

# Efficacy of pemetrexed plus platinum doublet chemotherapy as first-line treatment for advanced nonsquamous non-small-cell-lung cancer: a systematic review and meta-analysis

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**Purpose:** To assess the efficacy of pemetrexed plus platinum doublet chemotherapy as first-line treatment for advanced nonsquamous non-small-cell lung cancer (NSCLC) through a trial-level meta-analysis.

**Methods:** Trials published between 1990 and 2015 were identified by an electronic search of public databases (Medline, Embase, and Cochrane Library). All clinical studies were independently identified by two authors. Demographic data, treatment regimens, objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) were extracted and analyzed using comprehensive meta-analysis software (version 2.0).

**Results:** A total of 2,551 patients with advanced nonsquamous NSCLC from ten trials were included for analysis: 1,565 patients were treated with pemetrexed plus platinum doublet chemotherapy and 986 with platinum plus other first-line chemotherapy. Pooled ORR for pemetrexed plus platinum chemotherapy was 37.8% (95% confidence interval [CI]: 31.7%–44.3%), with median PFS and OS of 5.7 and 16.05 months, respectively. When compared to other platinum-based doublet chemotherapies, the use of pemetrexed plus platinum chemotherapy significantly improved OS (hazard ratio [HR] =0.86, 95% CI: 0.77–0.97,  $P=0.01$ ) but not PFS (HR =0.90, 95% CI: 0.80–1.01,  $P=0.084$ ) in advanced nonsquamous NSCLC patients.

**Conclusion:** Pemetrexed plus platinum doublet regimen is an efficacious treatment for advanced nonsquamous NSCLC patients. Our findings support the use of pemetrexed plus platinum doublet regimen as first-line treatment in advanced nonsquamous NSCLC patients because of its potential survival benefits.

**Keywords:** chemotherapy-naive, lung cancer, pemetrexed, pooled analysis, randomized controlled trials

## Introduction

Lung cancer is the most common cause of cancer death worldwide.<sup>1</sup> Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases, and approximately two-thirds of NSCLC patients are diagnosed with advanced disease, which cannot be successfully treated by surgery.<sup>2</sup> Currently, platinum combined with a third-generation agent (docetaxel, paclitaxel, gemcitabine, vinorelbine, and pemetrexed) is the standard treatment option for advanced NSCLC.<sup>3–6</sup> However, NSCLC is a heterogeneous disease with respect to tumor histology, and those subtypes can be broadly categorized as squamous and nonsquamous. Recent clinical research related to histology has shown important differences within the population

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of patients with NSCLC.<sup>7</sup> In 2008, Scagliotti et al<sup>8,9</sup> conducted a Phase III trial comparing first-line treatment using pemetrexed plus cisplatin with gemcitabine plus cisplatin and found that pemetrexed significantly improved overall survival (OS) in patients with nonsquamous histology (hazard ratio [HR]=0.81, 95% confidence interval [CI]: 0.70–0.94). However, in 2009, Gronberg et al<sup>10</sup> found that pemetrexed plus carboplatin provided similar OS when compared with gemcitabine plus carboplatin and that there was also no difference in OS when analyzing patients with nonsquamous histology (7.8 versus 7.5 months,  $P=0.77$ ). As a result, whether pemetrexed plus platinum chemotherapy (PPC) is superior to other platinum-based doublet chemotherapy as first-line chemotherapy for advanced nonsquamous NSCLC patients remains unknown. To our best knowledge, there are no systematic review specially investigating the efficacy of PPC as first-line treatment for advanced nonsquamous NSCLC patients. We thus perform this study of published data to assess the efficacy of PPC in advanced nonsquamous NSCLC and compare the efficacy of PPC with other platinum-based doublet chemotherapy in those patients.

## Materials and methods

### Study design

We developed a protocol that defined inclusion criteria, search strategy, outcomes of interest, and analysis plan. The reporting of this systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.<sup>11</sup>

### Identification and selection of studies

To identify studies for inclusion in our systematic review and meta-analysis, we did a broad search of four databases, including Embase, Medline, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews, from the date of inception of every database to July 2015. The search included the following terms: “lung neoplasms”, “lung carcinoma”, “lung cancer”, “pemetrexed”, “first-line”, “chemotherapy naïve”, “prospective study”, and “clinical trials”. Additional references were searched through manual searches of the reference lists and specialist journals. No language restrictions were applied.

To be eligible for inclusion in our systematic review and meta-analysis, study populations (referred to hereafter as cohorts) had to meet all the following criteria: 1) chemotherapy-naïve advanced nonsquamous NSCLC patients; 2) trials investigating the efficacy of PPC or comparing

efficacy of PPC with other platinum-based doublet chemotherapy; 3) studies reporting outcomes of interest (ie, objective response rate [ORR], progression-free survival [PFS], and OS); and 4) reports from a prospective trial (ie, randomized controlled trial and nonrandomized clinical trial). If multiple publications of the same trial were retrieved or if there was a case mix between publications, only the most recent publication (and the most informative) was included.

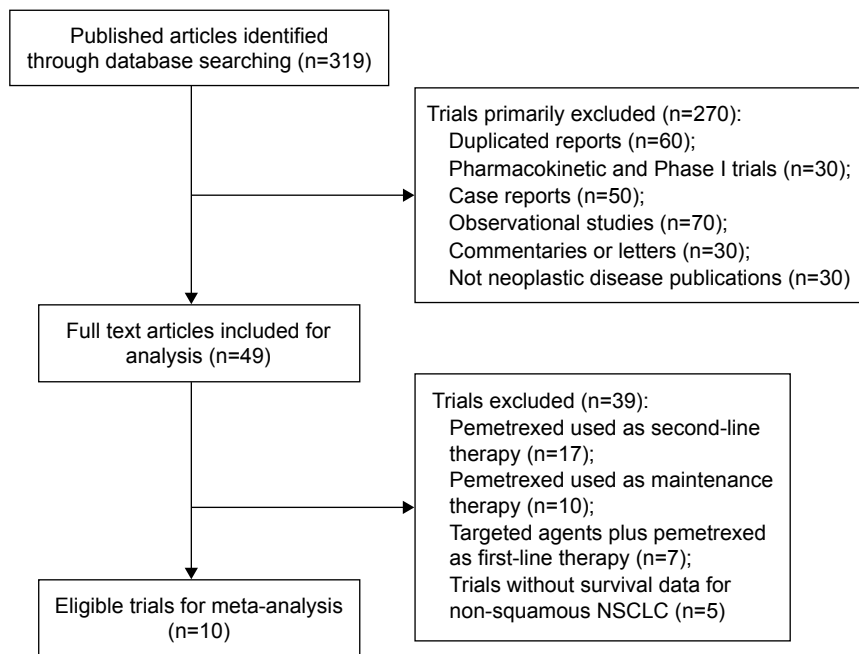
### Data extraction

Two investigators screened the titles and abstracts of potentially relevant studies. We retrieved the full text of relevant studies for further review by the same two reviewers. A third senior investigator resolved any discrepancies between reviewers. If reviewers suspected an overlap of cohorts in a report, they contacted the corresponding author for clarification; we excluded studies with a clear overlap.

The same pair of reviewers extracted study details independently, using a standardized pilot-tested form. A third investigator reviewed all data entries. We extracted the following data: author, study design, study period, median age, interventions (chemotherapy regimens and dose), sample size, and outcomes of interest. We defined outcomes of interest as ORR, PFS, and OS. The quality of reports of clinical trials was assessed and calculated using the 5-item Jadad scale including randomization, double-blinding, and withdrawals as previously described.<sup>12</sup>

### Statistical analysis

We prespecified the analysis plan in the protocol. We analyzed all patients who started PPC, regardless of their adherence to treatment. We calculated event rates of outcome (the proportion of patients who developed outcomes of interest) from the included cohorts for PPC groups. We pooled log-transformed event rates with DerSimonian and Laird random-effect models according to heterogeneity among studies.<sup>13</sup> We also pooled the overall HR for OS and PFS. A statistical test with a  $P$ -value  $<0.05$  was considered significant. To measure overall heterogeneity across the included cohorts, we calculated the  $I^2$  statistic, with  $I^2 > 50\%$  indicating high heterogeneity. If heterogeneity existed, data were analyzed using a random-effects model. In the absence of heterogeneity, a fixed-effects model was used. We did all statistical analyses with comprehensive meta-analysis software version 2.0 (Biostat, Englewood, NJ, USA).



**Figure 1** Studies eligible for inclusion in the meta-analysis.  
**Abbreviation:** NSCLC, non-small-cell lung cancer.

## Results

### Search results

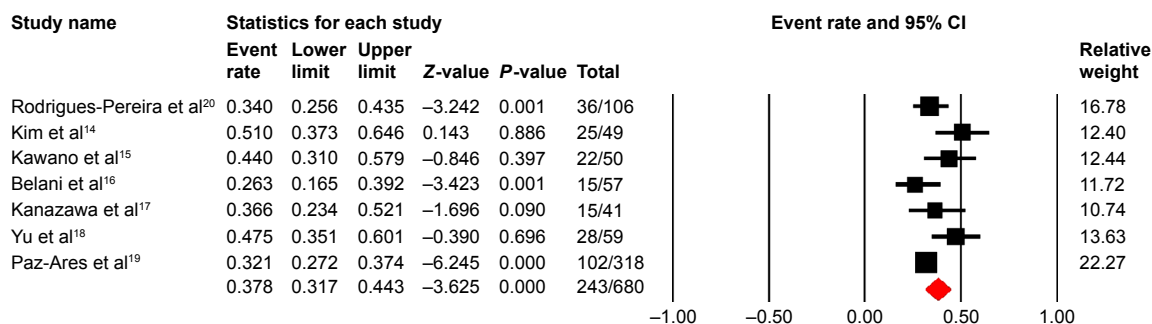
A total of 319 potentially relevant studies were retrieved electronically, 309 of which were excluded for the reasons shown in Figure 1. Six cohorts from six trials<sup>14–19</sup> assessing the efficacy of PPC in patients with nonsquamous histology and four randomized controlled trials (RCTs)<sup>8,10,20,21</sup> comparing PPC with other platinum-based doublet chemotherapy were included in the meta-analysis. The baseline characteristics of each trial are presented in Table 1. The quality of four

RCTs was approximately assessed according to Jadad scale. Four of the included trials did not mention the blinding of allocation clearly in the randomization process and thus had Jadad scores of 3. Overall, a total of 1,565 patients with advanced nonsquamous NSCLC receiving PPC and 986 with other platinum-based doublet chemotherapy were included; the pooled median PFS and OS were 5.7 and 16.05 months, respectively. A total of 680 patients from seven trials receiving PPC as first-line chemotherapy were included for ORR analysis. The pooled overall response rate was 37.8%

**Table 1** Baseline characteristics of ten trials included for meta-analysis

Source	Country	Chemotherapy regimen	Patients enrolled	Median age (years)	Median OS (months)	Median PFS (months)	ORR (%)
Scagliotti et al <sup>8</sup>	Multicenter	Pemetrexed + cisplatin	618	NR	11.8	5.3	NR
		Gemcitabine + cisplatin	614	NR	10.4	4.7	NR
Gronberg et al <sup>10</sup>	Multicenter	Pemetrexed + carboplatin	162	64	7.8	NR	NR
		Gemcitabine + carboplatin	167	66	7.5	NR	NR
Rodrigues-Pereira et al <sup>20</sup>	Multicenter	Pemetrexed + carboplatin	106	60.1	14.9	5.8	36
		Docetaxel + carboplatin	105	58.9	14.7	6	NR
Kim et al <sup>14</sup>	Japan	Pemetrexed + carboplatin	49	63	24.3	7.9	51
Kawano et al <sup>15</sup>	Japan	Pemetrexed + cisplatin	50	60	22.2	4.3	44.00
Zhang et al <sup>21</sup>	People's Republic of China	Pemetrexed + platinum	105	54	16.69	NR	NR
		Gemcitabine + platinum	100	55	16.66	NR	NR
Belani et al <sup>16</sup>	USA	Pemetrexed + cisplatin	57	59	15.9	7.1	26
Kanazawa et al <sup>17</sup>	Japan	Pemetrexed + carboplatin	41	63	16.2	4.7	37
Yu et al <sup>18</sup>	People's Republic of China	Pemetrexed + platinum	59	54.9	20.8	7	28
Paz-Ares et al <sup>19</sup>	Multicenter	Pemetrexed + cisplatin	318	60	11.5	5.6	32.08

**Abbreviations:** OS, overall survival; PFS, progression-free survival; ORR, objective response rate; NR, not reported.



**Figure 2** Random-effects model of ORR (95% CI) for pemetrexed plus platinum doublet chemotherapy. **Abbreviations:** CI, confidence interval; ORR, objective response rate.

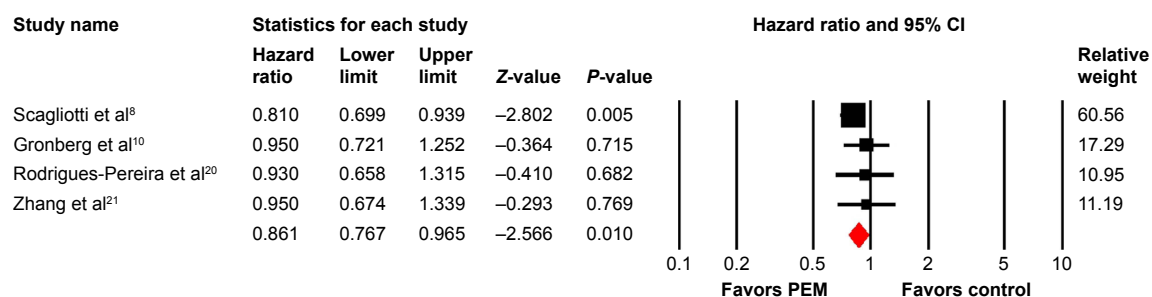
(95% CI: 31.7%–44.3%, Figure 2). There was significant heterogeneity between the trials ( $I^2=56.9\%$ ,  $P=0.031$ ), and the pooled overall response was performed using a random-effects model. All of the four RCTs reported OS data. The pooled results demonstrated that PPC significantly improved OS in comparison with other platinum-based doublet chemotherapy treatments (0.86, 95% CI: 0.77–0.97,  $P=0.01$ , Figure 3) using a fixed-effects model ( $I^2=0\%$ ,  $P=0.65$ ). Two of four RCTs reported PFS data. The pooled hazard ratio for PFS demonstrated that PPC tends to improve PFS by giving HR 0.90 (95% CI: 0.80–1.01,  $P=0.084$ , Figure 4), compared with other platinum-based doublet chemotherapy in advanced nonsquamous NSCLC patients. There was no significant heterogeneity between trials ( $I^2=0\%$ ,  $P=0.95$ ), and the pooled HR for PFS was performed by using fixed-effects model.

### Publication bias

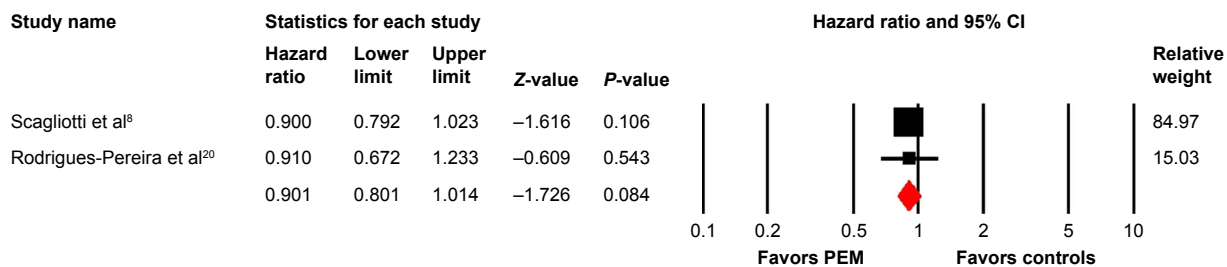
Begg’s funnel plot and Egger’s test were performed to assess the publication bias of literatures. The Begg’s funnel plots did not reveal any evidence of obvious asymmetry ( $P=0.50$  for OS, Figure 5). Then, Egger’s test was used to provide statistical evidence of funnel plot symmetry. The results still did not suggest any evidence of publication bias for OS ( $P=0.05$ ).

### Discussion

Many comprehensive and systematic reviews of the literature on PPC have been reported recently and are available for patients with advanced NSCLC.<sup>3,22–24</sup> However, to the best of our knowledge, this study is the first meta-analysis specifically focusing on investigating the efficacy of PPC as first-line chemotherapy in advanced nonsquamous NSCLC patients. Our study includes a total of 1,565 patients with advanced nonsquamous NSCLC receiving PPC and 986 with other platinum-based doublet chemotherapy. The pooled results demonstrate that pooled ORR for PPC is 37.8% (95% CI: 31.7%–44.3%), with median PFS and OS of 5.7 and 16.05 months, respectively. In addition, the use of PPC significantly improves OS (HR =0.86, 95% CI: 0.77–0.97,  $P=0.01$ ) but not PFS (HR =0.90, 95% CI: 0.80–1.01,  $P=0.084$ ) in advanced nonsquamous NSCLC patients. Based on pooled results, we found that pemetrexed plus platinum doublet regimen is an efficacious treatment for advanced nonsquamous NSCLC patients when compared to other platinum-based doublet chemotherapies. However, the results of our meta-analysis regarding survival data are not solid because of the limited number of RCTs included for analysis. Further RCTs specifically comparing PPC with other platinum-based doublet chemotherapy as



**Figure 3** Fixed-effects model of HR (95% CI) of OS associated with PEM plus platinum versus other platinum-based chemotherapy. **Abbreviations:** CI, confidence interval; HR, hazard ratio; OS, overall survival; PEM, pemetrexed.

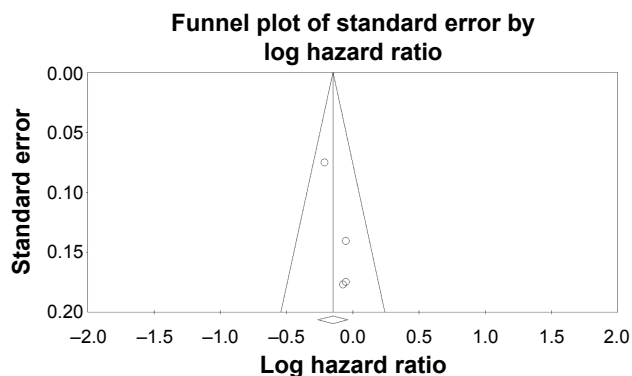


**Figure 4** Fixed-effects model of HR (95% CI) of PFS associated with PEM plus platinum versus other platinum-based chemotherapy. **Abbreviations:** CI, confidence interval; HR, hazard ratio; PEM, pemetrexed; PFS, progression-free survival.

first-line chemotherapy in advanced nonsquamous NSCLC patients are still needed.

The pathogenesis of the higher treatment effect of PPC in nonsquamous NSCLC remains unknown. One possible mechanism to explain this effect could be that the expression of thymidylate synthase is higher in squamous NSCLC and lower in nonsquamous NSCLC, leading to lower sensitivity to pemetrexed in the squamous histotype and higher sensitivity in nonsquamous types.<sup>25</sup>

Our study has several limitations that need to be taken into account. First, all included studies were conducted at major academic institutions among patients with adequate major organ function; thus, the results may not entirely apply to the general patient population in the community or patients with organ dysfunction. Second, this is a meta-analysis at the study level; data are extracted from published clinical trial results, and individual patient information is not available. Therefore, subgroup analyses according to patients' characteristics are not possible in this analysis. Finally, in the meta-analysis of published studies, publication bias is important because trials with positive results are more likely to be published and trials with null results tend not to be published. Our research detects no publication bias for OS.



**Figure 5** Funnel plot of publication bias in the meta-analysis.

## Conclusion

In conclusion, pemetrexed plus platinum doublet regimen is an efficacious treatment for advanced nonsquamous NSCLC patients. Our findings support the use of pemetrexed plus platinum doublet regimens as first-line treatment in advanced nonsquamous NSCLC patients because of its potential survival benefits. Further investigation of this regimen as first-line treatment in nonsquamous NSCLC patients is still warranted.

## Disclosure

The authors report no conflicts of interest in this work.

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