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ORIGINAL RESEARCH

Systematic review and meta-analysis of the benefit of celecoxib in treating advanced non-small-cell lung cancer

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Background: The clinical benefit of a selective cyclooxygenase-2 inhibitor, celecoxib, combined with anticancer therapy in advanced non-small-cell lung cancer (NSCLC) remains unclear. A meta-analysis was performed to address the efficacy and safety of celecoxib in patients with advanced NSCLC.

Materials and methods: Three databases, including PubMed, EMBASE, and the Cochrane Library, were systematically searched for available literature until March 1, 2018. Data on tumor response rates, one-year survival, overall survival, progression-free survival, and toxicities were extracted from the included randomized clinical trials. Subgroup analysis was carried out according to the line of treatment. Review Manager 5.3 software was applied to conduct the meta-analysis.

Results: A total of 7 randomized controlled trials involving 1,559 patients with advanced NSCLC were enrolled for analysis. The pooled overall response rate (ORR) of celecoxib added to systemic therapy was not significantly improved (risk ratio [RR] =1.14, 95% CI =0.96–1.35, *P*=0.13). Additionally, no differences were observed between the celecoxib and placebo groups regarding 1-year survival (RR =0.99, 95% CI =0.88–1.12, *P*=0.91). Subgroup analysis showed that adding celecoxib to the first-line treatment significantly improved the ORR (RR =1.21, 95% CI =1.01–1.44, *P*=0.04) and partial response rate (RR =1.26, 95% CI =1.01–1.58, *P*=0.04). The aggregated Kaplan–Meier analysis found no significant difference between celecoxib and placebo regarding the 5-year overall survival (median, 12.9 vs 12.5 months, *P*=0.553) and 5-year progression-free survival (median, 7.4 vs 7.2 months, *P*=0.641). The increased RR of leukopenia (RR =1.25, 95% CI =1.03–1.50) and thrombocytopenia (RR =1.39, 95% CI =1.11–1.75) indicated that celecoxib increased hematologic toxicities (grade ≥III). However, celecoxib did not increase the related risks of thrombosis or embolism (RR =1.26, 95% CI =0.66–2.39) and cardiac ischemia (RR =1.16, 95% CI =0.39–3.44).

Conclusion: Celecoxib had no benefit on survival indices for advanced NSCLC but improved the ORR of first-line treatment. Additionally, celecoxib increased the rate of hematologic toxicities without increasing the risk of cardiovascular events.

Keywords: celecoxib, non-small-cell lung cancer, NSCLC, systematic review, meta-analysis

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Introduction

Globally, lung cancer is a serious health problem. This disease has become the leading cause of cancer death in men and the second leading cause of cancer death (after breast cancer) in women worldwide.[1] It is estimated that there will be >230,000 new cases and >150,000 deaths in the United States in 2018.[2] Non-small-cell lung cancer (NSCLC) is the most common subtype, accounting for ~80%–85% of all lung cancer cases.[3] More than 50% of newly diagnosed NSCLC patients have advanced

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stage (IIIB or IV) disease and have, therefore, lost the opportunity for early surgical treatment.[4] EGFR tyrosine kinase inhibitors (TKIs) have a significant effect in the treatment of advanced NSCLC patients, but the efficacy is limited to EGFR wild-type patients.[5] External radiotherapy is often accompanied by many complications, such as radiation pneumonia, esophagitis, and bone marrow depression. In addition, the radiation dose is limited by the complications of normal tissue and important organs in the surrounding area.[6,7] Platinum-based chemotherapy is the cornerstone of treatment for advanced NSCLC patients who are unable to be cured. However, traditional chemotherapy is not ideal for tumor control of inoperable patients, and the median overall survival (OS) is still not >15 months.[8,9] Furthermore, the development of chemotherapy has reached a bottleneck for patients with advanced NSCLC.[10] Accordingly, new treatment strategies are urgently needed.

Accumulating evidence has demonstrated a relationship between cancer and inflammation and has shown that inflammation in the tumor microenvironment has a tumor-promoting effect.[11,12] At present, 1 target for inhibiting lung cancer-related inflammation is cyclooxygenase-2 (COX-2), an enzyme connected to prostaglandin generation and involved in pathological processes, such as the inflammation and cancer. Overexpression of COX-2 is common in NSCLC and is associated with a poor prognosis.[13–17] Preclinical studies indicated that COX-2 may be a suitable target for antitumor treatment of NSCLC.[18–20] COX-2 inhibitors were confirmed to induce apoptosis, enhance the cytotoxicity of anticancer drugs, exert antiangiogenesis effects in lung cancer models, restore antitumor immunity, and reduce tumor invasion.[18–23] Some clinical trials have made a special assessment of the role of the highly selective COX-2 inhibitor, celecoxib, in advanced/metastatic NSCLC. Csiki et al[24] evaluated the efficacy of celecoxib combined with docetaxel in the second-line treatment of metastatic NSCLC and showed that prostaglandin E2 (PGEM) levels produced by COX-2 were inhibited and that the survival time of patients was prolonged. Fidler et al[25] suggested that celecoxib combined with erlotinib for the treatment of previously treated stage IIIB/IV NSCLC patients significantly prolonged progression-free survival (PFS) in those with high expression of COX-2 (5.6 vs 2.0 months, P=0.048). The Cancer and Leukemia Group B 30,203 study reported that advanced NSCLC patients with overexpression of COX-2 who received celecoxib had a better prognosis than those who did not receive celecoxib. Moreover, tumor response was better in patients with intermediate and high levels of COX-2 based on median OS (11.2 vs 3.8 months).[17] These studies suggested that celecoxib may have clinical therapeutic effects in the treatment of patients with advanced NSCLC.

Based on these observations, many clinical trials have been conducted to investigate the efficacy and safety of celecoxib in advanced NSCLC. However, the rates of tumor response, survival, and toxicity among these trials are statistically incompatible. Some clinical Phase II trials have shown that the efficacy of a selective COX-2 inhibitor, celecoxib, combined with chemotherapy in NSCLC was better than that of chemotherapy alone.[26,27] However, other trials have shown that celecoxib combinations did not improve the survival rate of patients with advanced NSCLC.[28] This variability may be due to the limited number of patients in each trial or combinations with celecoxib in different lines of treatment. A meta-analysis assessed the efficacy of COX-2 inhibitors (celecoxib, rofecoxib, or apricoxib) in combination with chemotherapy in advanced NSCLC patients.[29] The results of this study showed that COX-2 inhibitors combined with first-line chemotherapy significantly improved the overall response rate (ORR) (risk ratio [RR] =1.27, 95% CI =1.07–1.50), but subgroup analysis including only 4 studies showed that celecoxib plus chemotherapy yielded no significant difference in patients with advanced NSCLC (RR =1.18, 95% CI =0.98–1.42, I^2=0.0%, P=0.562). Additionally, this study reported that COX-2 inhibitors with chemotherapy led to higher incidences of cardiovascular events (RR =2.39, 95% CI =1.06–5.42). Currently, there is no relevant report on evaluating the efficacy of celecoxib combined with systemic therapy (including chemotherapy, radiotherapy, and TKIs) exclusively for advanced NSCLC.

To improve the effects of celecoxib, we conducted this systematic review and meta-analysis to assess the efficacy and safety of celecoxib combined with systemic therapies in the treatment of advanced NSCLC and to explore the potential mechanisms. The primary endpoints were ORR, one-year survival, OS, and PFS. In addition, subgroup analysis was performed according to different lines of treatment in terms of ORR, 1-year survival, and partial response (PR).

Materials and methods

Search strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[30] Three databases, including PubMed, EMBASE, and the Cochrane Library, were systematically searched to identify studies related to celecoxib combined with systemic therapy in NSCLC patients. The search was performed from the date of inception through March 1, 2018, in each database without restrictions

of time and language. The following search terms were used: "Celecoxib or COX-2 inhibitor or COX-2 inhibition," "non-small cell lung cancer or non-small cell lung carcinoma or NSCLC," and "clinical trial." Additionally, we manually searched the references of all retrieved articles to identify additional studies that met the inclusion criteria.

Selection criteria

Studies that met all the following criteria were included: 1) patients histologically diagnosed with NSCLC; 2) randomized clinical trials (RCTs) designed to evaluate the efficacy and safety profile of adding celecoxib to systemic therapy in only patients with advanced NSCLC; 3) the eligible patients enrolled were adult patients with Eastern Cooperative Oncology Group (ECOG) performance status 0–2 and normal hematologic, renal, and hepatic functions; 4) number of advanced NSCLC patients enrolled <20; 5) full paper in English was published; 6) the retrieved study had sufficient data on tumor response, survival, and toxicities; and 7) the most recent and complete report of the trial was included when the same investigator reported data resulting from the same patients. Single-arm trials, case reports, animal or in vitro experiments, and other irrelevant studies were excluded. Trials with incomplete data were also excluded.

Data extraction and quality assessment

Two reviewers (LLY and WZ) searched potentially relevant papers and reviewed all the studies according to the selection criteria independently. Data extraction was performed by two reviewers independently after developing the data extraction template in advance. Any discrepancies between the 2 reviewers were resolved through discussion and consultation with the third reviewer (PL). The following items were collected from all the retrieved studies: first investigator's name, study design, country, study period, line of treatment, age (years), ECOG performance status, sample size, treatment pattern, treatment program, and dose and length of celecoxib treatment. When the necessary data were provided in a graph in the paper, Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/) was employed to extract the corresponding data. The risk of bias of the included RCTs was evaluated by two reviewers applying the Cochrane Collaboration Tool (Cochrane Library, Oxford, UK).[31]

Statistical analysis

The intent-to-treat analysis was employed to calculate tumor response, one-year survival, OS, and PFS. The differences between the experimental and control groups were estimated by pooling the RR, and the corresponding 95% CI was presented for each effect size. The heterogeneity among studies was determined by the χ^2 test and I^2 statistic. An I^2 statistic <50% indicated no statistically significant heterogeneity between studies.[32] In the absence of heterogeneity, the fixed-effects model was used to calculate the pooled RR; otherwise, the random-effects model was used. All *P*-values were 2-sided, and a statistical *P*-value of <0.05 was considered significant. Publication bias was visually assessed in a funnel plot. Additionally, Begg's test and Egger's test were employed to quantitatively estimate the publication bias of the included studies. Aggregated OS and PFS survival curves were plotted using the Kaplan–Meier method with SPSS 23 (IBM Corporation, Armonk, NY, USA). The log-rank test was applied to examine the differences in OS and PFS between study groups. The meta-analysis was conducted using Review Manager 5.3 developed by the Cochrane Collaboration (Cochrane Library).

Results

Characteristics of the studies and quality assessment

The detailed process of the PRISMA flowchart is shown in Figure 1. A total of 128 potentially relevant records were reviewed based on the initial search strategy. Eventually, a total of 7 RCTs that met the inclusion criteria were identified.[17,28,33–37] The baseline characteristics of the 7 RCTs included are presented in Table 1. The eligible studies involved 1,559 patients with advanced NSCLC, of whom 780 received combination therapy with celecoxib and 779 received systemic therapy alone. The studies included were published from 2006 to 2017, and the sample size in each study ranged from 20 to 281. Four studies were Phase II RCTs, while three studies were Phase III RCTs. The ECOG performance status of patients ranged from 0 to 2. Almost all included patients had advanced or metastatic NSCLC, but 1 patient each with stage IIB was included in both the celecoxib group and placebo group.[33] Two trials investigated second-line treatments, and 5 trials investigated first-line treatments.[17,33–35,37] Five studies involved celecoxib combined with chemotherapy,[17,28,34,35,37] while celecoxib was combined with radiotherapy in one trial,[33] and the other was related to TKIs.[36] Except for a dose of 600 mg used in 1 trial,[36] the dose of celecoxib used was 400 mg in the other 6 trials.[17,28,33–35,37] The risk of bias assessment for each study is summarized in Figure 2.

Tumor response

Six RCTs reported ORR data. The pooled ORR of celecoxib added to systemic therapy was 31.3% (196/626) and that

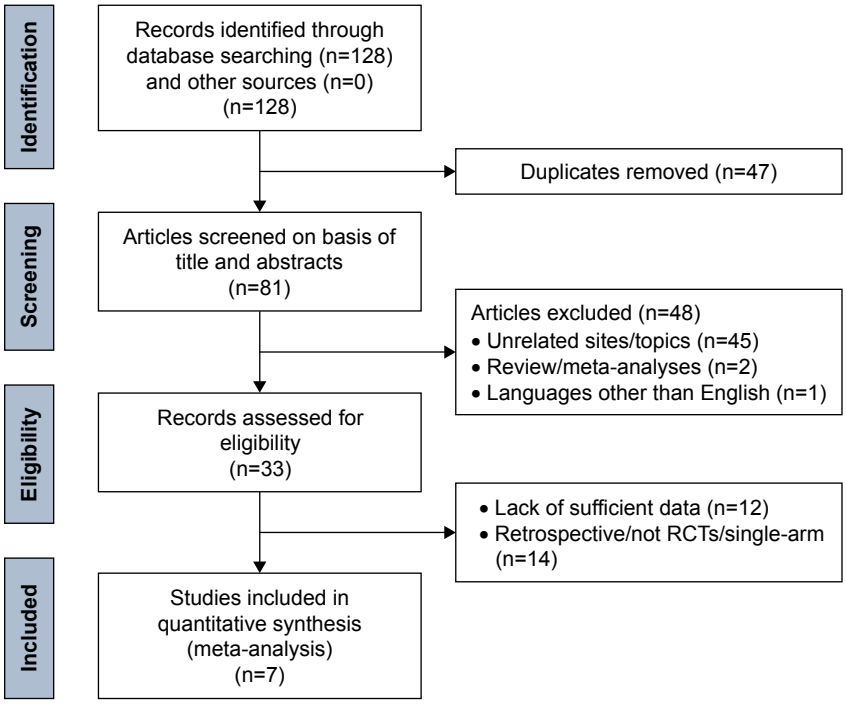

Figure 1 Flowchart of study selection according to PRISMA guidelines.
Abbreviations: PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCTs, randomized clinical trials.

of therapy without celecoxib was 27.5% (171/621), with no significant difference (RR =1.14, 95% CI =0.96–1.35, *P*=0.13) (I^2=0%, *P*=0.50). To better evaluate the efficacy of celecoxib in advanced NSCLC, we performed further subgroup analysis of ORR according to the line of treatment. The ORR was 36.0% (182/505) for patients who received celecoxib and 29.9% (150/502) for patients treated with the placebo. Thus, the ORR was significantly increased for celecoxib as a first-line treatment (RR =1.21, 95% CI =1.01–1.44, *P*=0.04) (I^2=0%, *P*=0.90). However, there was no significant difference in ORR between the celecoxib and placebo groups in the second-line treatment setting (RR =0.65, 95% CI =0.36–1.19, *P*=0.16) (Figure 3).

Four RCTs including 824 patients reported PR data. Similarly, the combined PR was 29.7% (123/414) vs 24.1% (99/410) in the celecoxib vs placebo groups (RR =1.23, 95% CI =0.99–1.54, *P*=0.06) (I^2=0%, *P*=0.55) (Table 2). Subgroup analysis showed that the PR was significantly increased in the celecoxib group during first-line treatment (RR =1.26, 95% CI =1.01–1.58, *P*=0.04) (I^2=0%, *P*=0.63) (Figure S1).

Clinical benefit (CB) and stable disease (SD) were reported in 6 studies including 1,247 patients. The pooled CB values in patients receiving celecoxib and placebo were 71.9% (450/626) and 69.9% (434/621), respectively, with no significant difference (RR =1.03, 95% CI =0.96–1.10, *P*=0.38) (I^2=0%, *P*=0.79) (Table 2). In addition, there was no significant increase in the celecoxib group in terms of SD (RR =0.96, 95% CI =0.84–1.09, *P*=0.53) (I^2=0%, *P*=0.43) (Table 2).

Survival

The 1-year survival rate was 39.2% (306/780) for patients treated with celecoxib and 39.5% (308/779) for patients treated with placebo. Accordingly, the effect was ambiguous for both celecoxib and placebo, with an RR of 0.99 (95% CI =0.88–1.12, *P*=0.91) (I^2=0%, *P*=0.57). Based on the lack of significant improvement in the one-year survival in nonselected patients, further analysis was carried out to explore the subgroups that might benefit from celecoxib. According to the subgroup analysis mentioned above, additional celecoxib did not significantly differ from systemic therapy in terms of first-line treatment (RR =1.04, 95% CI =0.91–1.19, *P*=0.58) (I^2=0%, *P*=0.79). It also did not yield a significant difference in second-line therapy (RR =0.79, 95% CI =0.59–1.05, *P*=0.11) (I^2=0%, *P*=0.33) (Figure 3). On the basis of the reported 6-month OS (OS-6), the combined analysis showed that the difference in OS-6 between the celecoxib and placebo groups was not statistically significant (RR =0.98, 95% CI =0.92–1.06, *P*=0.67) (I^2=0%, *P*=0.55) (Table 2). In addition, pooled analysis demonstrated that the 6-month PFS (PFS-6) of celecoxib and placebo was similar, at 37.2% (178/478) and 38.0% (182/479), respectively (RR =0.98,

Table 1 Characteristics of the included studies

Study, year	Phase	Country	Study period	Treatment line	Age (years)	ECOG PS	Sample size (number of case/control)	Treatment pattern		Treatment program	Dosage and length of celecoxib
								Celecoxib	Placebo	Drugs/dosage (mg/m^2)/d/frequency of cycles	
Lilenbaum et al,[28] 2006	II	America	2002–2003	Second	37–84	0–1	133 (67/66)	CT + celecoxib	CT	Irinotecan 100+ gemcitabine 1,000/irinotecan 60+ docetaxel 35/d 1, 8/3 weekly	400 mg, bid, to PD
De Ruysscher et al,[33] 2007	II	The Netherlands	2003–2004	First	41–86	0–2	41 (21/20)	RT + celecoxib	RT	Radiotherapy 60 Gy, 2 Gy/d, 5 times/weekly	400 mg, bid, 2 years
Edelman et al,[17] 2008	II	America	2003–2004	First	NR	0–2	89 (45/44)	CT + celecoxib	CT	Carboplatin AUC 5.5/d 1+ gemcitabine 1,000/d 1, 8+ zileuton 600 mg/qid	400 mg, bid, to PD or 6 cycles
Groen et al,[34] 2011	III	The Netherlands	2003–2007	First	33–84	0–2	561 (281/280)	CT + celecoxib	CT	Carboplatin AUC 6.0/d 1+ docetaxel 75/d 1/3 weekly	400 mg, bid, to PD and ≤3 years
Koch et al,[35] 2011	III	Sweden	2003–2006	First	37–85	0–2	316 (158/158)	CT + celecoxib	CT	Carboplatin/cisplatin + a third-generation drug/3 weekly	400 mg, bid, 1 year
Reckamp et al,[36] 2015	II	America	2007–2011	Second	30–80	0–1	107 (54/53)	TKIs + celecoxib	TKIs	Erlotinib 150 mg/d	600 mg, bid, to PD
Edelman et al,[37] 2017	III	America	2010–2013	First	36–89	0–2	312 (154/158)	CT + celecoxib	CT	Carboplatin AUC 6.0+ pemetrexed 500/d 1/carboplatin AUC 5.5/d 1+ gemcitabine 1,000/d 1, 8/3 weekly	400 mg, bid, to PD

Abbreviations: AUC, area under the curve; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; NR, not reported; PD, progression disease; RT, radiotherapy; TKIs, tyrosine kinase inhibitors.

95% CI =0.84–1.15, P=0.82) (I^2=36%, P=0.18) (Table 2). A similar result was found for the 12-month PFS (PFS-12) in both the celecoxib and placebo groups (RR =0.99, 95% CI =0.69–1.41, P=0.94) (I^2=24%, P=0.27) (Table 2).

After the available data from the included studies were pooled, the five-year OS for the celecoxib and placebo groups was similar (median, 12.9 vs 12.5 months, P=0.553, Figure 4A). Additionally, the 5-year PFS was not significantly improved in the celecoxib arm (median, 7.4 vs 7.2 months, P=0.641, Figure 4B).

Toxicities

Grade III or higher toxicities of celecoxib combined with systemic therapy in patients with advanced NSCLC were evaluated. The common toxicities caused by celecoxib were analyzed, including hematologic toxicities such as anemia, leukopenia, neutropenia, and thrombocytopenia, as well as nonhematologic toxicities such as nausea or vomiting, diarrhea, fatigue, thrombosis or embolism, cardiac ischemia, dyspnea, and rash. The pooled relative risk of leukopenia and thrombocytopenia was 1.25 (95% CI =1.03–1.50, P=0.02) and 1.39 (95% CI =1.11–1.75, P=0.005), respectively, which indicated that celecoxib increased the hematologic toxicity associated with systemic therapy. However, additional celecoxib did not increase the risks of thrombosis or embolism (RR =1.26, 95% CI =0.66–2.39, P=0.48) and cardiac ischemia (RR =1.16, 95% CI =0.39–3.44, P=0.78). In addition, the risk of rash in the celecoxib group was significantly increased (RR =7.75, 95% CI =1.43–42.10, P=0.02). No significant increase in the risk of other toxicities was observed (Table 3).

Publication bias

Funnel charts were used to estimate the publication bias of ORR and 1-year survival, which showed no obvious asymmetry (Figure S2). Moreover, both Begg's test and Egger's test indicated no significant publication bias (P>0.05). This finding suggested that no publication bias affected the results of this meta-analysis.

Discussion

COX-2 can be upregulated by growth factors, cytokines, carcinogens, and other stimulants and is overexpressed in a variety of malignant tumors, including NSCLC.[16] COX-2 affects tumor progression by multiple approaches, including angiogenesis, resistance to apoptosis, tumor invasion, metastasis, and host immunity.[38] In addition, COX-2 was associated with the overexpression of phosphorylated

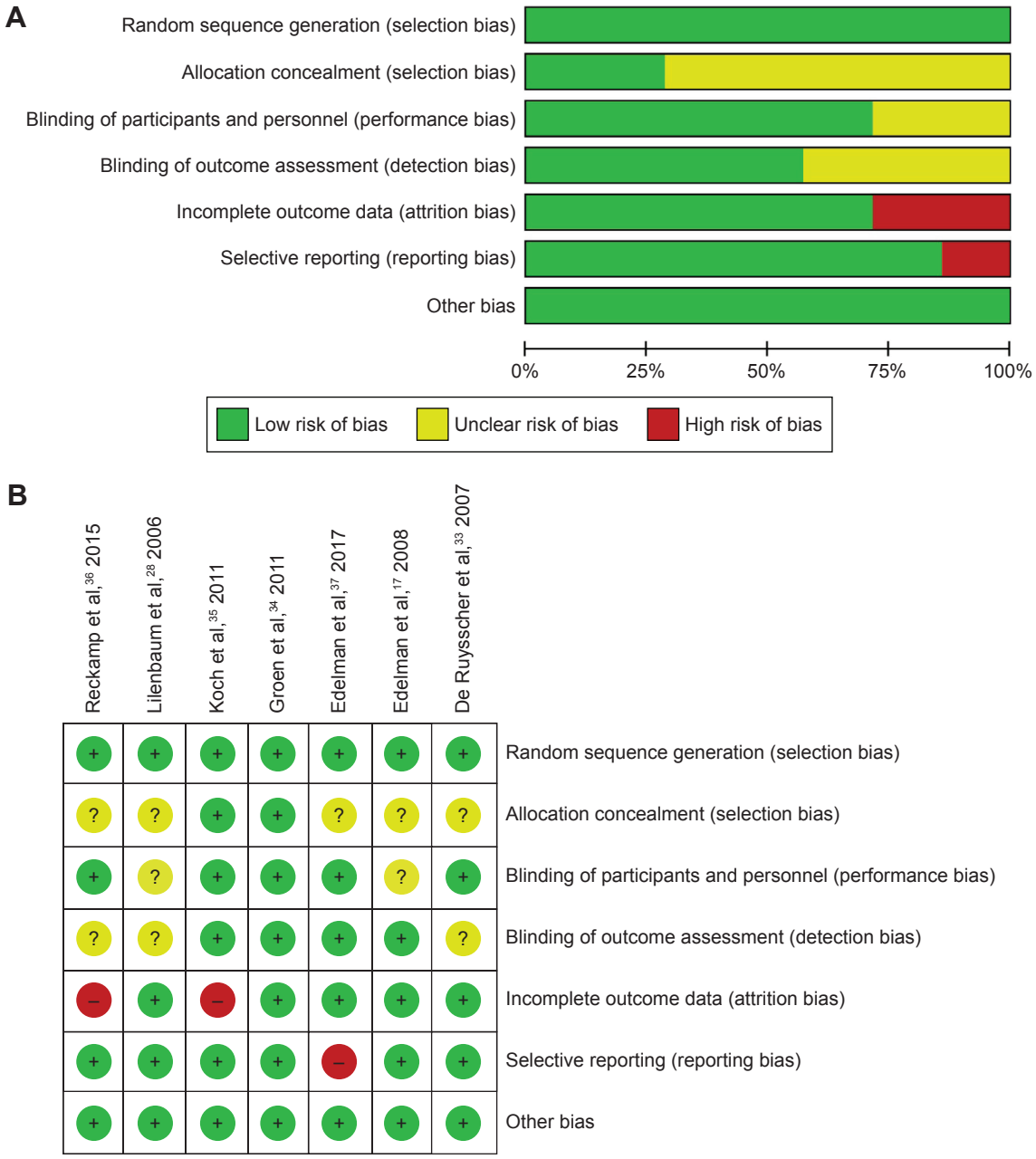

Figure 2 Risk of bias graph (**A**) and risk of bias summary (**B**) of enrolled studies.

glycoproteins, and the inhibition of COX may potentially reverse drug resistance.[39] Moreover, new evidence suggests that the mechanism of COX-2 is related to immune evasion (an important focus for the validation of immune checkpoint inhibitors in advanced NSCLC).[40] The highly selective COX-2 inhibitor celecoxib induces the apoptosis of NSCLC cells and enhances the antitumor activity of standard chemotherapeutic drugs.[41] In addition, celecoxib has been reported to reduce the adverse reactions caused by radiotherapy, such as radioactive pneumonia.[33] However, there are differences in the outcomes among clinical trials of celecoxib in advanced NSCLC.[17,28] Thus, it is necessary to assess the CBs of celecoxib for advanced NSCLC patients.

Seven eligible RCTs with 1,559 patients were identified to obtain summary statistics in the present meta-analysis. The pooled results showed that celecoxib combined with systemic treatment failed to significantly increase the tumor response rate, including ORR, CB, PR, and SD in patients with advanced NSCLC. This result may be due to the several different treatment combinations in the included studies. According to the exploratory analysis of differ-

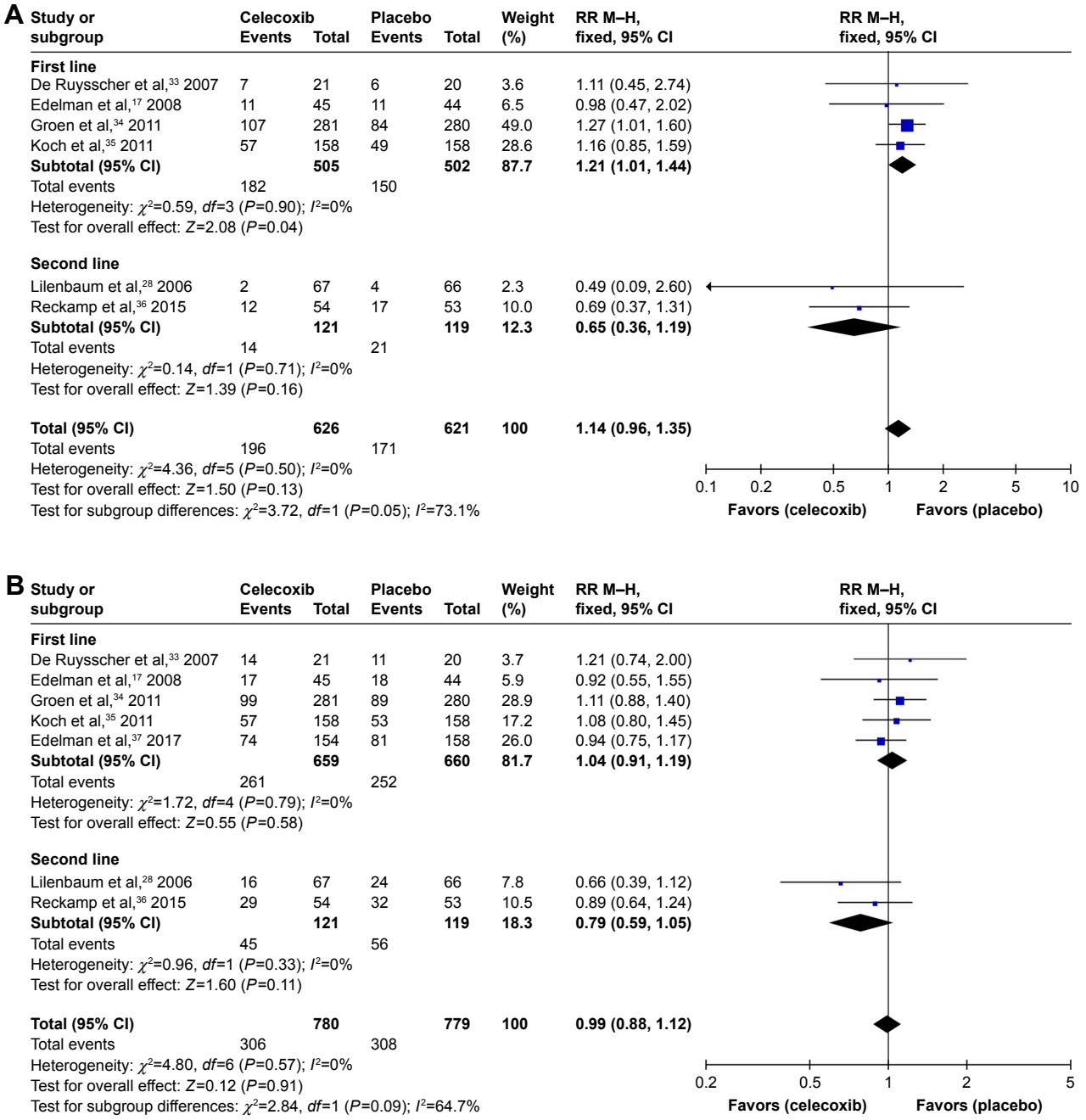

Figure 3 Forest plots for subgroup analysis of the ORR and 1-year survival (OS-12) according to the line of treatment.
Note: (**A**) ORR and (**B**) OS-12.
Abbreviations: M–H, Mantel–Haenszel; ORR, overall response rate; OS, overall survival; RR, risk ratio.

Table 2 Meta-analysis of secondary endpoints in advanced NSCLC

Outcomes	Number of RCTs	Patients		RR (95% CI)	*P*-value	Heterogeneity (I^2, *P*-value)
		Celecoxib	Placebo			
CB	6	450/626	434/621	1.03 (0.96–1.10)	0.38	0%, 0.79
PR	4	123/414	99/410	1.23 (0.99–1.54)	0.06	0%, 0.55
SD	6	254/626	263/621	0.96 (0.84–1.09)	0.53	0%, 0.43
OS-6	6	496/759	504/759	0.98 (0.92–1.06)	0.67	0%, 0.55
PFS-6	5	178/478	182/479	0.98 (0.84–1.15)	0.82	36%, 0.18
PFS-12	4	53/411	54/413	0.99 (0.69–1.41)	0.94	24%, 0.27

Abbreviations: CB, clinical benefit; NSCLC, non-small-cell lung cancer; OS-6, 6-month overall survival; PFS-6, 6-month progression-free survival; PFS-12, 12-month progression-free survival; PR, partial response; RCTs, randomized controlled trials; RR, risk ratio; SD, stable disease.

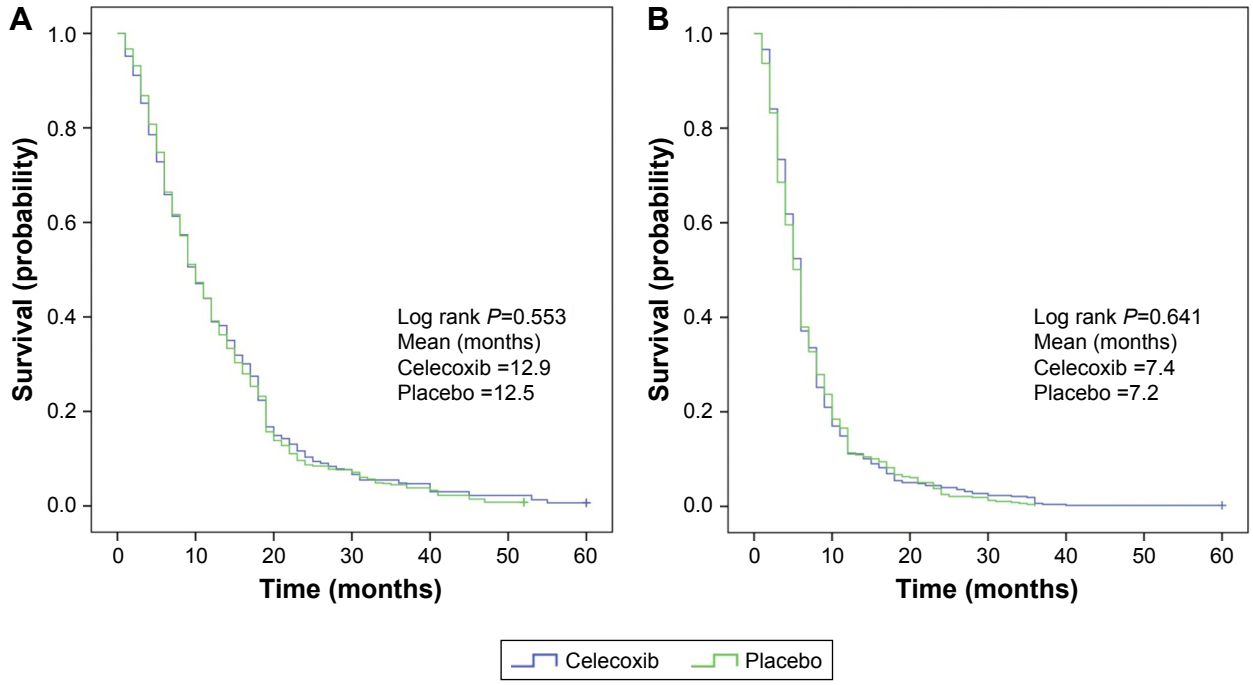

Figure 4 Kaplan–Meier estimates of OS and PFS of patients treated with celecoxib or placebo.
Note: (**A**) OS and (**B**) PFS.
Abbreviations: OS, overall survival; PFS, progression-free survival.

ent joint modes, celecoxib combined with chemotherapy, radiotherapy, or TKI treatment had no significant difference compared to the placebo arm (data not shown). Interestingly, based on subgroup analysis of the line of treatment, celecoxib significantly improved ORR (*P*=0.04) and PR (*P*=0.04) in first-line treatment. However, there was no significant increase in ORR (*P*=0.16) for second-line treatment involving celecoxib. Indeed, several studies have shown that COX-2 enhances the antitumor activity of traditional chemotherapeutic drugs, especially taxanes, in vivo and in vitro.[26,42] Moreover, studies have indicated that the additional application of COX-2 inhibitors increases the toxicity of various chemotherapeutic drugs. Compared with etoposide and cisplatin, the combination of COX-2 and irinotecan and docetaxel significantly induced the apoptosis of NSCLC cells.[18] In addition, Mutter et al[43] suggested an apparent relationship between PGEM levels and tumor response (*P*=0.005) but not survival (*P*=0.114). Therefore,

Table 3 Meta-analysis of toxicities in advanced NSCLC patients randomly assigned to celecoxib or placebo

Toxicity	N	Celecoxib	Placebo	RR (95% CI)	*P*-value	Heterogeneity (I^2, *P*-value)
		No ≥Grade III				
Hematologic						
Anemia	4	66/424	54/426	1.24 (0.90–1.69)	0.19	45%, 0.14
Leucopenia	3	173/593	139/596	1.25 (1.03–1.50)	0.02	24%, 0.27
Neutropenia	4	202/547	179/548	1.13 (0.96–1.32)	0.14	0%, 0.85
Thrombocytopenia	5	133/705	96/706	1.39 (1.11–1.75)	0.005	0%, 0.60
Febrile neutropenia	4	35/547	34/548	1.03 (0.66–1.61)	0.9	0%, 0.58
Nonhematologic						
Nausea/vomiting	3	20/480	18/482	1.22 (0.32–4.66)	0.78	67%, 0.05
Diarrhoea	2	12/435	11/438	1.09 (0.50–2.39)	0.83	50%, 0.16
Fatigue/Asthenia	2	26/435	27/438	0.97 (0.58–1.64)	0.91	0%, 0.45
Thrombosis or embolism	3	19/357	15/360	1.26 (0.66–2.39)	0.48	0%, 0.66
Cardiac ischaemia	3	6/480	5/482	1.16 (0.39–3.44)	0.78	0%, 0.41
Rash	2	11/435	1/438	7.75 (1.43–42.10)	0.02	0%, 0.45
Dyspnea	2	5/435	4/438	1.26 (0.34–4.67)	0.73	0%, 0.36

Abbreviations: CI, confidence interval; N, number of included studies; RR, risk ratio.

celecoxib may improve local control by increasing the efficacy of chemotherapy and may have little or no impact on survival.

This study found that celecoxib had no significant effects on OS and PFS in patients with advanced NSCLC, including 1-year survival, OS-6, PFS-6, and PFS-12. This finding may be associated with the use of celecoxib in unselected NSCLC patients. Biomarkers, such as COX-2 and PGEM, may have predictive value for the treatment of celecoxib, contributing to the identification of patients who will benefit from celecoxib. The Phase III RCT performed by Groen et al[34] showed that celecoxib combined with carboplatin and docetaxel did not significantly improve OS in unselected NSCLC patients. The CALGB 30203 study suggested that patients with overexpression of COX-2 had better effects with celecoxib than those who did not receive celecoxib, and multivariate analysis confirmed the independent predictive value of COX-2 and the response to celecoxib (HR =0.17, 95% CI =0.06–0.49, P=0.001).[17] However, the CALGB 30801 (Alliance) study did not confirm that the combination with celecoxib in advanced NSCLC patients based on COX-2 expression could improve clinical outcomes.[37] Another option to estimate the effect of COX-2 is to measure the urine PGEM, which can be evaluated in real time. Csiki et al[24] indicated that celecoxib combined with chemotherapy did not improve the OS of patients with advanced NSCLC, but OS was significantly prolonged in patients with low levels of PGEM. Another study suggested that the combination of celecoxib and erlotinib improves PFS in patients with higher baseline levels of PGEM.[36] The partial benefit to patients is probably because celecoxib inhibits COX-2 expression induced by chemotherapy and reduces the level of intratumoral COX-2 and PGEM. Altorki et al[44] evaluated the expression of COX-2 after neoadjuvant chemotherapy in locally advanced NSCLC patients and showed that the level of intratumoral COX-2 was 3 times as high as that in patients who were not subjected to chemotherapy. This effect was inhibited when celecoxib was combined with chemotherapy. Furthermore, if the serum levels of VEGF were <200 pg/mL before treatment, celecoxib could improve the survival of patients with NSCLC compared to the controls.[45] Consequently, the use of the optimum biomarkers may provide additional improvements for combination treatments with celecoxib for NSCLC patients.

The cardiovascular toxicity of celecoxib has always been a topic of debate in this field.[46] Cardiovascular toxicities associated with COX-2 inhibitors have restricted its application and research in cancer. Therefore, 2 RCTs failed to accomplish volunteer recruitment according to the original plan.[28,33] The current meta-analysis found that celecoxib did not significantly increase the risk of thrombus or embolism (P=0.48) or the risk of myocardial ischemia (P=0.78) at grade III or higher. Celecoxib at a high dose (800 mg bid) may be related to a high risk of cardiovascular events, while 400 mg celecoxib bid had little risk of cardiovascular events.[47] Except one study that used a dose of 600 mg bid, celecoxib was used at a dose of 400 mg bid in 6 studies. Nevertheless, the hematological toxicity of leukopenia and thrombocytopenia was significantly higher in the celecoxib group than in the placebo group (Table 2). The expression of COX-2 is increased in tumor bone marrow cells, and COX-2 plays an important role in the recovery of bone marrow after chemotherapy, which may be related to leukopenia and thrombocytopenia.[48] Preclinical data showed that mice lacking the *COX-2* gene have a slower recovery of bone marrow after exposure to 5-fluorouracil than wild-type mice. When hemolysis was induced in COX-2-deficient mice, erythrocyte formation was unimpeded compared to wild-type mice. These data suggested that COX-2 is essential for repairing bone marrow damage but is not necessary for normal bone marrow hematology.[49]

Additionally, this study still has some potential limitations. First, although there was no significant publication bias evident in the funnel plot, the small number of trials, especially in the subgroup analysis, restricted the statistical efficacy. Second, only published RCTs were included, with three Phase III trials and four Phase II trials. Third, not all RCTs provided sufficient data on the ORR and survival indices, which affected the summarized results of the present meta-analysis. Furthermore, the numbers of eligible studies and enrolled patients were not significant. These factors suggest that our study may have clinical and methodological heterogeneity. Therefore, we could not draw exact conclusions from the data, and research endeavors should be continued in future trials.

Conclusion

Celecoxib had moderate antitumor activity for advanced NSCLC without increasing the risk of cardiovascular events. In first-line treatment, celecoxib combined with systemic therapy may improve the tumor response rate in patients with advanced NSCLC. In addition, celecoxib may also increase hematological toxicities. Whether or not it is worth trying adding COX-2 to the combination of chemotherapy and immunotherapy would further improve the outcome is debatable.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

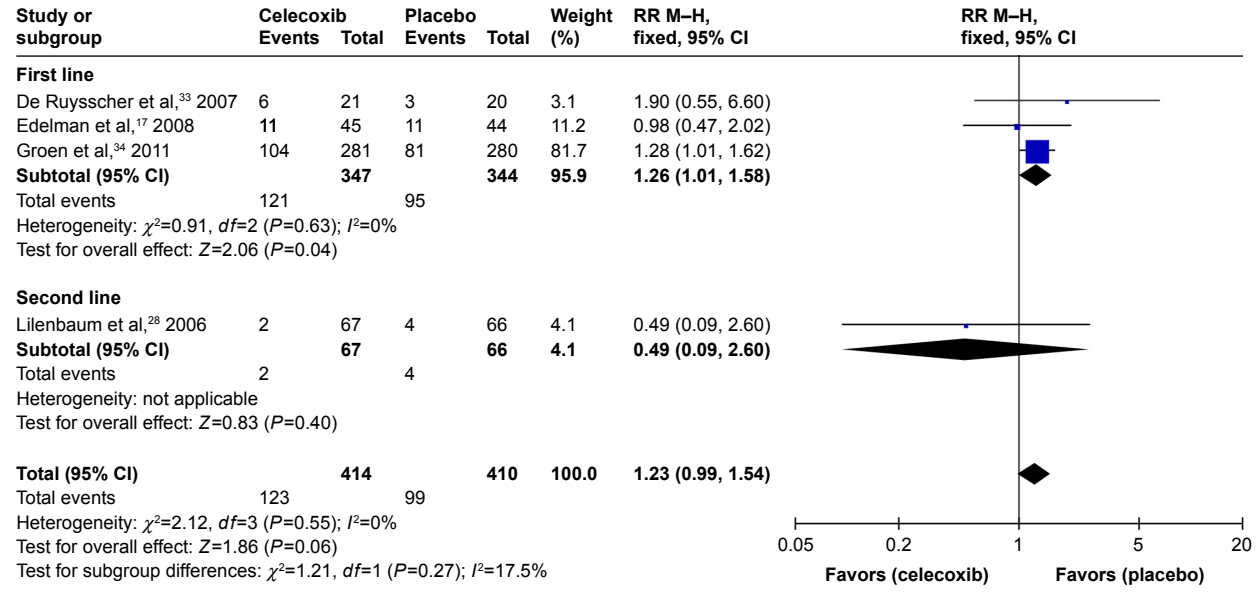

Figure S1 Forest plot for subgroup analysis of the PR according to line of treatment.
Abbreviations: M–H, Mantel–Haenszel; PR, partial response; RR, risk ratio.

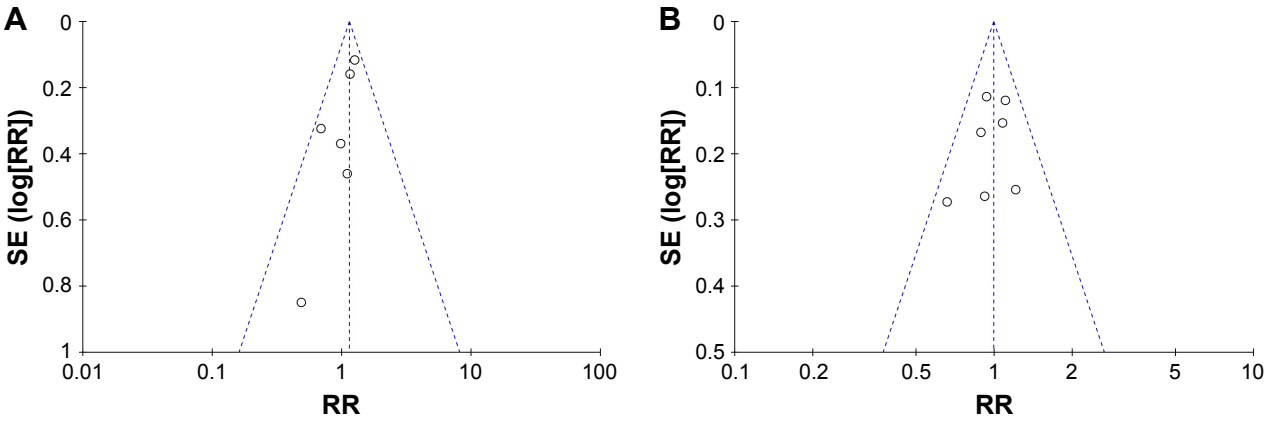

Figure S2 Funnel plot of ORR and OS-12 for studies included in the meta-analysis.
Note: (**A**) ORR and (**B**) OS-12.
Abbreviations: ORR, overall response rate; OS-12, 1-year survival; RR, risk ratio; SE, standard error.