

# The efficacy and safety of pemetrexed-based doublet therapy compared to pemetrexed alone for the second-line treatment of advanced non-small-cell lung cancer: an updated meta-analysis

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**Background:** Pemetrexed is currently recommended as the second-line treatment for patients with advanced non-small-cell lung cancer (NSCLC). However, it is unclear whether pemetrexed-based doublet therapy improves treatment efficacy and safety. Thus, this meta-analysis was performed to resolve this controversial question.

**Methods:** Electronic databases, including PubMed, Embase, and the Cochrane Central Register of Controlled Trials were searched for relevant articles before April 2015. Hazard ratios (HRs) were used to estimate overall survival (OS) and progression-free survival (PFS), and odds ratios (ORs) were used to analyze the overall response rate (ORR) and grade  $\geq 3$  toxicities. Subgroup analysis, sensitivity analysis, and publication bias were also evaluated.

**Results:** A total of 2,519 patients from ten randomized controlled trials were included. Compared to pemetrexed alone, PFS and ORR significantly improved in the pemetrexed-based doublet group (HR, 0.86; 95% CI [confidence interval], 0.75–0.99;  $P=0.038$ ; and OR, 1.98; 95% CI, 1.25–3.12;  $P=0.003$ , respectively). However, no statistically significant differences in OS were observed between groups (HR, 0.92; 95% CI, 0.83–1.02;  $P=0.132$ ). In addition, subgroup analyses indicated that improved OS was only observed in nonsquamous NSCLC patients who received the combination of pemetrexed and erlotinib. An increasing incidence of grade  $\geq 3$  neutropenia and thrombocytopenia was observed in the pemetrexed-based doublet group.

**Conclusion:** Among patients with advanced NSCLC, pemetrexed-based doublet treatment tended to be associated with improved PFS, ORR, and increased toxicity, but not OS.

**Keywords:** non-small-cell lung cancer, pemetrexed, second-line, meta-analysis

## Introduction

Lung cancer is a leading cause of cancer-related mortality that accounts for 13% and 18% of all cancer-related cases and deaths, respectively, worldwide.<sup>1</sup> Approximately, 80%–85% of lung cancer cases are non-small-cell lung cancer (NSCLC). At the time of diagnosis, 75% of patients with NSCLC present with locally advanced or metastatic disease.<sup>2</sup> Although surgical excision and chemotherapy are attainable in some patients with advanced NSCLC, the therapeutic options for locally advanced or metastatic disease remain limited.

Platinum-based doublets are recommended as the first-line treatment for advanced NSCLC.<sup>3</sup> However, after cytotoxic therapy, 60%–70% of patients exhibit an initial nonresponse and the disease eventually progresses.<sup>4</sup> Therefore, a second-line therapy is required. Docetaxel is the standard second-line treatment for advanced NSCLC.<sup>5,6</sup> Pemetrexed, another chemotherapy drug, was also approved for the second-line

treatment of advanced NSCLC, and it resulted in equivalent outcomes to docetaxel in a randomized Phase III trial.<sup>7</sup> The use of either docetaxel or pemetrexed alone has several limitations, with a median survival time of 8 months, a 1-year survival rate of 30%, and a response rate of 10%.<sup>8</sup> Compared to docetaxel, pemetrexed results in fewer adverse events with comparable efficacy.<sup>9</sup> Thus, pemetrexed-based combination chemotherapy is a potential approach to combining several different agents and enhancing the antitumor effects in patients with advanced NSCLC.

Recently, several randomized controlled trials (RCTs) compared pemetrexed-based doublet therapy with pemetrexed alone as a second-line treatment for advanced NSCLC.<sup>10–19</sup> However, the conclusion drawn from these small-sample-size studies were inconsistent. Although previous meta-analyses conducted by Qi et al<sup>20</sup> and Sun et al<sup>21</sup> showed that the combination of pemetrexed and chemotherapy was not superior to single-agent pemetrexed as a second-line treatment for NSCLC, these analyses only included four and five studies, respectively, which is only ~50% of the available data. In addition, subgroup and sensitivity analyses were not performed, so the results might not be robust. Therefore, we conducted a meta-analysis to solve the abovementioned deficiencies and provide a more reliable conclusion.

## Materials and methods

### Search strategy

Electronic databases, including PubMed, Embase, and the Cochrane Central Register of Controlled Trials were searched up to April 2015 using the following terms: “non-small-cell lung cancer”, “pemetrexed”, “second-line therapy”, and “randomized”. Abstracts from the annual meetings of the European Society of Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) in the past 10 years were also retrieved. The references of the included studies were also screened manually. No language limitation was applied.

### Selection criteria

The relevant clinical trials were selected manually based on the following criteria: 1) trials that compared pemetrexed-based doublet with single-agent pemetrexed; 2) patients diagnosed pathologically with NSCLC and treated previously; 3) randomized Phase II and III RCTs; and 4) studies with sufficient data for extracting at least one overall survival (OS), progression-free survival (PFS), overall response rate (ORR), and grade 3 or 4 toxicities. The exclusion criteria were as follows: 1) non-RCTs, 2) truncated RCTs (since

truncated RCTs could provide misleading estimates of treatment effects),<sup>22</sup> and 3) ongoing studies. If duplicate trials were reported, only the most complete study was included.

### Data extraction

Two reviewers (Zhong AY and Xiong XL) extracted the data independently. If a disagreement between reviewers occurred, a third reviewer (Xu HJ) participated, and the issue was resolved by group discussion. The data extracted from the included studies were as follows: authors, publication year, Phase, number of patients analyzed, number of patients per arm, median age, percentage of male subjects, percentage of smokers, percentage of patients with squamous carcinoma, and Eastern Cooperative Oncology Group performance status (ECOG PS). Hazard ratios (HRs) for OS and PFS, odds ratios (ORs) for ORR and grade 3 or 4 toxicities, and 95% confidence intervals (CIs) were also extracted.

### Quality assessment

The Cochrane Collaboration’s tool for assessing risk of bias was used to evaluate the quality of the included RCTs, based on the following criteria related to random sequence generation: allocation concealment; blinding of patients, personnel, outcome assessors; incomplete outcome data; selective reporting.<sup>23</sup>

### Data analysis

HRs were used to estimate OS and PFS, and ORs were used to analyze ORR and grade 3 or 4 toxicities. Interstudy heterogeneity was assessed using Cochran’s test ( $P < 0.1$ ). The  $I^2$  statistic was also calculated, and an  $I^2 > 50\%$  indicated significant heterogeneity across studies.<sup>24</sup> A random-effects model was used if significant heterogeneity was seen among the trials.<sup>25</sup> Otherwise, the results were obtained from a fixed-effects model.<sup>26</sup> Subgroup analyses were performed according to the stratified phase, agent, and histology. Sensitivity analyses were performed by omitting one study each time. Publication bias was evaluated using subjective funnel plots and objective Begg’s and Egger’s tests.<sup>27,28</sup> All of the data analyses were performed using STATA software (version 12.0, StataCorp, College Station, TX, USA). In addition to a special statement,  $P < 0.05$  was considered to be significant.

## Results

### Search results

A total of 300 potentially relevant references identified in electronic databases were reviewed, 110 were excluded because they were duplicate studies. After reviewing the

titles and abstracts, another 153 studies were excluded for the following reasons: 42 were abstracts and case reports, 65 were non-RCTs, 9 were randomized Phase I trials, 15 were meta-analysis, 20 were not relevant to NSCLC, and 2 were truncated RCTs.<sup>29,30</sup> Thus, a total of 37 potentially eligible articles were considered for further analysis. Another 27 articles were excluded because they did not compare pemetrexed-based doublet with pemetrexed alone. Finally, ten randomized trials were eligible for inclusion in this meta-analysis. A flowchart showing the study selection process is shown in Figure 1.

## Characteristics of the included studies

In total, ten trials that pooled 1,281 patients in the pemetrexed-based doublet arm and 1,238 patients in the pemetrexed-alone arm were included in this meta-analysis. Of the ten studies, eight were randomized Phase II trials,<sup>10–13,15,16,18,19</sup> and the other two were randomized Phase III trials.<sup>14,17</sup> Among these studies, two compared pemetrexed plus carboplatin with pemetrexed alone,<sup>10,15</sup> two compared pemetrexed plus erlotinib with pemetrexed alone,<sup>16,18</sup> one compared pemetrexed plus enzastaurin with pemetrexed alone,<sup>11</sup> one compared pemetrexed plus bortezomib with pemetrexed alone,<sup>12</sup> one compared pemetrexed plus matuzumab with pemetrexed alone,<sup>13</sup> one compared pemetrexed plus vandetanib with pemetrexed alone,<sup>14</sup> one compared pemetrexed plus nintedanib with pemetrexed alone,<sup>17</sup> and one compared pemetrexed plus eribulin mesylate with

pemetrexed alone.<sup>19</sup> Using the Jadad scale, three trials scored 5, two scored 4, four scored 3, and one scored 2. The baseline characteristics of the included studies are shown in Table 1.

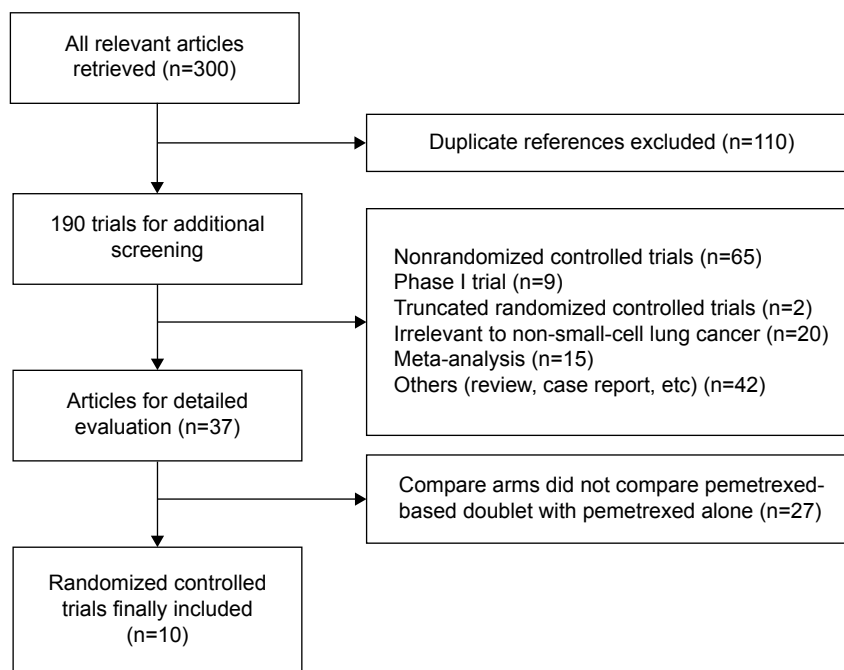
## Pooled analysis

### OS and PFS

The pooled HR for OS revealed that there were no significant differences between pemetrexed-based doublet therapy and pemetrexed alone (HR, 0.92; 95% CI, 0.83–1.02;  $P=0.137$ ). In addition, no significant interstudy heterogeneity was found ( $I^2=28.5%$ ,  $P=0.174$ ; Figure 2). Regarding PFS, the pooled HR demonstrated that pemetrexed-based doublet therapy was associated with a 14% reduced risk of progression compared to pemetrexed alone (HR, 0.86; 95% CI, 0.75–0.99;  $P=0.038$ ). There was some heterogeneity among the included studies ( $I^2=47.5%$ ,  $P=0.039$ ; Figure 3).

### Subgroup analysis

As shown in Table 2, subgroup analyses were performed according to trial phase, agents and trial histology. Compared to pemetrexed alone, an improved PFS was observed in Phase III trials (HR, 0.83; 95% CI, 0.73–0.95;  $P=0.005$ ) in those that received a combination with erlotinib (HR, 0.61; 95% CI, 0.46–0.81;  $P=0.001$ ), treated with targeted drug (HR, 0.85; 95% CI, 0.77–0.94;  $P=0.001$ ), and with a non-squamous histology (HR, 0.80; 95% CI, 0.71–0.91;

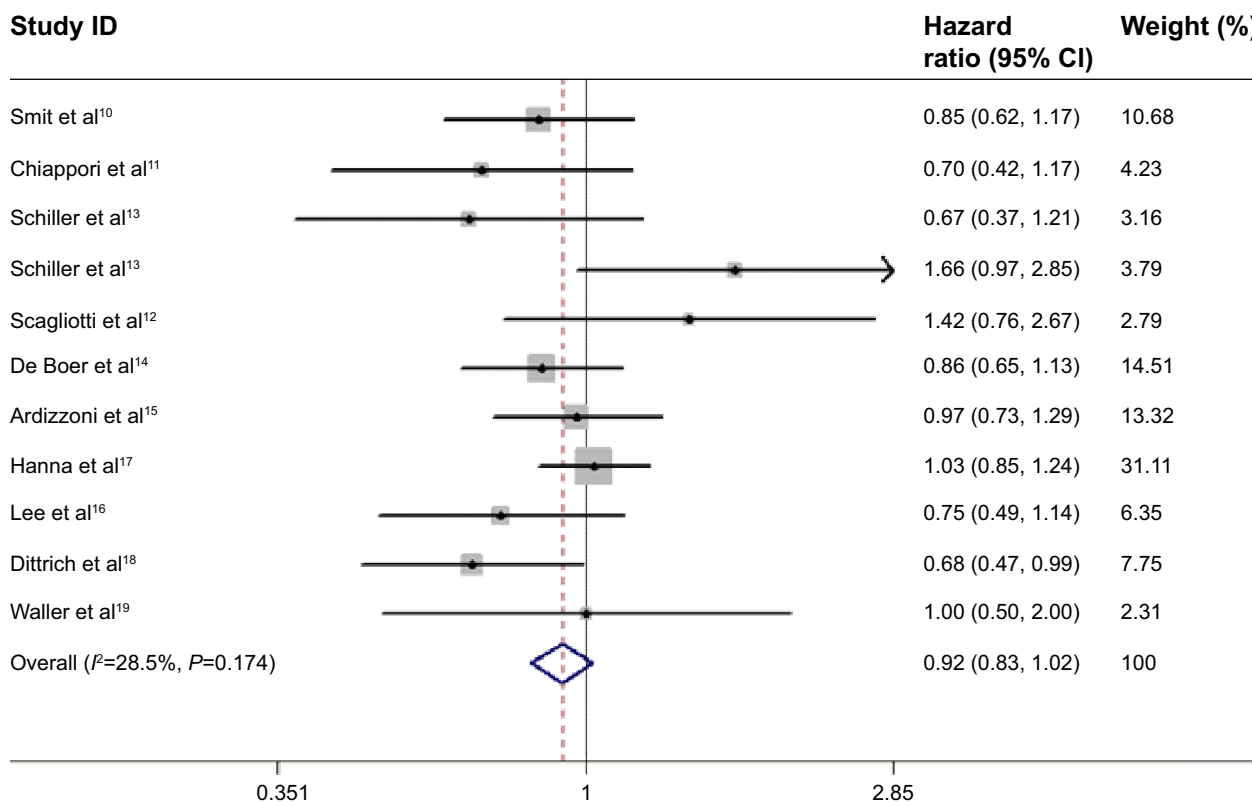


**Figure 1** Study selection process for the meta-analysis.

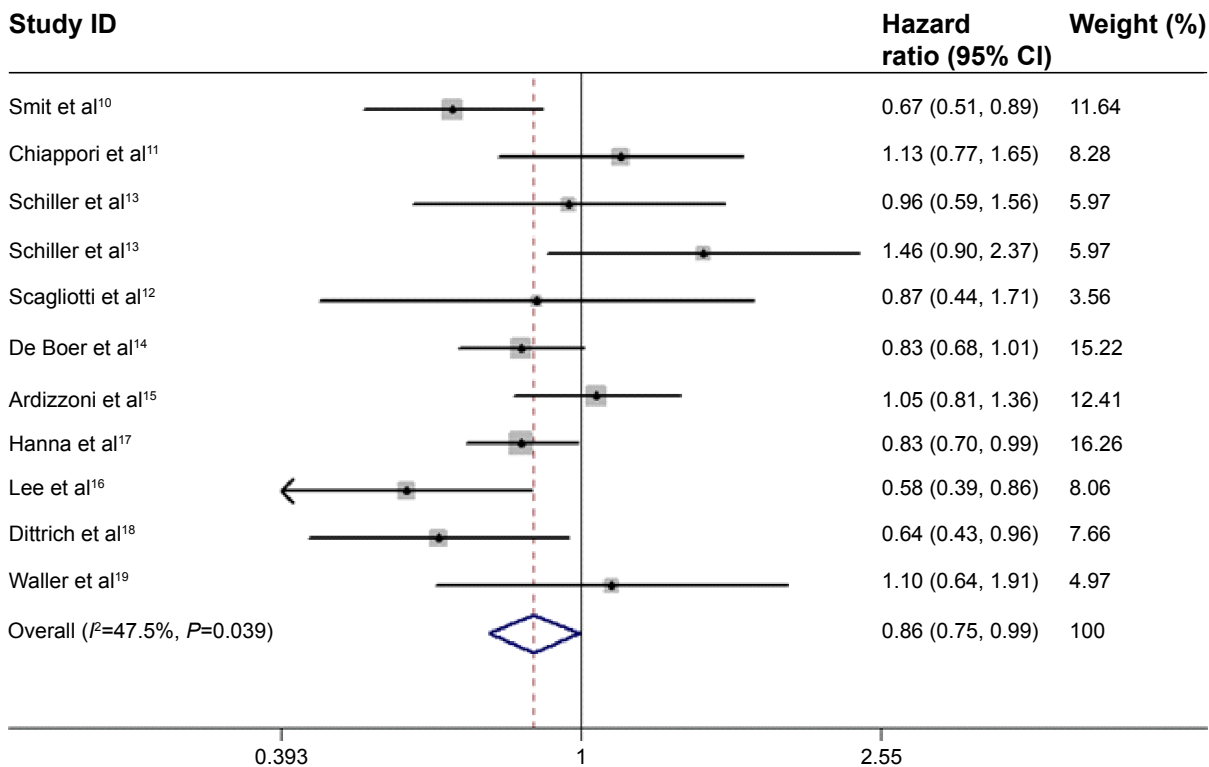
**Table 1** Baseline characteristics of the included studies

Authors	Phase	Regimes	No of patients analyzed	Patients per arm	Median age	Male (%)	Smoker (%)	Squamous histology (%)	ECOG PS 0 (%)	Jadad score
Smit et al <sup>10</sup>	Phase II	Pemetrexed plus carboplatin	240	119	59	62	NR	24	29	3
Chiappori et al <sup>11</sup>	Phase II	Pemetrexed	160	121	59	64	NR	26	31	5
		Pemetrexed plus enzastraurin	80	80	62.1	67.5	85.9	34	NR	
Scagliotti et al <sup>12</sup>	Phase II	Pemetrexed plus placebo	90	80	60.7	67.5	85.9	23	NR	3
		Pemetrexed plus bortezomib	45	45	60	65	79	44	25	
Schiller et al <sup>13</sup>	Phase II	Pemetrexed	148	51	58	71	88	39	20	3
		Pemetrexed plus matuzumab (800 mg/wk)	47	47	62	69	NR	22	NR	
De Boer et al <sup>14</sup>	Phase III	Pemetrexed plus matuzumab (1,600 mg/3 wk)	534	50	61	66	NR	36	NR	5
		Pemetrexed	278	278	60	62	78	21	41	
Ardizzone et al <sup>15</sup>	Phase II	Pemetrexed plus vandetanib	239	119	64	72.3	NR	14.3	58	4
		Pemetrexed plus placebo	120	120	64	75.8	NR	10	63.3	
Lee et al <sup>16</sup>	Phase II	Pemetrexed plus erlotinib	156	76	55.8	25.6	0	0	NR	4
		Pemetrexed	80	80	55.9	43.8	0	0	NR	
Hanna et al <sup>17</sup>	Phase III	Pemetrexed plus nintedanib	683	353	59	45	NR	0	NR	2
		Pemetrexed plus placebo	159	330	59	42	NR	0	NR	
Dittrich et al <sup>18</sup>	Phase II	Pemetrexed plus erlotinib	83	76	64	60.5	86.8	0	44	5
		Pemetrexed	80	83	61	59	83.1	0	39.8	
Waller et al <sup>19</sup>	Phase II	Pemetrexed plus eribulin	80	41	59	61	NR	NR	24	3
		Pemetrexed	39	39	60	67	NR	NR	8	

**Abbreviations:** ECOG PS 0, Eastern Cooperative Oncology Group performance status (normal activity); NR, no report; wk, week.



**Figure 2** Forest plot of overall survival in patients treated with pemetrexed-based doublet therapy and pemetrexed alone. **Abbreviation:** CI, confidence interval.



**Figure 3** Forest plot of progression-free survival in patients treated with pemetrexed-based doublet therapy and pemetrexed alone. **Note:** Weights are from random effects analysis. **Abbreviation:** CI, confidence interval.

**Table 2** Pooled and subgroup analysis of OS and PFS

Subgroup	Number of trials	OS, HR (95% CI)	PFS, HR (95% CI)
All	10	0.92 (0.83–1.02)	<b>0.86 (0.75–0.99)</b>
Phase			
II	8	0.89 (0.74–1.07)	0.89 (0.72–1.09)
III	2	0.97 (0.83–1.14)	<b>0.83 (0.73–0.95)</b>
Combined agent			
Erlotinib <sup>a</sup>	2	<b>0.71 (0.54–0.94)</b>	<b>0.61 (0.46–0.81)</b>
Target drug	8	0.93 (0.82–1.05)	<b>0.85 (0.77–0.94)</b>
Carboplatin	2	0.92 (0.74–1.13)	0.84 (0.54–1.31)
Histology			
Squamous	3	0.62 (0.31–1.21)	0.94 (0.64–1.40)
Nonsquamous	6	0.98 (0.94–1.02)	<b>0.80 (0.71–0.91)</b>

**Notes:** <sup>a</sup>Patients all had a nonsquamous histology. The figures in bold indicate the pooled HR was significantly different between pemetrexed-based doublet therapy and pemetrexed alone.

**Abbreviations:** OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

$P=0.001$ ). Regarding OS, a prolonged survival time was observed in nonsquamous NSCLC patients who received the combination of pemetrexed and erlotinib (HR, 0.71; 95% CI, 0.54–0.94;  $P=0.02$ ). No statistically significant differences were observed in other subgroup analyses.

### Overall response rate

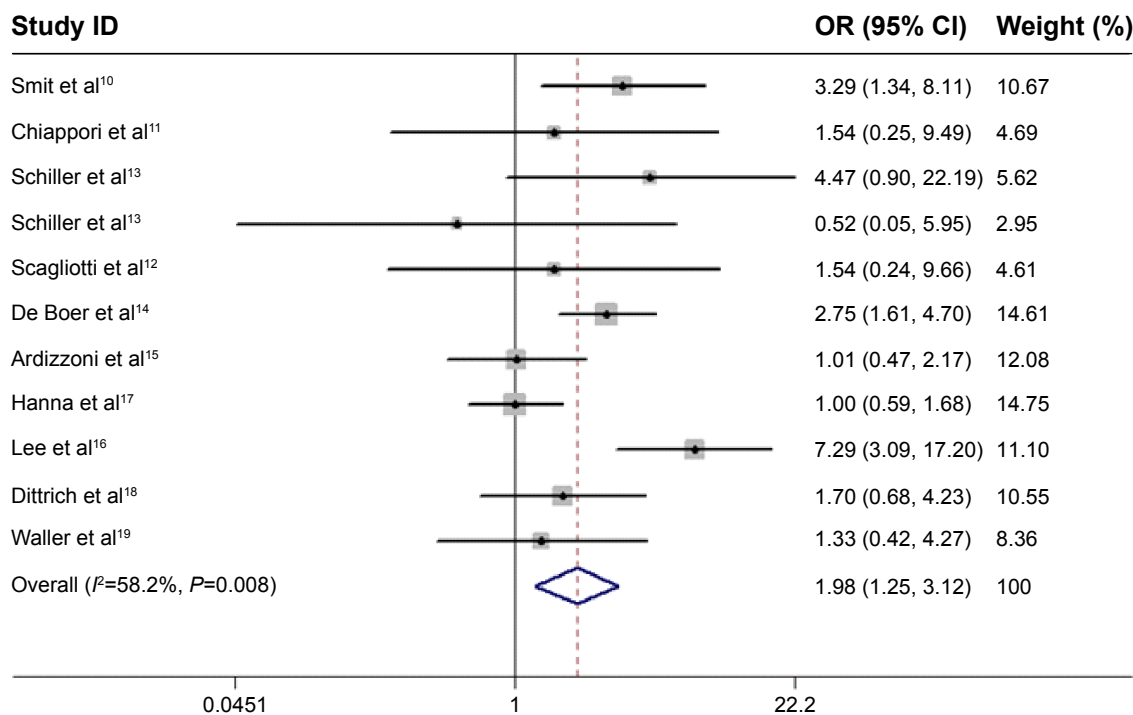
As shown in Figure 4, pemetrexed-based doublet therapy significantly improved ORR in patients with advanced NSCLC compared with pemetrexed alone (OR, 1.98; 95% CI, 1.25–3.12;  $P=0.003$ ). Moderate heterogeneity was noted among studies ( $I^2=58.2\%$ ,  $P=0.008$ ).

### Safety

There were significantly higher incidences of grade 3–4 neutropenia and thrombocytopenia in the pemetrexed-based doublet arm compared with the single-agent pemetrexed arm. However, there were no significant differences in the incidence of grade 3–4 anemia, fatigue, or leukopenia between groups (Table 3). Except for the grade 3–4 anemia and leukopenia, no significant interstudy heterogeneity was observed.

### Sensitivity analyses

Sensitivity analyses were performed to assess the stability of this meta-analysis by omitting individual trials sequentially.



**Figure 4** Forest plot of objective response rate in patients treated with pemetrexed-based doublet therapy and pemetrexed alone.

**Note:** Weights are from random effects analysis.

**Abbreviations:** OR, odds ratio; CI, confidence interval.



**Table 3** Outcome of grade 3 or 4 toxicities in a meta-analysis comparing pemetrexed-based doublet therapy with pemetrexed alone

Toxicity	Trials	Pemetrexed-based doublet therapy	Pemetrexed alone therapy	Heterogeneity		OR (95% CI)	P-value
				<i>P</i>	<i>I</i> <sup>2</sup>		
Grade 3–4 anemia	7	43/719	52/737	0.076	47.5	0.85 (0.56–1.28)	0.43
Grade 3–4 neutropenia	8	122/528	61/547	0.56	0	2.01 (1.45–2.78)	0.00
Grade 3–4 thrombocytopenia	6	57/479	16/476	0.44	0	3.77 (2.16–6.59)	0.00
Grade 3–4 fatigue	7	55/706	54/677	0.59	0	1.04 (0.70–1.55)	0.59
Grade 3–4 leukopenia	7	65/536	41/515	0.125	38.3	1.66 (0.90–3.05)	0.10

**Abbreviations:** OR, odds ratio; CI, confidence interval.

No single trial significantly altered the pooled results for OS (HRs ranged from 0.88 to 0.95), PFS (HRs ranged from 0.83 to 0.88), and ORR (ORs ranged from 1.65 to 2.06).

### Publication bias

No significant asymmetry was observed in funnel plots (data not shown). In addition, Begg's and Egger's linear regression tests revealed an absence of publication bias (OS:  $P=0.50$  and  $0.62$ ; PFS:  $P=0.67$  and  $0.74$ ; and ORR:  $P=0.76$  and  $0.87$ , respectively).

### Discussion

In this meta-analysis, data from 10 RCTs including 2,519 patients with advanced NSCLC were pooled, and the efficacy and safety of pemetrexed-based doublet therapy and pemetrexed alone were compared. Overall, the pooled analysis demonstrated that pemetrexed-based doublet treatment increased ORR and PFS compared to pemetrexed alone. However, there was no difference in OS between the two arms. Regarding toxicity, a higher frequency of drug-related grade 3–4 neutropenia and thrombocytopenia was observed in the pemetrexed-based doublet arm.

Pemetrexed, a novel multitargeted agent, inhibits a series of folate-requiring enzymes (including thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase) and prevents tumor cell growth.<sup>31</sup> It is now recommended as a second-line treatment for patients with advanced NSCLC; however, the ORR is low and the survival time is limited in these patients.<sup>8</sup> One of the traditional strategies to enhance the antitumor effects is combination chemotherapy. However, the results of RCTs conducted to evaluate and compare the efficacy of pemetrexed-based doublet with pemetrexed alone for the treatment of advanced NSCLC are inconsistent; therefore, whether pemetrexed alone or pemetrexed-based doublet is the optimal second-line treatment for advanced NSCLC remains controversial. These inconsistent results could be explained by several factors. First, different chemotherapy regimens were used for the first-line treatment in the different randomized trials, which might influence subsequent treatments.

Second, the drugs added to pemetrexed in the combination arm varied, namely, carboplatin,<sup>10,15</sup> enzastauri,<sup>11</sup> bortezomib,<sup>12</sup> matuzumab,<sup>13</sup> vandetanib,<sup>14</sup> erlotinib,<sup>16,18</sup> nintedanib,<sup>17</sup> and eribulin<sup>19</sup> were used. Finally, different histological types of NSCLC might affect the results because some RCTs only included nonsquamous tumors,<sup>16–19</sup> whereas others included all histological carcinomas.<sup>10–15</sup>

This meta-analysis was performed to resolve this controversial question. Our results showed that pemetrexed-based doublet therapy significantly improved PFS and ORR. However, with respect to survival outcomes, the improvement in PFS failed to translate into OS benefits. This was mostly due to the confounding effects from subsequent treatments. For example, in a Phase II trial,<sup>13</sup> of patients in the pemetrexed plus weekly matuzumab group, 37% received further chemotherapy (any) and 20% continued with an anti-EGFR treatment comprised of any EGFR TKI (tyrosine-kinase inhibitor) as subsequent therapy, compared with 20% and 30% in the pemetrexed alone group, compared with and 26% and 11% patients in the pemetrexed plus matuzumab every 3 weeks group. Additionally, in a randomized, double-blind Phase III trial,<sup>14</sup> ~50% of patients received some form of subsequent cancer therapy in this study, differences in response to postprogression therapy between treatment groups may have influenced the OS outcome. Since more and more active agents are emerging for the treatment of NSCLC, a PFS advantage is rarely associated with an OS advantage.<sup>32,33</sup> More work is still required to demonstrate the impact of PFS on OS.

Toxicity is particularly noteworthy in the second-line therapy of advanced NSCLC because most patients with NSCLC have suffered a long period of increasing frailty. In addition, toxicity could have a negative effect on quality of life. Regarding grade 3–4 toxicity profiles, the current meta-analysis demonstrated that there were more incidences of grade 3–4 neutropenia (OR, 2.01; 95% CI, 1.45–2.78;  $P<0.001$ ) and thrombocytopenia (OR, 3.77; 95% CI, 2.16–6.59;  $P<0.001$ ) in the pemetrexed-based doublet treatment group compared to pemetrexed alone. Thus, more

toxic effects were observed in patients with advanced NSCLC when more chemotherapy agents were administered.

Significant statistical interstudy heterogeneity was observed in PFS and ORR. The primary source of heterogeneity might arise from confounding factors among studies, including different baseline populations, study design, and data sources. Therefore, we performed a subsequent subgroup analysis stratified according to phase, agent, and histology, and the results showed that the heterogeneity disappeared in PFS subgroups according to randomized Phase III trials, combination treatment with erlotinib, and nonsquamous NSCLC, suggesting that phase, the combination agent used, and the histology might be sources of heterogeneity for PFS. However, none of abovementioned factors could explain the heterogeneity in ORR (data not shown). Interestingly, a prolonged survival time was observed in nonsquamous patients with advanced NSCLC who received the combination of pemetrexed and erlotinib. However, this conclusion is not definitive because only two RCTs were pooled.

To the best of our knowledge, this is the most comprehensive meta-analysis pooling well-designed RCTs, performed to date, to compare the efficacy and safety of pemetrexed-based doublet treatment versus pemetrexed alone in advanced NSCLC, using adequate methodology. It is noteworthy that no publication bias was detected in this meta-analysis, and no single study altered the results. All of the abovementioned statistical analyses showed that the results were robust. Nevertheless, several limitations still need to be addressed. First, some potentially relevant studies were excluded due to missing or unavailable data. Second, the total sample size included in this meta-analysis was relatively small. Finally, the treatment schedules and drugs added to the standard second-line chemotherapy in the combination arm differed.

In conclusion, the treatment of advanced NSCLC patients using pemetrexed-based doublet therapy improved PFS and ORR, but not OS, and it also increased toxicity. Thus, the use of pemetrexed-based combination chemotherapy as second-line treatment for NSCLC patients should be considered carefully. Additional RCTs with larger samples are warranted to confirm these findings. The effectiveness of other chemotherapy drugs in combination with pemetrexed needs to be evaluated for the treatment of NSCLC.

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## Disclosure

The authors report no conflicts of interest in this work.

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