Clinical benefit of COX-2 inhibitors in the adjuvant chemotherapy of advanced non-small cell lung cancer: A systematic review and meta-analysis

Yu-Qiong Xu, Xiang Long, Ming Han, Ming-Qiang Huang, Jia-Fa Lu, Xue-Dong Sun, Wei Han

ORCID number: Yu-Qiong Xu 0000-0001-9350-9065; Xiang Long 0000-0001-8539-9521; Ming Han 0000-0003-0600-5171; Ming-Qiang Huang 0000-0002-6507-7303; Jia-Fa Lu 0000-0001-7366-4682; Xue-Dong Sun 0000-0002-3629-7323; Wei Han 0000-0002-8509-1620.

Author contributions: Han W and Xu YQ contributed to the study conception and design, the acquisition of data, and the drafting of the manuscript; Xu YQ, Long X, Han M, Huang MQ, Lu JF, and Sun XD contributed to the analysis and interpretation of the quantitative data and the drafting of the manuscript; Xu YQ, Long X, and Han M contributed to the development of critical revising of the final draft; Xu YQ and Han W contributed to the analysis and interpretation of the descriptive and revising the final draft; All authors have read and approved the manuscript.

Supported by The Sanming Project of Medicine in Shenzhen, No. SZSM201911007.

Conflict-of-interest statement: The authors have declared that no conflict-of-interest exist.

PRISMA 2009 Checklist statement: The authors have read the PRISMA

BACKGROUND
Lung cancer is a major cause of death among patients, and non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancers in many countries.

AIM
To evaluate the clinical benefit (CB) of COX-2 inhibitors in patients with advanced NSCLC using systematic review.

METHODS
We searched the six electronic databases up until December 9, 2019 for studies that examined the efficacy and safety of the addition of COX-2 inhibitors to chemotherapy for NSCLC. Overall survival (OS), progression free survival (PFS), 1-year survival rate (SR), overall response rate (ORR), CB, complete response (CR), partial response (PR), stable disease (SD), and toxicities were measured with more than one outcome as their endpoints. Fixed and random effects models were used to calculate risk estimates in a meta-analysis. Potential publication bias was calculated using Egger’s linear regression test. Data analysis was performed using R software.

RESULTS
The COX-2 inhibitors combined with chemotherapy were not found to be more effective than chemotherapy alone in OS, progression free survival, 1-year SR, CB, CR, and SD. However, there was a difference in overall response rate for patients with advanced NSCLC. In a subgroup analysis, significantly increased ORR
INTRODUCTION

The proportion of non-small cell lung cancer (NSCLC) is more than 80% of all lung tumors. Most patients have advanced NSCLC at stage IIIIB or IV when diagnosed and confirmed and have to receive alleviative treatment in order to maintain their lives\(^\text{[3]}\). The median survival time is 6-10 mo for patients who are diagnosed with advanced NSCLC in performance status 0-2 while adopting palliative first-line chemotherapy\(^\text{[2,9]}\)\(\). For decades, chemotherapy has been the cornerstone of standard cancer treatment\(^\text{[4]}\). At present, the efficacy of various chemotherapy regimens has reached its peak\(^\text{[5]}\). New treatment strategies are hypothesized to improve the clinical benefit (CB) of advanced NSCLC.

Increased COX-2 expression was reported in close to 70% of NSCLC adenocarcinomas\(^\text{[6]}\). COX-2 expression is upregulated in the early stage of tumorigenesis, and it can lead to poor prognosis by promoting tumor cell proliferation, angiogenesis, invasion, and metastasis\(^\text{[8,9]}\). By any reasonable assessment, this targeted treatment initially achieved great success but also produced unpredictable and occasionally serious side effects. Comparison between nonselective nonsteroidal anti-inflammatory drugs and rofecoxib has shown that rofecoxib contributes to a decrease of gastrointestinal hemorrhage but not a decrease of thrombosis\(^\text{[10]}\). However, with respect to adverse events, celecoxib has no significant improvement on decreasing gastrointestinal events. The meta-analysis by Chen et al\(^\text{[1]}\) reported that celecoxib has a positive influence on the treatment of advanced cancers but increased the risk of cardiovascular events by using celecoxib, which cannot be ignored. Other studies\(^\text{[11,12]}\) indicated that celecoxib increased the overall response rate (ORR) of advanced NSCLC with no significant difference in cardiovascular events. The study related to COX-2 for intervention of NSCLC is mired in controversy in the medical field. Therefore, this systematic review based on randomized controlled trials (RCTs) was conducted to appraise the benefit of chemotherapy-assisted addition of COX-2 for advanced NSCLC.
MATERIALS AND METHODS

Search strategy
Six electronic databases, including the MEDLINE and EMBASE from Ovid, the Cochrane Library, CNKI, Wanfang Date, and CBD, were searched through December 9, 2019 using “cyclooxygenase-2 inhibitor,” “COX-2,” “apricoxib,” “celecoxib,” “rofecoxib,” “non-small cell lung cancer,” “NSCLC,” and “randomized controlled trial.”

Inclusion and exclusion criteria
The following inclusion criteria for clinical trials: (1) The language was limited to Chinese and English; (2) The benefit of the addition of COX-2 to chemotherapy (the principle of quantitative simplicity) were compared; (3) The NSCLC stage IIIB or IV patients used were defined and confirmed; (4) Outcomes such as overall survival (OS), progression free survival (PFS), 1-year survival rate (SR), ORR, CB, complete response (CR), partial response (PR), stable disease (SD), and toxicities were measured with more than one outcome as their endpoints. The primary outcomes were the OS, PFS, 1-year SR, ORR, and CB. The rate of CR and PR and the rate of grade 3 and 4 toxicity are regarded as the secondary endpoints; and (5) The study type was RCT.

Studies with criteria were excluded: (1) Patients experienced chemotherapy, immunotherapy, or any systemic therapy for NSCLC before; (2) The study was a duplicate; and (3) The data could not be extracted or obtained through contact with the author.

Data extraction and methodological quality
The data extracted were study design, patient characteristics, interventions, controls, and outcomes. The data acquisition was done independently by two authors.

The methodological quality was mainly focused on five aspects, including randomization methods, stratification factors, double blind, follow-up, and intent to treat, which were independently evaluated by two commentators. If there was a dispute, a third reviewer was consulted.

Statistical analysis
The hazard ratio (HR) was considered a reasonable effect size for OS and PFS outcomes after careful consideration. The existing HR with 95% confidence interval (CI) values provided from the original research, and then HR data was obtained. If the HR and 95%CI values were not provided, the Kaplan-Meier survival curve\cite{18} was adopted. The relative risk (RR) with 95%CI was employed for other dichotomous outcomes\cite{19,20}. The statistical test was performed for heterogeneity, and P > 40% and P < 0.1 were considered as evidence for heterogeneity as well\cite{20}. There is a theory that if the condition of the data were homogeneous under a fixed-effects model, then the heterogeneity of the results was derived from the type of Cox inhibitor and the difference in treatment line. Based on these modifiers, subgroups were conducted to address and analyze the heterogeneity. Ideally, the data are still heterogeneous, for which we introduce a stochastic effect model. The fixed-effects model was used instead when P ≤ 40%\cite{21}. Besides treatment line (first-line and second-line) and phase (II and III), COX-2 inhibitor types (celecoxib, rofecoxib, and apricoxib) were also identified as significant source of heterogeneity. Egger’s test was a methodological tool to solve quantitative detection publication bias\cite{20}. All data analyses were performed by R 5.3.1 software.

RESULTS

Characteristics of included studies
There are 1328 publications picked from the six databases (Figure 1). Ultimately, 12 studies\cite{22-33} involving 2273 patients were screened and included in this meta-analysis. The COX-2 inhibitors, including celecoxib, apricoxib, and rofecoxib, were adopted in these studies and with most of the trials opting for celecoxib. Only three studies chose rofecoxib or apricoxib. Table 1 showed the characteristics of the 12 studies.

Methodological quality
Of these 12 studies, only two trials\cite{31,33} have not reported a random component in their sequence-generation process. Five studies\cite{24,26,27,32,33} were designed with a double-blind
| Trials or Ref. | Year | Phase | Study period | Country | Sample (I/C) | Age (I/C) | Male (female) (I/C) | Histology (I/C, AC, SCC, Other) | Extent of disease, Stage | Karnofsky score | Treatment Line | Interventions | Control | Follow-up in mo |
|--------------|------|-------|--------------|---------|--------------|-----------|------------------|------------------|------------------|---------------|--------------|-------------|---------|----------------|
| Lilenbaum et al[21] | 2006 | II | Feb 2002 to Sept 2003 | United States | 133 (67/66) | 62.7 (37-84)/63.5 (41-78) | 40 (27)/40 (26) | NA, NA, NA | IIb, IV | ECOG 0-1 | Second | Celecoxib 400 mg po bid + DTX 35 mg/m² or GEM 1000 mg/m² + CPT-11 60-100 mg/m² ivgtt day 1 and day 8, q3w | DTX 35 mg/m² or GEM 1000 mg/m² + CPT-11 60-100 mg/m² ivgtt day 1 and day 8, q3w | NA |
| GECOC[22] | 2007 | III | Jan 2003 to May 2005 | Italy | 400 (149/251) | 61.5 (29-71)/59.0 (37-70) | 120 (29)/202 (49) | 68/134, 47/53, 34/64 | IIIB, IV | ECOG 0-1 | First | Rofecoxib 50 mg po qd + GEM 1200 mg/m² in 30-min or PCI GEM 1200 mg/m² over 120-min iv infusions days 1 and 8 + DDP 80 mg/m² ivgtt qd day 1, q3w | GEM 1200 mg/m² in 30-min or PCI GEM 1200 mg/m² over 120-min iv infusions days 1 and 8 + DDP 80 mg/m² ivgtt qd day 1, q3w | 22 |
| Zhou et al[23] | 2007 | II | June 2004 to June 2005 | China | 65 (32/33) | 57.0 (45-77)/55.5 (40-76) | 24 (8)/24 (9) | 17/19, 9/8, 5/3 | IIIB, IV | ECOG 0-2 | First | Celecoxib 400 mg po bid days 1-12 + NVB 25 mg/m² iv qd day 1 and 8 + DDP 75 mg/m² ivgtt qd days 1 and 2, q3w | NVB 25 mg/m² iv qd days 1 and 8 + DDP 75 mg/m² ivgtt qd days 1 and 2, q3w | NA |
| Xiong et al[24] | 2008 | II | Jan 2003 to Jan 2006 | China | 60 (30/30) | 56.4/58.3 | 16 (14)/17 (13) | 16/17, 10/10, 4/3 | IIIB, IV | ECOG 0-2 | First | Celecoxib 400 mg po bid + NVB 25 mg/m² iv qd days 1 and 8 + DDP 70 mg/m² ivgtt qd days 1-3, q3w | NVB 25 mg/m² iv qd days 1 and 8 + DDP 70 mg/m² ivgtt qd days 1-3, q3w | NA |
| CYCLUS[25] | 2011 | III | May 2003 to May 2006 | Sweden | 316 (158/158) | 66 (58-85)/65 (37-85) | 73 (85)/87 (71) | 77/94, 38/27, 43/36 | IIIB, IV | ECOG 0-2 | First | Celecoxib 400 mg po bid + GEM or NVB + CBP or DDP, ivgtt q3w | Placebo + GEM or NVB + CBP or DDP, ivgtt q3w | 36 |
| NVALT-4[26] | 2011 | III | July 2003 to Dec 2007 | Netherlands | 561 (281/280) | 62 (40-84)/61 (33-84) | 18 (97)/171 (109) | 138/132, 44/57, 99/91 | IIIB, IV | ECOG 0-2 | First | Celecoxib 400 mg po bid + DTX 75 mg/m² ivgtt qd day 1 + CBP ivgtt qd day 1, q3w | Placebo + DTX 75 mg/m² ivgtt qd day 1 + CBP ivgtt qd day 1, q3w | NA |
| Liu et al[27] | 2012 | NA | Jan 2006 to May 2011 | China | 46 (24/22) | 62 (49-75)/64 (52-76) | 14 (10)/15 (7) | 15/14, 9/8, 0/0 | IIIB, IV | Karnofsky ≥ 70 | First | Celecoxib 400 mg po bid days 1-5 + DTX 75 mg/m² ivgtt qd day 1 + DDP 100 mg/m² ivgtt qd day 1, q3w | DTX 75 mg/m² ivgtt qd day 1 + DDP 100 mg/m² ivgtt qd day 1, q3w | NA |
| Sterrenson et al[28] | 2013 | III | May 2006 to May 2009 | Sweden | 107 (52/55) | 65 (57-84) | 50/57 | 65, 16, 26 | IIIB, IV | NA | First | Celecoxib at a dose of 400 mg bid + carboplatin plus gemcitabine/vinorelbine | Carboplatin + gemcitabine/ vinorelbine | 5 |
| Gitlitz et al[29] | 2014 | II | NA | United States | 120 (78/42) | 63 (55-81)/65 (36-84) | 78 (42)/42 (25) | 45/24, 21/11, 12/7 | IIIB, IV | ECOG 0-2 | Second | Apricoraxib (400 mg/d) + erlotinib (150 mg/d) on 21-d cycles | Placebo + erlotinib (150 mg/d) on 21-d cycles | NA |
| 0822-GCC[30] | 2015 | II | NA | United States | 72 (36/36) | 62/66 | 20 (16)/20 (16) | 24/25, 8/6, 4/5 | IIIB, IV | ECOG 0-2 | Second | Apricoraxib 400 mg po qd + DTX 75 mg/m² or PET 500 mg/m², q3w | Placebo 400 mg po qd DTX 75 mg/m² or PET 500 mg/m², q3w | NA |
| Teng | 2015 | II | Aug | China | 81 (41/40) | 57.7 (28-60) | 30 (11)/26 | 28/26, 13/14 | IIIB, IV | ECOG 0-1 | First | Celecoxib 200 mg po bid + NVB 25 | NVB 25 mg/m² ivgtt days 1 | NA |
Results of primary outcomes

OS: A total of seven studies showed that compared with chemotherapy alone the result of combinations of treatments revealed that there was no statistically significant difference in OS (HR = 1.08, 95%CI: 0.96 to 1.22; I²: 0%) (Figure 2).

In order to evaluate the CB of COX-2 inhibitors, the subgroup analyses were conducted according to the type of COX-2 inhibitor and treatment line. No CB in OS was observed among the groups: apricoxib (HR = 1.04, 95%CI: 0.64 to 1.69), celecoxib (HR = 1.10, 95%CI: 0.96 to 1.27), and rofecoxib (HR = 1.00, 95%CI: 0.75 to 1.34) (Figure 2A). Conducting subgroup by the type of treatment line compared with chemotherapy alone, the COX-2 inhibitors plus chemotherapy of first-line treatment (HR = 1.06, 95%CI: 0.93 to 1.21) and second-line treatment (HR = 1.19, 95%CI: 0.88 to 1.60) were not statistically different (Figure 2B). In subgroup analyses of phase, phase II (HR = 1.19, 95%CI: 0.88 to 1.60) and phase III (HR = 1.06, 95%CI: 0.93 to 1.21) were not remarkably different (Figure 2C).

PFS: Six RCTs involving 1794 patients presented the relative data for PFS. Compared with chemotherapy alone, the COX-2 inhibitors plus chemotherapy (Figure 3) also did not represent a significant difference in PFS (HR = 0.97, 95%CI: 0.86 to 1.10).

Due to its lack of efficacy on PFS, we also performed further subgroup analysis, and all subgroup results were not significantly different (Figure 3A-C).

One-year SR: Eight RCTs including 1674 patients reported 1-year mortality rates (Figure 4). Compared with chemotherapy alone, the COX-2 inhibitors plus chemotherapy were not significantly different (RR = 1.11, 95%CI: 0.97 to 1.27).

Additionally, the results of the subgroup analysis were not significantly different trial. Although only five studies described specific follow-up times, and all studies used intention-to-treat strategy in the evaluation of outcome measures with the exception of one study. The result of methodological quality is shown in Table 2.

---

1The dose of chemotherapeutic agents was not mentioned in the trial. 2The dose of carboplatin was not mentioned in the trial. AC: Adenocarcinoma; I/C: Interventions/Control; Bid: Twice daily; CBP: Carboplatin; CR: Complete response; d: Day; DDP: Cisplatin; DTX: Docetaxel; iv: Intravenously; ECOG PS: Eastern Cooperative Oncology Group performance status; GEM: Gemcitabine; ivgtt: Intravenous drip; PCI: Prolonged constant infusion; NA: Not applicable; NVB: Vinorelbine; PET: Pemetrexed; OS: Overall survival; PFS: Progression free survival; Po: Orally; PR: Partial response; SCC: Squamous cell carcinoma; q: Every; w: Weeks.
Table 2 The risk of bias in the included studies

| Trial or Ref. | Year | Randomization methods | Stratification factors | Double blind | Follow-up | Intent to treat |
|--------------|------|-----------------------|-----------------------|--------------|-----------|----------------|
| Lilienbaum et al[26] | 2006 | Centralized | ECOG PS, age, sex, disease stage, response to treatment | No | NA | Yes |
| GECO[25] | 2007 | Centralized | Treatment, gender, PS, disease stage, tumor histology, center (three categories according to size) | No | Median follow-up of 22 mo of alive patients (range 0-40) | Yes |
| Zhou et al[24] | 2007 | Envelopes | Types | No | NA | No; 4 of 65 excluded from analysis |
| Xiong et al[28] | 2008 | Random number table | Disease stage, COX-2 expression | No | NA | Yes |
| CYCLUS[24] | 2011 | Minimization | ECOG PS, sex, stage, smoking status | Yes | After randomization, the follow-up time ranged from 0 to 36 mo | Yes |
| NVALT-4[29] | 2011 | Centralized | PS, extent of disease, use of salicylic acid, histology, COX-2 expression, treatment | No | NA | Yes |
| Liu et al[30] | 2012 | Mechanical sampling method | Stage | No | NA | Yes |
| Sörenson et al[31] | 2013 | Minimization | ECOG PS, sex, stage, smoking status | Yes | After randomization, the follow-up time ranged from 0 to 36 mo | Yes |
| Gitlitz et al[32] | 2014 | NA | ECOG PS, sex, age | Yes | The median follow-up time was 30 mo | Yes |
| 0822-GCC[28] | 2015 | Centralized | ECOG PS, sex, stage, race | Yes | NA | Yes |
| Teng et al[33] | 2015 | NA | Serum DKK-1 levels | No | NA | Yes |
| CALGB-30801[27] | 2017 | Stratified random permuted-blocks procedure | Sex, histology and chemotherapy, smoking status, stage, age group, PS | Yes | The median follow-up time was 31 mo | Yes |

ECOG: Eastern Cooperative Oncology Group; PS: Performance status; COX-2: Cylooxygenase-2; NA: Not available.

Figure 1 Summary of trial identification and selection.

among the types of COX-2 inhibitors: apricoxib (RR = 1.00, 95%CI: 0.15 to 6.72), celecoxib (RR = 1.12, 95%CI: 0.97 to 1.31), and rofecoxib (RR = 1.06, 95%CI: 0.78 to 1.44) (Figure 4A). However, when grouped by type of treatment line, the significant increase of 1-year SR (RR = 1.16; 95%CI: 1.01 to 1.34) was observed in first-line treatment, but there was no change in the second-line treatment (RR = 0.68; 95%CI: 0.41 to 1.14)
Figure 2 Subgroup analyses of forest plot for overall survival.
In subgroup analyses of phase, phase II (HR = 1.14, 95% CI: 0.71 to 1.84) and phase III (HR = 1.08, 95% CI: 0.92 to 1.27) were not significantly different (Figure 4C).

**ORR:** Eight RCTs including 1662 patients reported ORRs. Comparison of two groups as shown in Figure 3 resulted in an increase in the ORR (RR = 1.28, 95% CI: 1.10 to 1.49).

In the subgroup analysis, significantly increased ORRs were observed in celecoxib (RR = 1.23, 95% CI: 1.04 to 1.45), rofecoxib (RR = 1.56, 95% CI: 1.08 to 2.25), first-line treatment (RR = 1.30, 95% CI: 1.11 to 1.51), and phase III (RR = 1.27, 95% CI: 1.07 to 1.50). Second-line treatment (RR = 0.49, 95% CI: 0.09 to 2.60) and phase II (RR = 1.31, 95% CI: 0.88 to 1.95) with COX-2 inhibitors reported no significant differences (Figure 5A-C).

**CB:** Nine RCTs including 1776 patients reported a CB (Figure 6). Compared with chemotherapy alone, the COX-2 inhibitors plus chemotherapy did not represent a significant difference in CB (RR = 1.05, 95% CI: 0.98 to 1.11; P: 0%). As mentioned above, no significantly different results were found in the three subgroup analyses: apricoxib (RR = 1.10, 95% CI: 0.73 to 1.65; P: NA), celecoxib (RR = 1.05, 95% CI: 0.99 to 1.22; P: 14.4%), rofecoxib (RR = 0.99, 95% CI: 0.81 to 1.21; P: NA), first-line treatment (RR = 1.05, 95% CI: 0.99 to 1.22; P: 5.8%), second-line treatment (RR = 0.96, 95% CI: 0.69 to 1.33; P: 0.0%), phase II (RR = 1.07, 95% CI: 0.92 to 1.26; P: 0%), and phase III (RR = 1.53, 95% CI: 1.00 to 2.33; P: NA) (Figure 6A-C).

**Results of secondary outcome variables**

**CR:** When we assessed the effect on CR involving eight RCTs (1460 patients, there were no differences between combined treatment and chemotherapy alone (RR = 0.90, 95% CI: 0.31-2.57) (Figure 7).

The results of two subgroup analyses showed no significant difference: apricoxib (RR = 0.17, 95% CI: 0.01 to 4.18), celecoxib (RR = 0.75, 95% CI: 0.19 to 3.05), rofecoxib (RR = 5.08, 95% CI: 0.25 to 104.78), first-line treatment (RR = 1.18, 95% CI: 0.36 to 3.85), second-line treatment (RR = 0.17, 95% CI: 0.01 to 4.18), phase II (RR = 0.74, 95% CI: 0.12 to 4.38), and phase III (RR = 0.84, 95% CI: 0.03 to 28.0) (Figure 7A-C).

**PR:** When we assessed the effect on PR involving eight RCTs (1460 patients, COX-2 inhibitors combined with chemotherapy had a significant increase (RR = 1.31, 95% CI: 1.11 to 1.56) compared with chemotherapy alone (Figure 8).

The following details of subgroup analysis were represented, and the significantly increased ORRs were observed for celecoxib (RR = 1.27, 95% CI: 1.04 to 1.55), rofecoxib (RR = 1.49, 95% CI: 1.03 to 2.16), first-line treatment (RR = 1.34, 95% CI: 1.13 to 1.60), and phase III (RR = 1.33, 95% CI: 1.09 to 1.63). Apricoxib (RR = 1.17, 95% CI: 0.38 to 3.56), second-line treatment (RR = 0.88, 95% CI: 0.35 to 2.17), and phase II (RR = 1.26, 95% CI: 0.86 to 1.84) with COX-2 inhibitors showed no remarkably differences (Figure 8A-C).

**SD:** When we assessed the effect on SD involving nine RCTs with 1776 patients, COX-2 inhibitors plus chemotherapy resulted in a significant increase in SD (RR = 0.90, 95% CI: 0.80 to 1.02) compared with chemotherapy alone (Figure 9).

Subgroup analysis showed an insignificant increase in SD for apricoxib (RR = 1.16, 95% CI: 0.68 to 1.97), celecoxib (RR = 0.94, 95% CI: 0.83 to 1.07), first-line treatment (RR = 0.89, 95% CI: 0.79 to 1.01), second-line treatment (RR = 1.02, 95% CI: 0.68 to 1.52), phase II (RR = 0.99, 95% CI: 0.78 to 1.27), and phase III (RR = 0.84, 95% CI: 0.66 to 1.07). However, a change was noted for rofecoxib (RR = 0.57, 95% CI: 0.37 to 0.87).

**Toxicity:** The increase in COX-2 inhibitor was positively correlated with the increase in grade 3 and 4 toxicity of leukopenia (RR = 1.26, 95% CI: 1.03 to 1.40), thrombocytopenia (RR = 1.33, 95% CI: 1.05 to 1.68), and cardiovascular events (RR = 2.39, 95% CI: 1.06 to 5.42) (Table 3).

Subgroup analysis of leukopenia in Table 3 showed that all of celecoxib (RR = 1.26, 95% CI: 1.07 to 1.49), first-line treatment (RR = 1.20, 95% CI: 1.02 to 1.42), and phase III (RR = 1.21, 95% CI: 1.03 to 1.44) increased the risk of leukopenia. Subgroup analysis of thrombocytopenia showed that celecoxib (RR = 1.40, 95% CI: 1.08 to 1.81), second-line treatment (RR = 2.66, 95% CI: 1.14 to 6.17), and phase II (RR = 2.69, 95% CI: 1.19 to 6.07) significantly increased the incidence of thrombocytopenia. Subgroup analysis of cardiovascular events showed that rofecoxib (RR = 4.58, 95% CI: 1.01 to 20.7), first-line treatment (RR = 2.35, 95% CI: 1.01 to 5.49), and phase III (RR = 2.35, 95% CI: 1.01 to 5.49) increased the risk of cardiovascular events. However, the risks of other toxicities were not found to be increased significantly (Table 3).
Table 3: Subgroup analyses of the toxicities of COX-2 inhibitor

| Toxicity           | RCT, n | RR (95%CI) | P value for between groups | Toxicity           | RCT, n | RR (95%CI) | P value for between groups |
|--------------------|--------|------------|-----------------------------|--------------------|--------|------------|-----------------------------|
| Leucopenia         | 8      | 1.20 (1.03, 1.40) | 0.020                       | Diarrhea           | 3      | 1.31 (0.64, 2.71) | 0.460                       |
| COX-2 inhibitor type |      |            |                             | Celescoxb          | 6      | 1.26 (1.07, 1.49) | 0.280                       |
|                    |        |            |                             | Celecoxib          | 2      | 1.24 (0.59, 2.62) | 0.940                       |
| Rofecoxib          | 1      | 0.80 (0.43, 1.50) |                             | Rofecoxib          | 1      | 3.05 (0.13, 74.1) |                             |
| Apricoxib          | 1      | 0.92 (0.47, 1.80) |                             | Apricoxib          | 1      | 2.69 (0.33, 22.3) |                             |
| Treatment line     |        |            |                             | Treatment line     |        |            |                             |
| First-line         | 6      | 1.20 (1.02, 1.42) | 0.900                       | First-line         | 2      | 0.91 (0.40, 2.07) | 0.080                       |
| Second-line        | 2      | 1.19 (0.76, 1.87) |                             | Second-line        | 2      | 4.10 (0.95, 17.60) |                             |
| Phase              |        |            |                             | Phase              |        |            |                             |
| II                 | 4      | 1.14 (0.77, 1.69) | 0.720                       | II                 | 2      | 4.10 (0.95, 17.60) | 0.080                       |
| III                | 4      | 1.21 (1.03, 1.44) |                             | III                | 2      | 0.91 (0.40, 2.07) |                             |
| Thrombocytopenia   | 8      | 1.33 (1.05, 1.68) | 0.017                       | Gastric ulcer      | 2      | 1.00 (0.25, 3.97) | 0.997                       |
| COX-2 inhibitor type |      |            |                             | COX-2 inhibitor type |      |            |                             |
| Celecoxib          | 6      | 1.40 (1.08, 1.81) | 0.560                       | Celecoxib          | 2      | 1.00 (0.25, 3.97) | NA                         |
| Rofecoxib          | 1      | 1.02 (0.59, 1.76) |                             | Rofecoxib          | NA     | NA         |                             |
| Apricoxib          | 1      | 3.00 (0.13, 71.30) |                             | Apricoxib          | NA     | NA         |                             |
| Treatment line     |        |            |                             | Treatment line     |        |            |                             |
| First-line         | 6      | 1.24 (0.97, 1.58) | 0.090                       | First-line         | 2      | 1.00 (0.25, 3.97) | NA                         |
| Second-line        | 2      | 2.66 (1.14, 6.17) |                             | Second-line        | NA     | NA         |                             |
| Phase              |        |            |                             | Phase              |        |            |                             |
| II                 | 4      | 2.69 (1.19, 6.07) | 0.070                       | II                 | 2      | 1.00 (0.25, 3.97) | NA                         |
| III                | 4      | 1.23 (0.96, 1.56) |                             | III                | NA     | NA         |                             |
| Anemia             | 5      | 1.32 (0.75, 2.33) | 0.343                       | Anemia             | 7      | 0.84 (0.56, 1.28) | 0.426                       |
| COX-2 inhibitor type |      |            |                             | COX-2 inhibitor type |      |            |                             |
| Celecoxib          | 3      | 2.76 (0.96, 7.97) | 0.110                       | Celecoxib          | 5      | 0.94 (0.60, 1.48) | 0.590                       |
| Rofecoxib          | 1      | 0.80 (0.38, 1.69) |                             | Rofecoxib          | 1      | 0.53 (0.16, 1.64) |                             |
| Apricoxib          | 2      | 3.14 (0.51, 19.50) |                             | Apricoxib          | 2      | 0.94 (0.20, 4.44) |                             |
| Treatment line     |        |            |                             | Treatment line     |        |            |                             |
| First-line         | 3      | 1.07 (0.56, 2.05) | 0.140                       | First-line         | 5      | 0.92 (0.60, 1.42) | 0.560                       |
| Second-line        | 3      | 2.91 (0.89, 9.98) |                             | Second-line        | 3      | 0.53 (0.15, 1.88) |                             |
| Phase              |        |            |                             | Phase              |        |            |                             |
| II                 | 4      | 3.03 (1.00, 9.24) | 0.100                       | II                 | 4      | 0.75 (0.28, 2.02) | 0.900                       |
| III                | 2      | 1.01 (0.52, 1.97) |                             | III                | 3      | 0.86 (0.54, 1.39) |                             |
| Nausea             | 7      | 0.85 (0.53, 1.36) | 0.507                       | Nausea             | 5      | 2.39 (1.06, 5.42) | 0.037                       |
| COX-2 inhibitor type |      |            |                             | COX-2 inhibitor type |      |            |                             |
| Celecoxib          | 5      | 0.87 (0.50, 1.51) | 0.960                       | Celecoxib          | 3      | 1.55 (0.53, 4.50) | 0.540                       |
| Rofecoxib          | 1      | 0.76 (0.27, 2.13) |                             | Rofecoxib          | 1      | 4.58 (1.01, 20.70) |                             |
| Treatment line | COX-2 inhibitor type | Phase | Neurotoxicity | Treatment line | COX-2 inhibitor type |
|----------------|---------------------|-------|--------------|----------------|---------------------|
| First-line     | Apricoxib           | II    | 4            | NA             | NA                  |
|                | 2                   |       | 1.02 (0.23, 4.45) | NA             | NA                  |
|                | 1.00 (0.15, 6.72)   |       | 0.977        | NA             | NA                  |
|                | Apricoxib           | III   | 2            | NA             | NA                  |
|                | 2                   |       | 3.09 (0.13, 73.20) | NA             | NA                  |
|                | 1.00 (0.15, 6.72)   |       | 0.420        | NA             | NA                  |
|                | Celecoxib           | II    | 4            | NA             | NA                  |
|                | 3                   |       | 1.02 (0.23, 4.45) | NA             | NA                  |
|                | 1.02 (0.18, 5.83)   |       | 1.000        | NA             | NA                  |
|                | Rofecoxib           | III   | 2            | NA             | NA                  |
|                | 1                   |       | 3.09 (0.13, 73.20) | NA             | NA                  |
|                | 1.02 (0.06, 16.07)  |       | 0.420        | NA             | NA                  |
|                | Apricoxib           | II    | 4            | NA             | NA                  |
|                | 3.00 (0.13, 71.30)  |       | 0.880        | NA             | NA                  |
|                |                     |       |              | NA             | NA                  |
|                |                     |       |              | NA             | NA                  |

RCT: Randomized controlled trial; RR: Relative risk; CI: Confidence interval; NA: Not applicable.

Publication bias: In the results of publication bias using Egger’s test, all primary outcomes ($P_{OS}$: 0.314, $P_{PFS}$: 0.807, $P_{ORR}$: 0.883, $P_{1-year SR}$: 0.624, and $P_{CB}$: 0.220) were not significantly different. With respect to secondary outcomes, we did not obtain significant difference (data not shown).

**DISCUSSION**

Based on extensive preclinical and clinical studies, COX-2 inhibitors have shown significant CBs in both therapy and the chemoprevention of lung cancer. In this study, COX-2 inhibitors can increase the efficacy of chemotherapy regarding ORR. In a subgroup analysis, we found that celecoxib and rofecoxib might improve the ORR of patients with advanced NSCLC. Based on the treatment line, an increased ORR was found in first-line treatment with COX-2 inhibitors for advanced NSCLC patients. However, the second-line treatment with COX-2 inhibitors did not yield a significant effect in the ORR, possibly due to the inclusion of only one article. Teng et al.\(^3\) reported a higher ORR with celecoxib added to chemotherapy, whereas a study by Schneider et al.\(^\text{a}^4\) showed that celecoxib did not seem to improve the response rate. The most plausible explanation may be that different chemotherapy regimens were used. Teng et al.\(^\text{a}^5\) used gemcitabine/cisplatin, whereas Schneider et al.\(^\text{a}^6\) used docetaxel. However, for the CB, a significant difference was not discovered. The findings of the subgroup analysis were consistent with those of previous studies.\(^\text{a}^2,\text{a}^3,\text{a}^4\) Although no evidence showed that COX-2 inhibition could improve the CB for advanced NSCLC patients, Edelman et al.\(^\text{a}^7\) highlighted the importance of seeking molecular oriented therapy using COX-2 inhibitors. COX-2 inhibitors plus chemotherapy has no improvement on the 1-year SR for advanced NSCLC patients. In the subgroup analysis of the treatment line, COX-2 inhibitors in first-line treatment revealed a significant increase of the 1-year SR. Accordingly, the conclusion was made that COX-2 inhibitors more effectively improved both ORR and the 1-year SR for people suffering with
Figure 3 Subgroup analyses of forest plot for progression free survival.
advanced NSCLC using first-line chemotherapy. The meta-analysis by Zhou et al[16] stated that the COX-2 inhibitors may increase the ORR with advanced NSCLC.

Toxicity exists differently for individuals in incidence and severity[36]. Compared to chemotherapy alone, COX-2 inhibitors associated with chemotherapy might have a higher incidence of hematological toxicity, except for anemia. In addition, it was confirmed by subgroup analysis that combined treatment (celecoxib plus chemotherapy) could increase the risk of hematological toxicity, particularly for two periods (in that first-line treatment with leukopenia and second-line treatment with thrombocytopenia). This is consistent with previous meta-analyses[15,16]. Nevertheless, it is likely that COX-2 is necessary for marrow recovery after cytotoxic chemotherapy[37]. A study[38] suggested that the directed differentiation of erythroid, myeloid, and megakaryocytic progenitors is related to the level of COX-2. Therefore, COX-2 inhibitors may also result in higher risk of hematological toxicity while increasing the ORR by using COX-2 inhibitors.

This study illustrated that COX-2 augmented the risk of cardiovascular events as well. Cardiovascular events with higher incidences happened when using rofecoxib. The influence of rofecoxib on cardiovascular events still needed to be investigated for a few studies, whereas celecoxib had no effect on cardiovascular events. On the basis of classifying the treatment line, it slightly increased the risk of cardiovascular events of advanced NSCLC through first-line treatment associated with COX-2, but no obvious differences were observed for second-line treatment. Prostacyclin[39], a substance that associates with the expression of COX-2, existed in rofecoxib. Therefore, rofecoxib might participate in the process of formation of thrombosis. In vitro experiments have proven that celecoxib has a lower specific effect on COX-2 than rofecoxib and is less likely to cause thrombosis, which indicates the rationality of our hypothesis. Given that patients may not benefit from COX-2 selective nonsteroidal anti-inflammatory drugs[40], it makes sense to use aspirin to prevent vascular events again.

There are several meta-analyses concerning published research on the CB profile of COX-2[14-17]. The superiority of the ORR alone made it difficult to adequately demonstrate that the inhibition of the COX-2 inhibitors could improve the efficacy. A relevant study[10] analyzed six studies, setting forth all endpoints that did not conduct subgroup analysis. In addition, no subgroup analyses were performed when toxicities were assessed by Zhou et al[10]. Dai et al[11] study describing all efficacy endpoints with subgroup analysis, but other efficacy outcomes (CB, CR, PR and SD) were lacking, and toxicity was not performed by subgroup analysis to explore the difference in different types of COX-2 inhibitors and the treatment line. In this meta-analysis, 12 studies were included, and five main outcomes (ORR, CB, 1-year SR, OS and PFS) and four secondary outcomes (CR, PR, SD and toxicity) were defined above. Moreover, considering the potential clinical heterogeneity, subgroup analyses were employed based on the different types of COX-2 inhibitors and treatment line.

This study has some limitations. First, there are not many clinical trials that met the study design of this systematic review, especially in subgroup analysis, the small number of trials for rofecoxib, apric Coxib, or second-line treatment limited the analytical power. Hence, more clinical studies are needed to further confirm our results about combined treatment and chemotherapy alone for advanced NSCLC. Second, due to the lack of data on the response rate and survival outcomes in the included RCTs, this may result in too small a result sample and the accuracy of the results.

CONCLUSION

This meta-analysis demonstrated that, in terms of ORR for patients who received adjuvant chemotherapy of advanced NSCLC, COX-2 inhibitors improved the ORR and have no improvement on prolonged mortality. However, the COX-2 inhibitors could enhance both the ORR and improve the 1-year SR, particularly with first-line chemotherapy. Concerning toxicity, celecoxib plus chemotherapy resulted in a higher incidence of hematologic toxicities. Meanwhile, rofecoxib may augment the risk of cardiovascular events.
Figure 4 Subgroup analyses of forest plot for 1-year survival rate.
### A

| Study         | Experimental | Control | Risk Ratio | RR   | 95%CI       | W(fixed) | W(random) |
|---------------|--------------|---------|------------|------|------------|----------|-----------|
| **COX-2 Inhibitor Type = Celecoxib** |              |         |            |      |            |          |           |
| Lilienbaum 2006 | 2            | 67      | 466        | 0.49 | [0.09; 2.60] | 2.0%     | 0.8%      |
| Liu 2012      | 11           | 24      | 72         | 1.44 | [0.68; 3.05] | 3.6%     | 4.1%      |
| Zhou 2007     | 11           | 31      | 830        | 1.33 | [0.62; 2.84] | 4.0%     | 4.0%      |
| Xiong 2008    | 13           | 30      | 1230       | 1.08 | [0.59; 1.97] | 5.9%     | 6.4%      |
| Tang 2015     | 14           | 41      | 640        | 2.28 | [0.97; 5.33] | 3.0%     | 3.2%      |
| CYCLUS 2011   | 57           | 158     | 49 158     | 1.16 | [0.85; 1.59] | 24.2%    | 23.5%     |
| NVALT-4 2011 | 103          | 281     | 94 280     | 1.22 | [0.97; 1.55] | 41.6%    | 41.1%     |
| Fixed effect model | 632          | 626     |            | 1.23 | [1.04; 1.45] | 84.3%    |           |
| Random effects model |          |         |            | 1.23 | [1.04; 1.45] | 83.0%    |           |

Heterogeneity: I-squared = 0%, tau-squared = 0, P = 0.7197

| **COX-2 Inhibitor Type = Rofecoxib** |              |         |            |      |            |          |           |
| GECO 2007  | 49           | 119     | 32 121     | 1.56 | [1.08; 2.25] | 18.8%    | 17.0%     |
| Fixed effect model | 119          | 121     |            | 1.56 | [1.08; 2.25] | 17.0%    |           |
| Random effects model |          |         |            | 1.56 | [1.08; 2.25] | 17.0%    |           |

Heterogeneity: not applicable for a single study

### B

| Study         | Experimental | Control | Risk Ratio | RR   | 95%CI       | W(fixed) | W(random) |
|---------------|--------------|---------|------------|------|------------|----------|-----------|
| **Treatment Line = First** |              |         |            |      |            |          |           |
| Liu 2012      | 11           | 24      | 72         | 1.44 | [0.68; 3.05] | 3.6%     | 4.1%      |
| Zhou 2007     | 11           | 31      | 830        | 1.33 | [0.62; 2.84] | 4.0%     | 4.0%      |
| Xiong 2008    | 13           | 30      | 1230       | 1.08 | [0.59; 1.97] | 5.9%     | 6.4%      |
| Tang 2015     | 14           | 41      | 640        | 2.28 | [0.97; 5.33] | 3.0%     | 3.2%      |
| CYCLUS 2011   | 57           | 158     | 49 158     | 1.16 | [0.85; 1.59] | 24.2%    | 23.5%     |
| NVALT-4 2011 | 103          | 281     | 94 280     | 1.22 | [0.97; 1.55] | 41.6%    | 41.1%     |
| Fixed effect model | 684          | 681     |            | 1.30 | [1.11; 1.51] | 98.0%    |           |
| Random effects model |          |         |            | 1.29 | [1.11; 1.50] | 99.2%    |           |

Heterogeneity: I-squared = 0%, tau-squared = 0, P = 0.7075

| **Treatment Line = Second** |              |         |            |      |            |          |           |
| Lilienbaum 2006 | 2            | 67      | 466        | 0.49 | [0.09; 2.60] | 2.0%     | 0.8%      |
| Fixed effect model | 0.49         | [0.09; 2.60] | 2.0%     | 0.8%      |
| Random effects model |          |         |            | 0.49 | [0.09; 2.60] | 2.0%     | 0.8%      |

Heterogeneity: not applicable for a single study

### C

| Study         | Experimental | Control | Risk Ratio | RR   | 95%CI       | W(fixed) | W(random) |
|---------------|--------------|---------|------------|------|------------|----------|-----------|
| **Phase = II** |              |         |            |      |            |          |           |
| Lilienbaum 2006 | 2            | 67      | 466        | 0.49 | [0.09; 2.60] | 2.0%     | 0.8%      |
| Zhou 2007     | 11           | 31      | 830        | 1.33 | [0.62; 2.84] | 4.0%     | 4.0%      |
| Xiong 2008    | 13           | 30      | 1230       | 1.08 | [0.59; 1.97] | 5.9%     | 6.4%      |
| Tang 2015     | 14           | 41      | 640        | 2.28 | [0.97; 5.33] | 3.0%     | 3.2%      |
| Fixed effect model | 169          | 166     |            | 1.31 | [0.88; 1.95] | 14.9%    |           |
| Random effects model |          |         |            | 1.29 | [0.84; 1.99] | 14.3%    |           |

Heterogeneity: I-squared = 10%, tau-squared = 0.0207, P = 0.3428

| **Phase = III** |              |         |            |      |            |          |           |
| GECO 2007      | 49           | 119     | 32 121     | 1.56 | [1.08; 2.25] | 15.7%    | 17.0%     |
| CYCLUS 2011   | 57           | 158     | 49 158     | 1.16 | [0.85; 1.59] | 24.2%    | 23.5%     |
| NVALT-4 2011  | 103          | 281     | 94 280     | 1.22 | [0.97; 1.55] | 41.6%    | 41.1%     |
| Fixed effect model | 558          | 559     |            | 1.27 | [1.07; 1.50] | 81.5%    |           |
| Random effects model |          |         |            | 1.27 | [1.07; 1.50] | 81.6%    |           |

Heterogeneity: I-squared = 0%, tau-squared = 0, P = 0.4507

| **Phase = none** |              |         |            |      |            |          |           |
| Liu 2012      | 11           | 24      | 72         | 1.44 | [0.68; 3.05] | 3.6%     | 4.1%      |
| Fixed effect model | 1.44         | [0.68; 3.05] | 3.6%     | 4.1%      |
| Random effects model |          |         |            | 1.44 | [0.68; 3.05] | 3.6%     | 4.1%      |

Heterogeneity: not applicable for a single study

| Fixed effect model | 1.28          | [1.10; 1.49] | 100%      |         |
| Random effects model |          |         |            | 1.28 | [1.10; 1.49] | 100%      |

Heterogeneity: I-squared = 0%, tau-squared = 0, P = 0.6557

### Figure 5
Subgroup analyses of forest plot for overall response rate.
Figure 6 Subgroup analyses of forest plot for clinical benefit.
Figure 7  Subgroup analyses of forest plot for complete response.
**Figure 8** Subgroup analyses of forest plot for partial response.
**Figure 9** Subgroup analyses of forest plot for stable disease.
ARTICLE HIGHLIGHTS

Research background
The proportion of non-small cell lung cancer (NSCLC) is more than 80% of all lung tumors. Most patients have advanced NSCLC at stage IIIB or IV when diagnosed and have to receive alleviative treatment in order to maintain their lives. The median survival time is 6-10 mo for patients who are diagnosed with advanced NSCLC in performance status 0-2 when adopting palliative first-line chemotherapy.

Research motivation
The motivation of this study is to investigate COX-2 for intervention of NSCLC, which is mired in controversy in the medical field.

Research objectives
This systematic review based on randomized controlled trials was conducted to appraise the benefit of chemotherapy-assisted addition of COX-2 for advanced NSCLC.

Research methods
We searched the six electronic databases up until December 9, 2019 for studies that examined the efficacy and safety of the addition of COX-2 inhibitors to chemotherapy for NSCLC. Overall survival (OS), progression free survival (PFS), 1-year survival rate (SR), overall response rate (ORR), clinical benefit (CB), complete response (CR), partial response (PR), stable disease (SD), and toxicities were measured with more than one outcome as their endpoints. Fixed and random effects models were used to calculate risk estimates in a meta-analysis. Potential publication bias was calculated using Egger’s linear regression test. Data analysis was performed using R software.

Research results
The COX-2 inhibitors combined with chemotherapy were not found to be more effective than chemotherapy alone in OS, PFS, 1-year SR, CB, CR, and SD. However, there was a difference in ORR for patients with advanced NSCLC. In a subgroup analysis, significantly increased ORR results were found for celecoxib, rofecoxib, first-line treatment, and PR. For adverse events, the increase in COX-2 inhibitor was positively correlated with the increase in grade 3 and 4 toxicity of leukopenia, thrombocytopenia and cardiovascular events.

Research conclusions
COX-2 inhibitor combined with chemotherapy increased total effective rate of advanced NSCLC with the possible increased risk of blood toxicity and cardiovascular events and had no effect on survival index.

Research perspectives
This study can provide reference value for the application of COX-2 in the treatment of lung cancer.

REFERENCES

1. Grønberg BH, Bremnes RM, Fletten O, Amundsen T, Brunsvig PF, Hjelde HH, Kaasa S, von Plessen C, Stromnes F, Tollåli T, Wammer F, Aasebo U, Sundstrom S. Phase III study by the Norwegian lung cancer study group: pemetrexed plus carboplatin compared with gemcitabine plus carboplatin as first-line chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2009; 27: 3217-3224 [PMID: 19433683 DOI: 10.1200/JCO.2008.20.9114]

2. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaya Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA, Fukuoka M. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009; 361: 947-957 [PMID: 19692680 DOI: 10.1056/NEJMoa0810699]

3. Helbekkmo N, Sundstrom SH, Aasebo U, Brunsvig PF, von Plessen C, Hjelde HH, Garpestad OK, Bailey A, Bremnes RM; Norwegian Lung Cancer Study Group. Vinorelbine/carboplatin vs gemcitabine/carboplatin in advanced NSCLC shows similar efficacy, but different impact of toxicity. Br J Cancer 2007; 97: 283-289 [PMID: 17595638 DOI: 10.1038/sj.bjc.6603869]

4. von Plessen C, Bergman B, Andresen O, Bremnes RM, Sundstrom S, Gilleryd M, Stephens R, Välsvik J, Aasebo U, Sorenson S. Palliative chemotherapy beyond three courses conveys no survival
Xu YQ et al. COX-2 inhibitors for advanced NSCLC

or consistent quality-of-life benefits in advanced non-small-cell lung cancer. Br J Cancer 2006; 95: 966-973 [PMID: 17047644 DOI: 10.1038/sj.bjc.6603383]

5 Sederholm C, Hillerdal G, Lamberg K, Kolbeck K, Dufmats M, Westberg R, Gawande SR. Phase III trial of gemcitabine plus carboplatin versus single-agent gemcitabine in the treatment of locally advanced or metastatic non-small-cell lung cancer: the Swedish Lung Cancer Study Group. J Clin Oncol 2005; 23: 8380-8386 [PMID: 16293868 DOI: 10.1200/JCO.2005.01.2781]

6 Lasalvia-Prisco E, Goldschmidt P, Galmanniri F, Cucelli S, Vazquez J, Agahazarian M, Lasalvia-Galante E, Golomar W, Gordon W. Addition of an induction regimen of antiangiogenesis and antitumor immunity to standard chemotherapy improves survival in advanced malignancies. Med Oncol 2012; 29: 3626-3633 [PMID: 22810591 DOI: 10.1007/s12032-012-0301-1]

7 Brown JR, DuBois RN. COX-2: a molecular target for colorectal cancer prevention. J Clin Invest 2001; 107: 2191-2195 [PMID: 11413152 DOI: 10.1172/JCI13271]

8 Achini H, Yatabe Y, Hida T, Kuroishi T, Kozaki K, Nakamura S, Ogawa M, Sugura T, Mitsudomi T, Takahashi T. Prognostic significance of elevated cyclooxygenase 2 expression in primary, resected lung adenocarcinomas. Clin Cancer Res 1999; 5: 1001-1005 [PMID: 10353732]

9 Masferrer JL, Leahy KM, Koki AT, Zweifel BS, Settle SL, Woerner BM, Edwards DA, Flickinger AG, Moore RJ, Seibert K. Antiangiogenic and antitumor activities of cyclooxygenase-2 inhibitors. Cancer Res 2000; 60: 1306-1311 [PMID: 10728691]

10 Hida T, Yatabe Y, Achiwa H, Muramatsu H, Kozaki K, Nakamura S, Ogawa M, Mitsudomi T, Sugura T, Takahashi T. Increased expression of cyclooxygenase 2 occurs frequently in human lung cancers, specifically in adenocarcinomas. Cancer Res 1998; 58: 3761-3764 [PMID: 9731479]

11 Li Y, Li S, Sun D, Song L, Liu X. Expression of 15-hydroxyprostaglandin dehydrogenase and cyclooxygenase-2 in non-small cell lung cancer: Correlations with angiogenesis and prognosis. Oncol Lett 2014; 8: 1589-1594 [PMID: 25202373 DOI: 10.3892/ol.2014.2371]

12 Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR. Nonsteroid drug selectivities for cyclooxygenase-1 rather than cyclooxygenase-2 are associated with human gastrointestinal toxicity: a full in vivo analysis. Proc Natl Acad Sci USA 1999; 96: 7563-7568 [PMID: 10377455 DOI: 10.1073/pnas.96.13.7563]

13 Chen J, Shen P, Zhang XC, Zhao MD, Zhang XG, Yang L. Efficacy and safety of celecoxib for treating advanced cancers: a meta-analysis of 11 randomized clinical trials. Clin Ther 2014; 36: 1253-1263 [PMID: 25016505 DOI: 10.1016/j.clinthera.2014.06.015]

14 Hou LC, Huang F, Xu HB. Does celecoxib improve the efficacy of chemotherapy for advanced non-small cell lung cancer? Br J Clin Pharmacol 2016; 81: 23-32 [PMID: 26331772 DOI: 10.1111/bcp.12757]

15 Zhou YY, Hu ZG, Zeng FJ, Han J. Clinical Profile of Cyclooxygenase Inhibitors in Treating Non-Small Cell Lung Cancer: A Meta-Analysis of Nine Randomized Clinical Trials. PLoS One 2016; 11: e0151939 [PMID: 27007231 DOI: 10.1371/journal.pone.0151939]

16 Dai P, Li J, Ma XP, Huang J, Meng JJ, Gong P. Efficacy and safety of COX-2 inhibitors for advanced non-small-cell lung cancer with chemotherapy: a meta-analysis. Onco Targets Ther 2018; 11: 721-730 [PMID: 29440919 DOI: 10.2147/OTT.S148670]

17 Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007; 8: 16 [PMID: 17555582 DOI: 10.1186/1745-6215-8-16]

18 Deeks JJ. Issues in the selection of a summary statistic for meta-analysis of clinical trials with binary outcomes. Stat Med 2002; 21: 1575-1600 [PMID: 12111921 DOI: 10.1002/sim.1188]

19 Higgins JP. Cochrane handbook for systematic reviews of interventions, v.5.1. 2011 Available from: https://training.cochrane.org/handbook/archive/v5.1/

20 Barili F, Parolari A, Kappestein PA, Freemantle N. Statistical Primer: heterogeneity, random- or fixed-effects models in meta-analyses? Interact Cardiovasc Thorac Surg 2018; 27: 317-321 [PMID: 29868857 DOI: 10.1093/icvts/ivy163]

21 Lilenbaum R, Socinski MA, Altorki NK, Hart LL, Keresztes RS, Harilarian S, Morrison ME, Fayyad R, Bonomi P. Randomized phase II trial of docetaxel/irinotecan and gemcitabine/irinotecan with or without celecoxib in the second-line treatment of non-small-cell lung cancer. J Clin Oncol 2006; 24: 4825-4832 [PMID: 17050867 DOI: 10.1200/JCO.2006.07.4773]

22 Gridelli C, Gallo C, Ceribelli A, Gabbiia V, Gamucci T, Ciardiello F, Carozza F, Favaretto A, Daniele B, Galetta D, Barbera S, Rosetti F, Rossi A, Maione P, Cognetti F, Testa A, Di Maio M, Morabito A, Perrone F, GECO investigators. Factorial phase III randomised trial of rofecoxib and prolonged constant infusion of gemcitabine in advanced non-small-cell lung cancer: the GEMcitabine-Coxib in NSCLC (GECO) study. Lancet Oncol 2007; 8: 500-512 [PMID: 17513173 DOI: 10.1016/S1470-2247(07)70146-8]

23 Koch A, Bergman B, Holmberg E, Sederholm C, Ek L, Kosieradzki J, Lamberg K, Thaning L, Ydreborg SO, Sörenson S; Swedish Lung Cancer Study Group. Effect of celecoxib on survival in patients with advanced non-small cell lung cancer: a double blind randomised clinical phase III trial (CYCLUS study) by the Swedish Lung Cancer Study Group. Eur J Cancer 2011; 47: 1546-1555 [PMID: 21565487 DOI: 10.1016/j.ejca.2011.03.035]

24 Groen HJ, Sietxma H, Vincent A, Hochstenbag MM, van Putten JW, van den Berg A, Dalesio O, Biesma B, Smit HJ, Termeer A, Hillemann TJ, van den Borne BE, Schramel FM. Randomized,
placebo-controlled phase III study of docetaxel plus carboplatin with celecoxib and cyclooxygenase-2 expression as a biomarker for patients with advanced non-small-cell lung cancer: the NVALT-4 study. *J Clin Oncol* 2011; 29: 4320-4326 [PMID: 21990410 DOI: 10.1200/JCO.2011.35.5214]

26 **Edelman MJ**, Tan MT, Fidler MJ, Sanborn RE, Otterson G, Sequist LV, Evans TL, Schneider BJ, Keresztes R, Rogers JS, de Mayojo JA, Feliciano J, Yang Y, Medeiros M, Zaknoen SL. Randomized, double-blind, placebo-controlled, multicenter phase II study of the efficacy and safety of apricobix in combination with either docetaxel or pemetrexed in patients with biomarker-selected non-small-cell lung cancer. *J Clin Oncol* 2015; 33: 189-194 [PMID: 25452446 DOI: 10.1200/JCO.2014.55.5789]

27 **Edelman MJ**, Wang X, Hodgson L, Cheney RT, Baggsstrom MQ, Thomas SP, Gajra A, Bertino E, Reekamp KL, Molina J, Schiller JH, Mitchell-Richards K, Friedman PN, Ritter J, Milne G, Hahn OM, Stinchcombe TE, Vokes EE; Alliance for Clinical Trials in Oncology. Phase III randomized, Placebo-Controlled, Double-Blind Trial of Celecoxib in Addition to Standard Chemotherapy for Advanced Non-Small-Cell Lung Cancer With Cyclooxygenase-2 Overexpression: CALGB 30801 (Alliance). *J Clin Oncol* 2017; 35: 2184-2192 [PMID: 28489511 DOI: 10.1200/JCO.2016.71.3743]

28 **Xiong J**, Xiang X, Zhang L, Zhong L, Chen W, Yu F. A Phase II Study of Vinorelbin/Cisplatin with or without Cox-2 Inhibitor in First-Line Treatment of Non-small Cell Lung Cancer. *Zhongliu Fangzhi Yanjiu* 2008; 35: 201-203

29 **Zhou SW**, Zhou CC, Xu JF, Lv MJ. First-line regimen of vinorelbin and cisplatin (NP) combined with cyclooxygenase-2 inhibitor celecoxib in advanced nonsmall-cell lung cancer. *Tongji DaXue Xuebao* 2007; 28: 87-91

30 **Liu GH**, Huang JA. Clinical study of celecoxib combined with chemotherapy in the treatment of patients with advanced lung cancer. *Zhonghua Zhongliu Fangzhi Zazhi* 2012; 19: 1661-1663

31 **Teng JJ**, Pei J, Han BH, Jiang LY, Zhong H, Gu AQ, Chu TQ. Serum DKK-1 Levels in the advanced non-small cell lung cancer patients: a randomized clinical study on combination of celecoxib with cisplatin-based chemotherapy. *Shijie Linchuang Yaxue* 2015; 36: 388-394

32 **Sörenson S**, Fohlin H, Lindgren A, Lindskog M, Bergman B, Sederholm C, Ek L, Lamberg K, Clinchey B. Predictive role of plasma vascular endothelial growth factor for the effect of celecoxib in advanced non-small cell lung cancer treated with chemotherapy. *Eur J Cancer* 2013; 49: 115-120 [PMID: 22951014 DOI: 10.1016/j.ejca.2012.07.032]

33 **Gitlitz BJ**, Bernstein E, Santos ES, Otterson GA, Milne G, Syto M, Burrowes F, Zaknoen S. A randomized, placebo-controlled, multicenter, biomarker-selected, phase 2 study of apricoxib in combination with erlotinib in patients with advanced non-small-cell lung cancer. *J Thorac Oncol* 2014; 9: 577-582 [PMID: 24736085 DOI: 10.1097/JTO.0000000000000082]

34 **Schneider BJ**, Kalemkerian GP, Kraut MJ, Wozniak AJ, Worden FP, Smith DW, Chen W, Gadgeel SM. Phase II study of celecoxib and docetaxel in non-small cell lung cancer (NSCLC) patients with progression after platinum-based therapy. *J Thorac Oncol* 2008; 3: 1454-1459 [PMID: 19057272 DOI: 10.1097/JTO.0b013e31818de1d2]

35 **Edelman MJ**, Watson D, Wang X, Morrison C, Kratzke RA, Jewell S, Hodgson L, Mauer AM, Gajra A, Masters GA, Bedor M, Vokes EE, Green MJ. Eicosanoid modulation in advanced lung cancer: cyclooxygenase-2 expression is a positive predictive factor for celecoxib + chemotherapy--Cancer and Leukemia Group B Trial 30203. *Cancer and Leukemia Group B Trial 30203*. *J Clin Oncol* 2008; 26: 848-855 [PMID: 18281656 DOI: 10.1200/JCO.2007.13.8081]

36 **Rabib CA**, Dolan ME. Molecular mechanisms of resistance and toxicity associated with platinating agents. *Cancer Treat Rev* 2007; 33: 9-23 [PMID: 17084534 DOI: 10.1016/j.ctrv.2006.09.006]

37 **Lorenz M**, Slaughter HS, Wescott DM, Carter SI, Schnyder B, Dinchuk JE, Car BD. Cyclooxygenase-2 is essential for normal recovery from 5-fluorouacil-induced myelotoxicity in mice. *Exp Hematol* 1999; 27: 1494-1502 [PMID: 10517400 DOI: 10.1016/s0014-2999(99)00887-9]

38 **Soza-Ried C**, Hess I, Netschul N, Schopp M, Boehm T. Essential role of c-myb in definitive hematopoiesis is evolutionarily conserved. *Proc Natl Acad Sci USA* 2010; 107: 17304-17308 [PMID: 20823231 DOI: 10.1073/pnas.1004640107]

39 **McAdam BF**, Catella-Lawson F, Mardini IA, Kapoor S, Lawson JA, FitzGerald GA. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2. *Proc Natl Acad Sci USA* 1999; 96: 272-277 [PMID: 9874808 DOI: 10.1073/pnas.96.1.272]

40 **Belknap S**. Review: studies on the cardiovascular effects of selective COX-2 inhibitors show mixed results. *ACP J Club* 2002; 136: 53 [PMID: 11874278]
