinical trials showed that using tivantinib as monotherapy or combined with other drugs had a probable advantage for many tumors and showed the possibility that MET protein expression and MET amplification are predictive markers of efficacy.[19,28] Although these RCTs failed to reach their primary endpoints as expected, these clinical data indicated that the ET regimen may have a clinical advantage among subpopulations with high-level MET expression.[14,15,20,21] Additionally, Novello et al[29] found that the ET group had apparently better PFS and OS in a subpopulation that had high-level MET. A meta-analysis also demonstrated that participants using the combination of tivantinib and EGFR inhibitor had greater OS among the subpopulation of NSCLC patients with high-level MET.[26] The VeriStrat serum protein test plays a strong prognostic role in NSCLC patients.[30,31] A recent study retrospectively performed a detailed analysis of pretreatment plasma samples of participants with IIIb to IV

Table 2

Subgroup analysis for progression-free survival, overall survival, and objective response rate.

	PFS				OS				ORR			
Group	No. of studies	HR (95% CI)	*P*	I^2 (%)	No. of studies	HR (95% CI)	*P*	I^2 (%)	No. of studies	RR (95% CI)	*P*	I^2 (%)
Total	3	0.73 (0.67–0.80)	<.00001	0	3	0.91 (0.75–1.10)	.35	0	3	1.50 (1.06–2.12)	.02	0
Nation												
East Asia	1	0.72 (0.54–0.95)	.02	NA	1	0.89 (0.67–1.19)	.43	NA	1	1.29 (0.58–2.86)	.53	NA
North America–Europe and Australia	2	0.74 (0.67–0.81)	<.00001	0	2	0.93 (0.72–1.20)	.58	0	2	1.55 (1.05–2.28)	.03	0
Previous therapy												
1–2 Systemic anti-cancer regimens	2	0.74 (0.67–0.81)	<.00001	0	2	0.93 (0.74–1.15)	.49	0	2	1.51 (1.05–2.18)	.03	0
⩾1 chemotherapy regimens	1	0.68 (0.49–0.95)	.03	NA	1	0.87 (0.59–1.29)	.49	NA	1	1.36 (0.45–4.10)	.58	NA
Tivantinib dosage												
240 mg bid	1	0.38 (0.19–0.78)	.008	NA	1	0.58 (0.29–1.16)	.12	NA	0	NA	NA	NA
360 mg bid	3	0.74 (0.68–0.81)	<.00001	0	3	0.95 (0.78–1.16)	.6	0	2	1.55 (1.05–2.28)	.03	0
240/360 mg bid	1	0.72 (0.54–0.95)	.02	NA	1	0.89 (0.67–1.19)	.43	NA	1	1.29 (0.58–2.86)	.53	NA
VeriStrat labels												
Good	1	0.58 (0.46–0.73)	<.00001	NA	1	0.88 (0.83–0.93)	<.0001	NA	1	0.97 (0.77–1.22)	.79	NA
Poor	1	1.00 (0.98–1.03)	1	NA	1	1.00 (0.75–1.34)	1	NA	1	0.79 (0.50–1.24)	.31	NA
Mixed group	2	0.70 (0.57–0.87)	.001	0	2	0.88 (0.70–1.11)	.29	0	2	1.32 (0.69–2.50)	.4	0
Histology												
Nonsquamous NSCLC	3	0.70 (0.58–0.85)	.0004	0	3	0.89 (0.73–1.08)	.24	0	2	1.51 (1.05–2.18)	.03	0
Squamous NSCLC	1	1.05 (0.56–1.98)	.88	NA	0	NA	NA	NA	0	NA	NA	NA
Mixed group	0	NA	NA	NA	0	NA	NA	NA	1	1.36 (0.45–4.10)	.58	NA
EGFR												
Mutant	2	0.54 (0.35–0.83)	.005	0.43	1	1.04 (0.78–1.39)	.49	NA	1	1.40 (0.96–2.03)	.08	NA
Wild type	2	0.71 (0.56–0.91)	.006	0	3	0.85 (0.67–1.09)	.19	56	1	1.58 (1.04–2.38)	.03	NA
Unclear	0	NA	NA	NA	0	NA	NA	NA	1	1.36 (0.45–4.10)	.58	NA
KRAS												
Mutant	2	0.23 (0.09–0.57)	.001	0	3	0.83 (0.49–1.39)	.47	27	0	NA	NA	NA
Wild type	2	0.82 (0.64–1.07)	.14	4	2	0.92 (0.78–1.09)	.34	0	0	NA	NA	NA
Unclear	1	0.74 (0.67–0.81)	<.00001	NA	0	NA	NA	NA	3	1.50 (1.06–2.12)	.02	0
MET												
High	2	0.71 (0.56–0.91)	.007	0	2	0.76 (0.58–0.99)	.04	0	0	NA	NA	NA
Low	1	0.59 (0.37–0.96)	.03	NA	2	0.99 (0.76–1.30)	.94	0	0	NA	NA	NA
Unclear	1	0.68 (0.49–0.95)	.03	NA	1	0.87 (0.59–1.29)	.49	NA	3	1.50 (1.06–2.12)	.02	0

bid = bisindie, CI = confidence interval, EGFR epidermal growth factor receptor, HR = hazard ratio, NA = not available, NSCLC = non–small-cell lung cancer, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, RR = risk ratio.

nonsquamous NSCLC from an RCT, and it found that patients with good VeriStrat had a longer median OS (11.6 vs 10.2 months) and better median PFS (3.8 vs 2.0 months).[22] In conclusion, the ET regimen had better anticancer efficacy, especially among patients with high MET expression and patients with good VeriStrat. Therefore, we suggest that physicians should examine the MET expression and VeriStrat labels of patients with advanced NSCLC before starting the ET regimen. However, the findings need to be accepted with caution, especially positive outcomes from subanalyses, and more good-quality studies with good design will be required to verify our conclusion.

Response rates are an essential cornerstone that should be taken into account when appraising the antitumor efficacy of both arms. Our pooled outcomes demonstrated that the ET group had a higher ORR and better DCR among previously treated patients with stage IIIb/IV NSCLC. A double-blind, placebo-controlled RCT found that patients in the ET group had a higher ORR (10.3% vs 6.5%, $P = .03$) and better DCR (RR = 1.43, 95% CI: 1.23–1.67, $P < .00001$) compared with the EP group among previously treated participants with nonsquamous NSCLC.[15] In detail, our results demonstrated that there were no obvious differences between the 2 groups in CR (0% vs 2.4%, $P = .29$) or PR (RR = 1.52, 95% CI: 0.77–2.97, $P = .23$). Patients on the ET regimen had a far greater SD (RR = 1.29, 95% CI: 1.11–1.50, $P = .001$), which is believed to show the status of disease control. Under Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, SD was defined as an overall length of baseline tumor lesions that was decreased but did not reach 30% of the initial size or increased no more than 20% in size.[32] Scagliotti et al[15] also found a greater SD in patients on the ET regimen (35.5% vs 25.5%, $P = .0005$). Additionally, our results showed that dose discontinuations due to PD were less common in the ET group compared with the EP group (Fig. 4B), which also suggested that the ET regimen had better disease control. Therefore, it was no exaggeration to say that patients using the ET regimen had significantly greater response rates than those in the EP group among previously treated patients with clinical stage IIIb/IV NSCLC.

Toxicity also played an important role in comparing the therapeutic effectiveness of the two arms among patients with stage IIIb/IV NSCLC. The pooled outcomes indicated that the 10 most common toxic events had roughly similar rates between

groups, with the exception of some specific hematological toxicities, including neutropenia and febrile neutropenia. These 2 AEs were more common among patients treated with the EP regimen. Sequist et al[20] also reported that the ET regimen was well tolerated, and no significant differences were detected in AEs between the ET and EP arms in a phase-II RCT. Moreover, the subpopulation of a double-blind RCT among patients with stage IIIb to IV NSCLC found that the ET regimen had similar rates of common AEs but more grade 3–4 neutropenia.[29] Additionally, in an exploratory study of a phase-III RCT, Scagliotti et al found that most common AEs occurred equivalently between both groups, but high rates of neutropenia and febrile neutropenia were reported in the ET group.[21] ILD is one of the most important and severe AEs that directly threatens the survival of patients.[33] An Asian trial was forced to stop in advance due to the high incidence of ILD among patients in the ET group.[14] However, our pooled outcomes suggested that no apparent differences existed in any grade and grade ≥3 ILD. In brief, the higher incidence of severe hematological AEs (neutropenia and febrile neutropenia) suggests that regular hematological tests might be required for patients using an ET regimen for the early detection and timely treatment of hematological AEs.

Admittedly, there are some similar analyses[34,35] that have been published previously. Nevertheless, these previous studies have several limitations. First, erlotinib plus several molecular targeted agents versus erlotinib alone is compared in previous studies, such as tivantinib, bortezomib, everolimus, bevacizumab, sorafenib and sunitinib, revealing that substantial bias may exist if tivantinib and these agents are combined arbitrarily. Secondly, the 2 similar meta-analyses were published in 2013, and it has been 7 years since their publication date. Some important RCTs[14–15,21,22] have been published during the 7 years. Thirdly, Pan et al[34] include 8 studies, consisting of 7 RCTs and 1 conference abstract. Although the conference abstract in *Annals of Oncology* is authoritative, it may miss some important results due to short content, which may weaken the reliability of final outcomes greatly. However, there are some advantages of our study compared with previous studies[34,35]: our study compares erlotinib plus tivantinib and erlotinib alone, instead of erlotinib plus several molecular targeted agents, suggesting that higher accuracy and less bias in our study than previous analyses [34,35]; we still include these recent published RCTs into our meta-analysis, which is beneficial to generate the latest outcomes; we include relevant full-text RCTs, exclude conference abstracts, and make full use of the full texts and supplementary materials of all relevant RCTs; our meta-analysis firstly provides relevant registration information in PROSPERO (CRD42018102843).

Some inherent limitations of our meta-analysis must be considered. First, although all included studies were RCTs, the limited number of included RCTs (3) might influence the quality of results. Second, the number of participants in both arms was not large, which may have caused some unreliable outcomes. Third, some results of AEs had apparent heterogeneity, which might affect outcome quality. Fourth, some results were low-quality by GRADE, which may impair the quality of our results. Fifth, previous therapies of patients from the included RCTs were slightly different, which may influence the final results. Finally, we could not perfectly match the types of confounding factors (the time of treatments, treatment lines), and these confounding factors might influence the final outcomes.

5. Conclusion

ET appears to have more clinical benefits (similar OS, superior PFS, and higher response rates) than EP among clinical stage IIIb to IV NSCLC patients who had undergone ≥1 systemic anticancer regimen containing platinum-based therapy, especially patients with high-level MET expression, and good VeriStrat. However, the higher rate of hematological AEs necessitates extra attention be given to patients taking an ET regimen. The potential limitations of this meta-analysis indicate that it is necessary to add well-designed studies with good quality to better determine the ET group's role in intricate circumstances.

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