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ORIGINAL ARTICLE

Non-platinum regimens of gemcitabine plus docetaxel versus platinum-based regimens in first-line treatment of advanced non-small cell lung cancer: a meta-analysis on 9 randomized controlled trials

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Abstract
Purpose The aim was to compare the efficacy and toxicity of gemcitabine plus docetaxel (GD) with platinum-based regimens in patients with untreated advanced non-small cell lung cancer (NSCLC).
Methods We searched PubMed, Embase and the Cochrane Central Register of Controlled Trials databases for relevant trials. Reference lists of original articles and review articles were also examined. Abstracts presented at the ASCO and ESMO meetings were also searched. Studies were evaluated for eligibility and quality, and then, the data were extracted and analyzed. Statistical analyses were conducted by using RevMan 5.1. The primary end point was overall survival (OS). Secondary end points included 1-year survival, time to progression (TTP), overall response rate (ORR) and grade 3–4 toxicity.
Results Nine randomized controlled trials were identified ultimately. The meta-analysis demonstrated that the survival between GD and platinum-based regimens was comparable according to the pooled HR for overall survival (1.04, 95% CI = 0.96–1.12, $p = 0.39$) and RR for one-year survival (0.94, 95% CI = 0.84–1.06, $p = 0.33$). Platinum-based regimens had an advantage in TTP (HR = 1.12, 95% CI = 1.02–1.24, $p = 0.02$) and ORR (RR = 0.86, 95% CI = 0.74–0.99, $p = 0.03$). However, GD induced less grade 3–4 nausea/vomiting, anemia, neutropenia and febrile neutropenia (RR = 0.36, 95% CI = 0.15–0.86, $p = 0.02$; RR = 0.35, 95% CI = 0.23–0.53, $p = 0.00$; RR = 0.68, 95% CI = 0.52–0.88, $p = 0.003$; RR = 0.53, 95% CI = 0.34–0.82, $p = 0.004$, respectively). Grade 3–4 diarrhea, sensory neuropathy, fatigue and thrombocytopenia were comparable between the two groups.
Conclusions GD acquired similar survival with platinum-based regimens in first-line treatment of advanced NSCLC. Platinum-based regimens had an advantage in TTP and ORR with more grade 3–4 nausea/vomiting, anemia, neutropenia and febrile neutropenia compared with GD.

Keywords Carcinoma · Non-small cell lung · Gemcitabine · Docetaxel · Platinum · Cisplatin · Carboplatin

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Introduction

Lung cancer was the most commonly diagnosed cancer as well as the leading cause of cancer death in men in 2008 globally. Among women, it was the fourth most commonly diagnosed cancer and the second leading cause of cancer death. Lung cancer accounts for 13% (1.6 million) of the total cases and 18% (1.4 million) of the deaths in 2008 worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for at least 80% of all lung cancer cases, presenting as locally advanced disease in approximately 25–30% of cases and as metastatic disease in approximately 40–50% of cases [2]. The therapeutic scenario in advanced NSCLC is radically changed in the last few years. In the therapeutic armamentarium of this disease in first line, we have new agents like pemetrexed, bevacizumab, gefitinib and erlotinib in EGFR mutated patients. In order to acquire better efficacy, pemetrexed should combine with platinum and bevacizumab combine with a platinum-based doublet. For the EGFR wild patients and for the patients who cannot afford for gefitinib and erlotinib, the doublet regimens of platinum (cisplatin or

carboplatin) in combination with a third-generation agent including pemetrexed is still a good choice. The doublet regimens of platinum in combination with a third-generation agent were still recommended as the standard first-line chemotherapy for advanced NSCLC by American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Net (NCCN) [3, 4], but its impact on survival in advanced disease is still modest and cisplatin has significant toxicities including severe nausea and vomiting, renal toxicity, ototoxicity and neuropathy. In the attempt to optimize chemotherapy in advanced NSCLC, several strategies have been investigated including the use of non-platinum combinations. The combination of gemcitabine and docetaxel has emerged as one of the most promising regimens, showing equivalent efficacy with, and less toxicity than platinum-based therapies [5–7]. However, the results were still inconclusive. The goal of the study was to compare the efficacy and toxicity of gemcitabine plus docetaxel (GD) with platinum-based doublet in patients with untreated advanced NSCLC by a meta-analysis and systematic review of randomized controlled trials.

Methods

Search strategy and selection criteria

A literature search was performed in PubMed database, Embase database and the Cochrane Central Register of Controlled Trials (CENTRAL) in June 2011. Abstracts presented at the ASCO (2000–2010) and the European Society for Medical Oncology (ESMO, 2002–2010) meetings were also searched for relevant clinical trials. Reference lists of original articles and review articles were also examined for additional relevant trials. Our search strategy included terms for NSCLC (e.g, "non-small cell lung cancer", "Carcinoma, Non-Small Cell Lung"), docetaxel (e.g, "docetaxel", "taxotere"), and gemcitabine (e.g, "gemcitabine", "Gemzar") and was limited to randomized controlled trials and human studies. The published languages and years were not limited.

Trials that meeting all the following criteria were included in our analysis: randomized controlled trials, patients must be cytologically or pathologically confirmed of NSCLC and in clinical III-IV stage and patients must be chemotherapy-naïve, to compare the efficacy or toxicity of gemcitabine plus docetaxel (GD regimens) with cisplatin or carboplatin combined with a cytotoxic drug (platinum-based regimens).

Selection and quality assessment

Studies were evaluated for eligibility and quality by two investigators independently, and any discrepancies were resolved by consensus with a third expert. When more than one publication was identified from the same clinical trial, we used the most recent or complete report of that trial. The bias risk of trials was assessed with the components recommended by the Cochrane Collaboration: (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding of participants and personnel (performance bias), (4) blinding of outcome assessment (detection bias), (5) incomplete outcome data (attrition bias), (6) selective reporting (reporting bias) and (7) other bias [8].

Data extraction and synthesis

All the data were independently extracted by two investigators with the use of standardized data-abstraction forms. Disagreements were resolved by discussion with an independent expert. The following information was sought from each paper, although some papers did not contain all the information as followed: first author, year of publication, numbers of the patients randomized into both groups, numbers of the patients accepted at least one dose treatment, numbers of the patients eligible for evaluation, percentage of male patients, percentage of stage IV or recurrence, performance status (PS) of the patients, median age, percentage of patient with squamous cell carcinoma (SCC), numbers of patients acquired overall response (complete response plus partial response), chemotherapy regimens and 1-year survival rate. As trials rarely report all-grade or low-grade toxicity, only the adverse events of grade 3 or 4 according to the National Cancer Institute common toxicity criteria (NCI-CTC, version 2 or 3; http://ctep.cancer.gov) were included in the analysis. Toxicity data such as numbers of patients undergo grade 3 or 4 nausea or vomiting, diarrhea, sensory neuropathy, fatigue, anemia, neutropenia, febrile neutropenia and thrombocytopenia were extracted. As for time-to-event data, such as overall survival (OS) and time to progression of disease (TTP), we not only extracted median survival time (MST) and median TTP and their 95%CIs (confidence interval), we also estimated log HRs (hazard ratios) and variances from Kaplan–Meier curves based on published methodology [9].

Statistical analysis

The analyses were tested by pair-wise comparisons of the GD arms of the identified trials with the respective platinum-based arms. If there were three relevant arms in one trial, such as GD1(DOC 40 mg/m2 d1,8 + GEM 1,200 mg/m2 d1,8; q3w) versus GD2 (DOC 50 mg/m2 d1,15 + GEM 1,600 mg/m2 d1,15; q4w) versus platinum-based regimen (GEM 1,200 mg/m2 d1,8 +DDP 100 mg/

m2 d2; q3w), we added the GD1 and GD2 data together as GD arm to compare platinum-based arm for binary data and estimated the HRs and variances for GD1 versus platinum-based arm and GD2 versus platinum-based arm, respectively, for time-to-event data to conduct meta-analysis.

Analyses were performed in intention-to-treatment (ITT) for efficacy and in treatment-received analyses for toxicities. Statistical heterogeneity among trials included in the meta-analysis was assessed by using the Cochran Q statistic, and inconsistency was quantified with the I^2 statistic ($100\% \times [Q - df] \div Q$) that estimates the percentage of total variation across studies due to heterogeneity rather than chance [10]. We considered a p value less than 0.1 as indicative of substantial heterogeneity. When substantial heterogeneity was not observed, the fixed-effect model Mantel–Haenszel method was used to calculate relative risks (RRs) for binary data and fixed-effect inverse variance method to calculate HRs for time-to-event data. When substantial heterogeneity was observed, the random effect model DerSimonian-Laird method was used for binary data and random effect inverse variance for time-to-event data. A statistical test with a p-value less than 0.05 was considered significant. All p values were two sided. All CIs had a two-sided probability coverage of 95%CI. RR more than one reflects more relevant events in GD arms, and HR more than one reflects more deaths or progression in GD arms, and vice versa.

Results

Literature search, selection and assessment

Figure 1a illustrates the process of searching and evaluating articles for inclusion in the systematic review and meta-analysis. Two hundreds and thirty-eight publications were retrieved originally through database searching, and ten additional studies were identified by searching the abstracts of meeting and reference lists of original and review articles. One hundred and ninety-four records were acquired after duplicates removed. Nineteen articles assessed for eligibility after scanning titles and abstracts. Another 10 articles were excluded after peer review for the reasons shown in Fig. 1a [11–20]. Thus, 9 trials were ultimately assessed and analyzed [5–7, 21–26].

The bias risk of trials assessed with the components recommended by the Cochrane Collaboration is shown in Fig. 1b, c. Although none of the 9 trials described blinding of participants and personnel and of outcome assessment, our primary end point was overall survival, which was not likely to be influenced by lack of blinding [8]. One trial [23] that only reported an abstract and many important data could not be acquired was considered had high bias in incomplete outcome data and selective reporting items. One study [25] that was closed early and another study [26] that only reported preliminary results were considered have other bias.

Baseline characteristics of the 9 trials

All the nine trials meeting the inclusion criteria were published in English. Seven [5–7, 21, 22, 24, 25] of the 9 trials were published in full texts and two [23, 26] in abstracts. Four studies [5–7, 23] were phase III, and five [21, 22, 24–26] were phase II clinical trials. The detail regimens and baseline characteristics of the 9 trials are listed in Tables 1 and 2, respectively. In total, 2, 658 patients were randomized to receive GD regimens or platinum-based regimens. One trial compared three relevant arms [21]. Two trials compared 6 cycles GD regimens with 3 cycles platinum-based regimens plus 3 cycles docetaxel monotherapy (sequential regimens) [21, 24].

Overall survival

All the nine trial but one [26] reported overall survival data. The pooled HR for OS did not display a difference between the two groups (HR = 1.04, 95% CI = 0.96–1.12, p = 0.39). There was not heterogeneity, and the fixed-effect model was used (Fig. 2a).

One-year survival

Six trials reported one-year survival data [5–7, 21, 24, 25]. The pooled RR for 1-year survival also did not display a difference between the two groups (RR = 0.94, 95% CI = 0.84–1.06, p = 0.33, Fig. 2b).

Time to progression

Data of time to progression were acquired from five studies [5, 6, 21, 22, 24]. The pooled HR indicated that platinum-based regimens had an advantage in TTP (HR = 1.12, 95% CI = 1.02–1.24, p = 0.02) compared with GD regimens (Fig. 2c).

Overall response

All the 9 trials but one [23] reported overall response data. The pooled RR for overall response indicated that platinum-based regimens also had an advantage in ORR (RR = 0.86, 95% CI = 0.74–0.99, p = 0.03) compared with GD regimens (Fig. 2d).

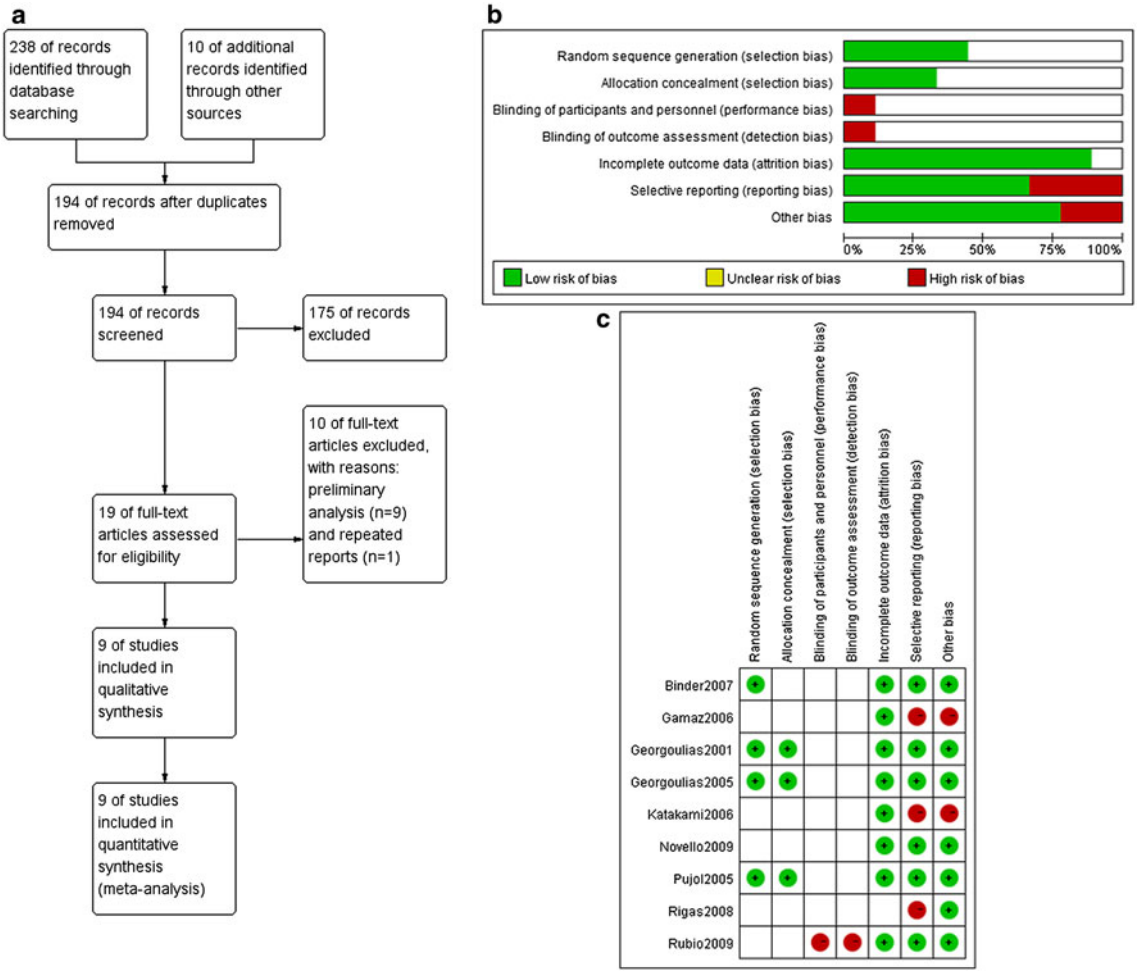

Fig. 1 **a** The process of searching and evaluating articles for inclusion in the systematic review and meta-analysis; **b** Methodological quality graph: review authors' judgments about each methodological quality item presented as percentages across all included studies; **c** Methodological quality summary: review authors' judgments about each methodological quality item for each included studies. "−", high risk of bias; "+", low risk of bias; blank, unclear of bias

Grade 3–4 toxicity

As shown in Figs. 3 and 4, respectively, we analyzed grade 3–4 non-hematologic toxicity such as nausea or vomiting, diarrhea, sensory neuropathy and fatigue, and grade 3–4 hematologic toxicity such as anemia, neutropenia, febrile neutropenia and thrombocytopenia between GD regimens and platinum-based regimens. GD induced less grade 3–4 nausea/vomiting, anemia, neutropenia and febrile neutropenia (RR = 0.36, 95% CI = 0.15–0.86, $p = 0.02$; RR = 0.35, 95% CI = 0.23–0.53, $p = 0.00$; RR = 0.68, 95% CI = 0.52–0.88, $p = 0.003$; RR = 0.53, 95% CI = 0.34–0.82, p = 0.004, respectively). Grade 3–4 diarrhea, sensory neuropathy, fatigue and thrombocytopenia were comparable between the two groups.

Sensitivity analyses

There were two trials that compared 6 cycles GD regimens with 3 cycles platinum-based regimens plus 3 cycles docetaxel monotherapy (sequential regimens). In order to avoid the bias bring by the sequential regimens, sensitivity analysis was conducted when the two trials used sequential regimens were removed. The pooled HR for OS (HR = 1.01, 95% CI = 0.92–1.10, $p = 0.87$) and RR for one-year survival (RR = 0.96, 95% CI = 0.84–1.10, $p = 0.57$) in the sensitivity analyses confirmed above results. What's more, when the two trials used sequential regimens were removed, the advantage of platinum-based regimens in TTP and ORR lost (HR = 1.06, 95% CI = 0.94–1.18, $p = 0.34$; RR = 0.89, 95% CI = 0.76–1.03, $p = 0.11$).

Table 1 Regimens of the 9 trials included in the meta-analysis

Study ID	Group	Regimens	ITT (*n*)	Patients receiving at least one dose of treatment	Eligible for evaluation
Novello2009	P	GEM 1,200 mg/m^2 d1,8 +DDP 100 mg/m^2 d2; q3w * 3 cycles → DOC 75 mg/m2, d1; q3w * 3 cycles	54	54	44
	GD1	DOC 40 mg/m^2 d1,8 + GEM 1,200 mg/m^2 d1,8; q3w * 6 cycles	54	54	41
	GD2	DOC 50 mg/m^2 d1,15 + GEM 1,600 mg/m^2 d1,15; q4w * 6 cycles	57	56	38
Rubio2009	P	GEM 1,250 mg/m^2 d1,8 +DDP 75 mg/m^2 d1; q3w * 6 cycles	56	55	55
	GD	GEM 1,000 mg/m^2 d1,8 +DOC 85 mg/m^2 d1; q3w * 6 cycles	52	50	50
Rigas2008	P	DOC 75 mg/m^2 d1 + CBP AUC 6 d1; q3w	930[#]	–	–
	GD	GEM 1,000 mg/m^2 d1,8 +DOC 40 mg/m^2 d1,8; q3w		–	–
Binder2007	P	GEM 900 mg/m^2 d1,8 +DDP 70 mg/m^2 d1; q3w * 3 cycles → DOC 100 mg/m2 d1; q3w * 3 cycles	58	54	51
	GD	GEM 900 mg/m^2 d1,8 +DOC 75 mg/m^2 d1; q3w * 6 cycles	54	53	43
Katakami2006	P	DOC 60 mg/m^2 d1 + DDP 80 mg/m^2 d1; q3w to disease progression or unacceptable toxicity	68	68	67
	GD	DOC 60 mg/m^2 d8 + GEM 800 mg/m^2 d1,8; q3w to disease progression or unacceptable toxicity	63	63	60
Gamaz2006	P	GEM 1,250 mg/m^2 d1,8 +DDP 70 mg/m^2 d1; q3w	22	22	22
	GD	GEM 1,250 mg/m^2 d1,8 +DOC 75 mg/m^2 d1; q3w	25	25	25
Pujol2005	P	NVB 30 mg/m^2 d1,8,15,22 +DDP 100 mg/m^2 d1; q4w * 6 cycles	156	156	140
	GD	GEM 1,000 mg/m^2 d1,8 +DOC 85 mg/m^2 d1; q3w * 8 cycles	155	155	142
Georgoulias2005	P	NVB 30 mg/m^2 d1,8 +DDP 80 mg/m^2 d8; q3w * 6 cycles	204	192	204
	GD	GEM 1,000 mg/m^2 d1,8 +DOC 100 mg/m^2 d8; q3w * 6 cycles	209	197	209
Georgoulias2001	P	DOC 100 mg/m^2 d1 + DDP 80 mg/m2 d2; q3w	219	212	205
	GD	GEM 1,100 mg/m^2 d1,8 +DOC 100 mg/m^2 d8; q3w	222	214	201

P platinum-based doublet regimens, *GD* gemicitabine plus docetaxel, *GEM* gemcitabine, *DDP* cisplatinum, *DOC* docetaxel, *CBP* carboplatinum, *AUC* area under curve, *ITT* intention-to-treatment

[#] Number of the patients in both groups

Discussion

Chemotherapy has been the mainstay of treatment in advanced non-small cell lung cancer (NSCLC) since an individual patient data (IPD) meta-analysis of 11 randomized trials definitively established its survival benefit over best supportive care, which showed a significant 27% lower risk for death and an absolute 10% higher 1-year survival rate [27]. Within the past two decades, new cytotoxic drugs with promising activity in NSCLC have been developed. These so-called third-generation agents include paclitaxel, docetaxel, gemcitabine and vinorelbine. Despite some conflicting results, a meta-analysis has established the superiority of modern platinum doublets over old-fashioned regimens [28]. In summary, based on the evidence, a two-drug regimen in which cisplatin or carboplatin is combined with a third-generation agent currently represents the worldwide standard treatment of chemotherapy-naïve patients with a good performance status and advanced disease [3, 29]. However, its impact on survival in advanced disease is still modest. In the attempt to optimize chemotherapy, several strategies have been investigated including the use of non-platinum combinations, especially two-third-generation agent combination such as gemcitabine plus docetaxel.

In 2001, Georgoulias et al. [7] performed a randomized multicentre trial and concluded that gemcitabine plus docetaxel had comparable activity with platinum-based doublet according to objective response rates, median duration of response, time to tumor progression, overall survival, and 1-year or 2-year survival rates in patients with advanced cancer who had not previously had chemotherapy; and gemcitabine plus docetaxel had the most favorable toxicity profile. After that, eight similar studies to compare the efficacy of gemcitabine plus docetaxe with platinum-based doublets had published [5, 6, 21–26]. Rubio et al. [22] reported that the overall response rate of gemcitabine plus docetaxe was higher than platinum-based doublet. However, none of the above trials acquired a difference in survival between the two regimens partially

Table 2 Baseline characteristics of the 9 trials included in the meta-analysis

Study ID	Group	Male (%)	PS0-1 (%)	Median age	SCC (%)	Stage IV (%)	OR (n)	MST (95% CI) (m)	Median TTP (95% CI) (m)	One-year OS (%)
Novello2009	P	71	100	62	28	81.0	15	14.6 (8.0–22.4)	6.6 (5.7–9.1)	53.9
	GD1	82	96	60	15	85.0	13	10.7 (6.8–15.6)	6.7 (4.8–9.7)	46.3
	GD2	81	100	61	23	81.0	7	8.9 (7.4–12.5)	5.6 (5.0–7.9)	37.9
Rubio2009	P	80	83.3	59.9	–	81.8	19	8.9 (6.3–10.5)	6.2 (4.2–7.1)	–
	GD	90	84	61.4	–	86.0	20	8.9 (3.9–10)	5.5 (4.1–7.2)	–
Rigas2008	P	–	–	–	–	–	–	7.9	–	–
	GD	–	–	–	–	–	–	7.9	–	–
Binder2007	P	71	79	64.5	26	–	18	9.4 (7.8–11.0)	5.2 (3.1–7.3)	35.0
	GD	72	78	64	33	–	11	8.7 (5.7–11.6)	3.6 (1.4–5.9)	34.0
Katakami2006	P	66.2	100	65	26.5	73.5	16	11.4	–	47.7
	GD	65.1	100	61	28.6	74.6	17	13.7	–	56.6
Gamaz2006	P	90	–	60.9	50	40.9	4	–	–	–
	GD	88	–	54.6	52	36.0	3	–	–	–
Pujol2005	P	79.5	91.7[#]	57	23.7	85.9	56	9.6 (8.1–12.2)	–	42.0
	GD	80	92.3[#]	60	31.6	78.7	48	11.1 (9.6–12.5)	–	46.0
Georgoulias2005	P	88	90	64	46	64.0	80	9.7 (8.3–11.2)	5.0	40.8
	GD	89	89	63	38	62.0	63	9.0 (7.7–10.2)	4.0	34.3
Georgoulias2001	P	89	89	61	66	63.0	71	10.0	8.0	42.0
	GD	87	87	62	63	65.0	67	9.5	9.0	39.0

P platinum-based doublet regimens, *GD* gemicitabine plus docetaxel, *PS* performance status according to Zubrod-ECOG-WHO, *SCC* squamous cell cancer, *OR* overall response, *MST* median survival time, *CI* confidence interval, *TTP* time to progression, *OS* overall survival, – data cannot be acquired

[#] Performance status over 70 according to karnofsky

because of the possible small difference of the activity between the two regimens and the relatively small sample size in each of published studies. To avoid the cause of small sample size in each of published studies, we pooled all the nine similar trials and performed this meta-analysis.

In our meta-analysis, we found that the efficacy was comparable between GD regimens and platinum-based regimens according to overall survival and 1-year survival. Although platinum-based regimen had an advantage in TTP and ORR, the advantage was lost when the two trials used sequential regimens were removed. As for toxicity, GD induced less grade 3–4 nausea/vomiting, anemia, neutropenia and febrile neutropenia. Grade 3–4 diarrhea, sensory neuropathy, fatigue and thrombocytopenia were comparable between the two groups. In 2005, D'addario et al. [30] performed a meta-analysis to compare platinum-based with non-platinum-based chemotherapy in advanced non-small cell lung cancer and concluded that response was significantly higher with platinum-containing regimens and the 1-year survival rate was increased by 5% with platinum-based regimen; however, one-year survival was not significantly prolonged when platinum-based therapies were compared with third-generation-based combination regimens. In D'addario et al's study, there were many triple or quadruple regimens and single regimens which were proved to be no more or less active than doublet regimens [3]. What's more, there were many old drugs in the regimens that are seldom used in nowadays in D'addario et al's study. Our meta-analysis compared the doublets of two-third-generation drugs, gemcitabine plus docetaxe, with platinum plus a third-generation drug. Our results showed GD regimen had similar 1-year survival with platinum-based doublet, which agreed with D'addario et al's subgroup analysis in comparing platinum-based therapies with third-generation-based combination regimens. Our meta-analysis also further intensified Georgoulias et al's conclusion [7].

A meta-analysis by Chen and colleagues showed that low/negative expression of ERCC1 was associated with higher objective response and median survival in advanced NSCLC patients treated with platinum-based chemotherapy and indicated that ERCC1 maybe a suitable marker of prognosis and sensitivity to platinum-based chemotherapy in patients with advanced NSCLC [31].

Accordingly, the non-platinum-based regimens of gemcitabine plus docetaxel maybe an alternative for

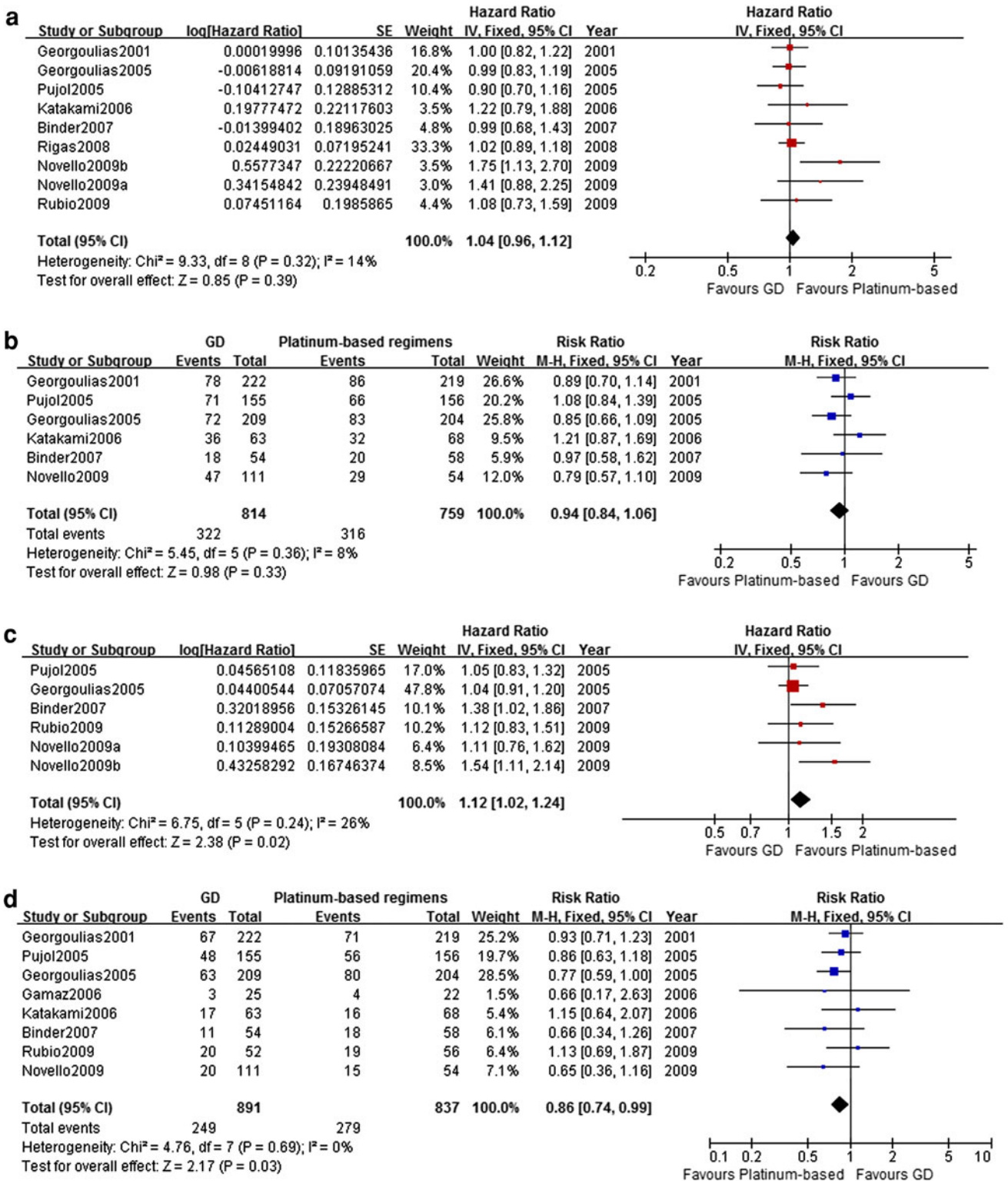

Fig. 2 The efficacy meta-analyses between gemcitabine plus docetaxel (GD) and platinum-based regimens. **a** The pooled HR for overall did not display a difference between the two groups (HR = 1.04, 95% CI = 0.96–1.12, $p = 0.39$); **b** The pooled RR for 1-year survival also did not display a difference between the two groups (RR = 0.94, 95% CI = 0.84–1.06, $p = 0.33$); **c** The pooled HR indicated that platinum-based regimens had an advantage in TTP (HR = 1.12, 95% CI = 1.02–1.24, $p = 0.02$) compared with GD regimens; and **d** The pooled RR for overall response indicated that platinum-based regimens also had an advantage in ORR (RR = 0.86, 95% CI = 0.74–0.99, $p = 0.03$) compared with GD regimens

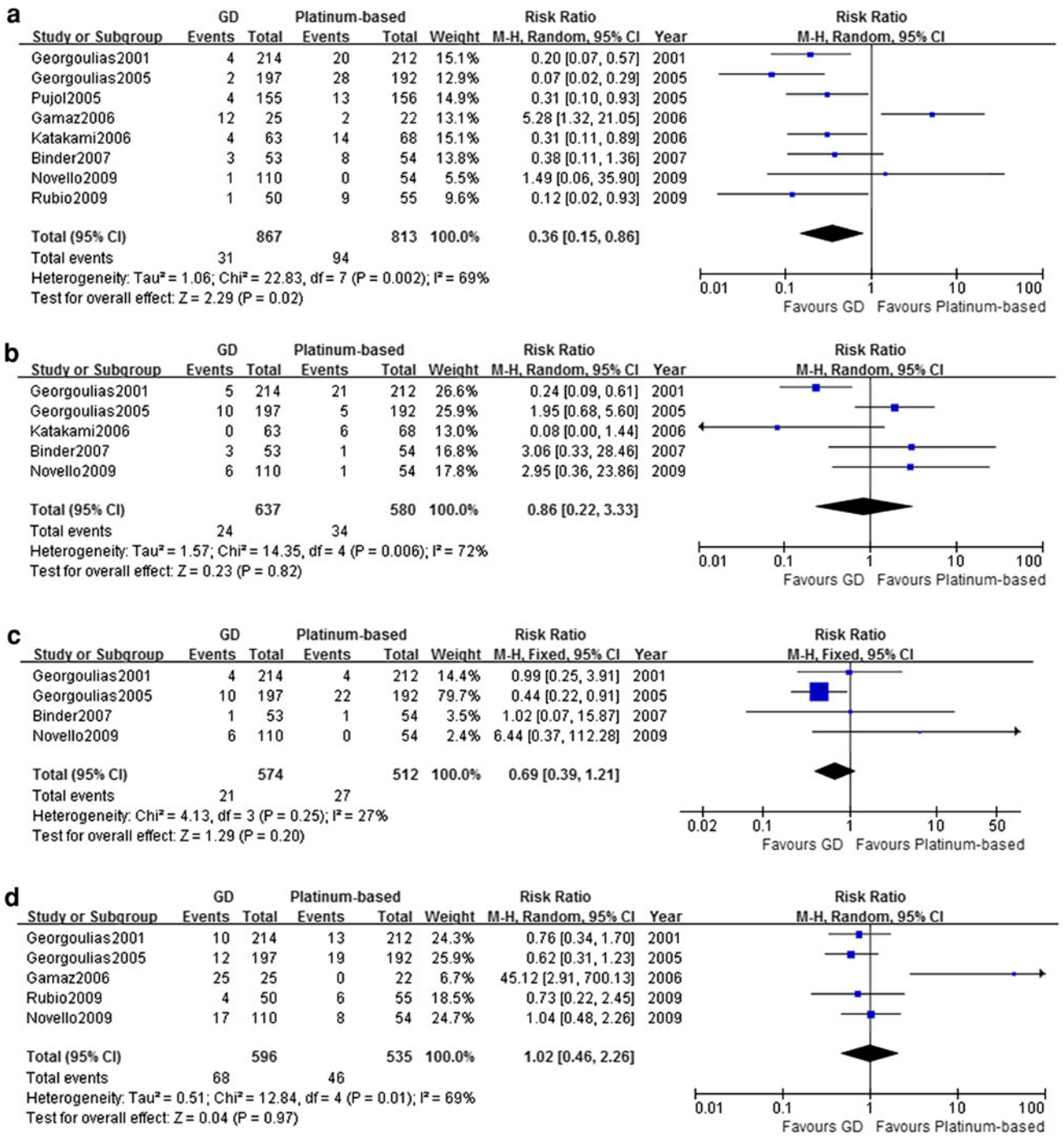

Fig. 3 Grade 3–4 non-hematologic toxicity meta-analyses between gemcitabine plus docetaxel (GD) and platinum-based regimens. **a** The pooled RR indicated that GD induced less grade 3–4 nausea/vomiting (RR = 0.36, 95% CI = 0.15–0.86, $p = 0.02$); **b** The pooled RR indicated that grade 3–4 diarrhea was comparable between the two groups; **c** The pooled RR indicated that grade 3–4 sensory neuropathy was comparable between the two groups; and **d** The pooled RR indicated that grade 3–4 fatigue was comparable between the two groups

platinum-based regimens in advanced NSCLC, especially in patients with tumor high/positive expression of ERCC1.

Although our results were promising, it should be treated with caution for there were several limitations to this study. Firstly, many trials were small-sample phase II trials; Secondly, some trials did not report all the relevant data; and Thirdly, the meta-analysis was based on the data from the published literature, but not individual patient data (IPD).

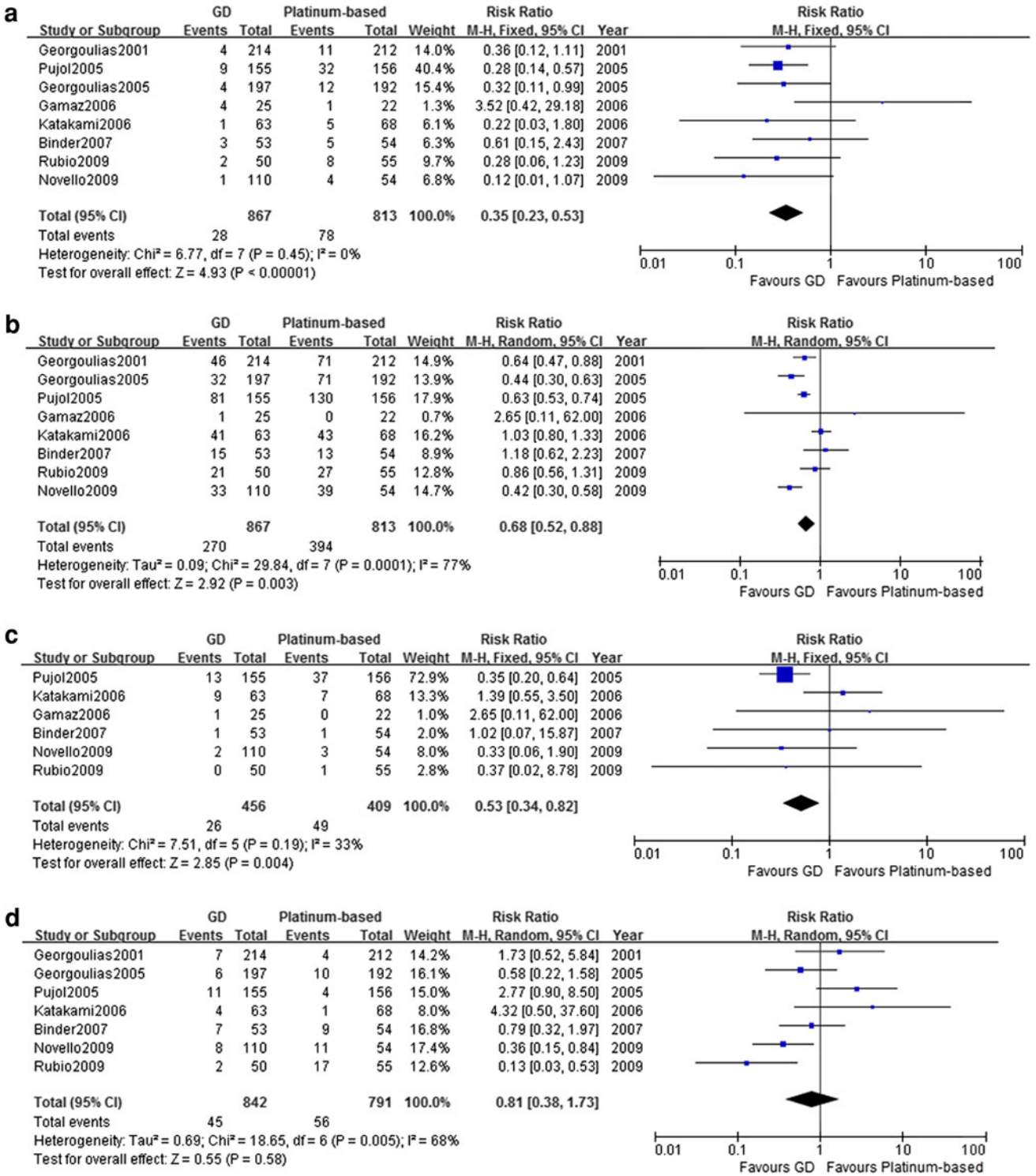

Fig. 4 Grade 3–4 hematologic toxicity meta-analyses between gemcitabine plus docetaxel (GD) and platinum-based regimens. **a** The pooled RR indicated that GD induced less grade 3–4 anemia (RR = 0.35, 95% CI = 0.23–0.53, $p = 0.00$); **b** The pooled RR indicated that GD induced less grade 3–4 neutropenia (RR = 0.68, 95% CI = 0.52–0.88, $p = 0.003$); **c** The pooled RR indicated that GD induced less grade 3–4 febrile neutropenia (RR = 0.53, 95% CI = 0.34–0.82, $p = 0.004$); and **d** The pooled RR indicated that grade 3–4 thrombocytopenia was comparable between the two groups

In conclusion, our meta-analysis showed the non-platinum regimens (gemcitabine plus docetaxel) had similar efficacy with platinum-based regimens in first-line treatment of advanced NSCLC with less toxicity.

Conflict of interest We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence this work.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D (2011) Global cancer statistics. CA Cancer J Clin 61:69–90
2. Novello S, Le Chevalier T (2003) Chemotherapy for non-small-cell lung cancer, Part 1: early-stage disease. Oncology (Williston Park) 17:357–364
3. Azzoli CG, Baker SJ, Temin S et al (2009) American society of clinical oncology clinical practice guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol 27:6251–6266
4. NCCN Non-Small Cell Lung Cancer Panel Members (2011) Non-small cell lung cancer. NCCN clinical practice guidelines in oncology version 3, 2011. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
5. Pujol JL, Breton JL, Gervais R et al (2005) Gemcitabine-docetaxel versus cisplatin-vinorelbine in advanced or metastatic non-small-cell lung cancer: a phase III study addressing the case for cisplatin. Ann Oncol 16:602–610
6. Georgoulias V, Ardavanis A, Tsiafaki X et al (2005) Vinorelbine plus cisplatin versus docetaxel plus gemcitabine in advanced non-small-cell lung cancer: a phase III randomized trial. J Clin Oncol 23:2937–2945
7. Georgoulias V, Papadakis E, Alexopoulos A et al (2001) Platinum-based and non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a randomised multicentre trial. Lancet 357:1478–1484
8. Julian PT Higgins, Douglas G Altman, Jonathan AC Sterne (2011) Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (ed) Cochrane handbook for systematic reviews of interventions version 5.1.0. The Cochrane Collaboration, 2011. Available from http://www.cochrane-handbook.org
9. Parmar MK, Torri V, Stewart L (1998) Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 17:2815–2834
10. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327:557–560
11. Rubio JC, Estevez SV, Rivera FV et al (2006) Gemcitabine/Docetaxel (GD) vs Gemcitabine/Cisplatin (GC) in stage IIIB/IV advanced non-small cell lung cancer (NSCLC). J Clin Oncol 2006 ASCO annual meeting proceedings part I, vol 24, no. 18S (June 20 Supplement): 17017
12. Rubio JC, Estevez SV, Rivera FV et al (2006) A randomized phase IIB trial of gemcitabine and cisplatin (GC) versus gemcitabine and docetaxel (GD) in stage IIIB/IV advanced non-small cell lung cancer (NSCLC). an galician lung cancer group study. ESMO annual meeting abstract 2006. 751P
13. Solomon B, Bunn PA Jr (2005) Gemcitabine plus docetaxel for advanced or metastatic non-small cell lung cancer: Similar survival to cisplatin plus vinorelbine and less toxicity. Cancer Treat Rev 31:571–576
14. Takiguchi Y, Katakami N, Yoshimori K et al (2004) Docetaxel in combination with either cisplatin (DC) or gemcitabine (DG) in unresectable non-small cell lung carcinoma (NSCLC): a randomized phase II study by the Japan lung cancer cooperative clinical study group. EMSO annual meeting abstract 2004. 635PD
15. Georgoulias V, Ardavanis A, Tsiafaki X et al (2004) Vinorelbine plus cisplatin versus docetaxel plus gemcitabine in advanced non-small cell lung cancer: a phase III randomized trial. ESMO annual meeting abstract 2004, 637PD
16. Binder D, Beinert T, Schweisfurth H et al (2004) Docetaxel-gemcitabine versus cisplatin-gemcitabine plus sequential docetaxel in the first-line treatment of metastatic non-small cell lung cancer (NSCLC): interim results of a randomized Phase II trial. ESMO Ann Meet Abstr 2004:7071
17. Binder D, Sailer V, Schweigert M et al (2002) A randomized phase II study of gemcitabine/docetaxel vs gemcitabine/cisplatin followed by docetaxel in patients with metastatic non-small cell lung cancer (NSCLC) [abstract]. In: Proceedings of the American Society of Clinical Oncology 2002
18. Kakolyris S, Tsiafaki X, Agelidou A et al (2002) Preliminary results of a multicentre randomised phase III trial of docetaxel plus gemcitabine (DG) versus vinorelbine plus cisplatin (VC) in patients with advanced non-small cell lung cancer [abstract]. In: Proceedings of the American Society of Clinical Oncology 2002
19. Georgoulias V, Samonis G, Papadakis E et al (2001) Comparison of docetaxel/cisplatin to docetaxel/gemcitabine as first-line treatment of advanced non-small cell lung cancer: early results of a randomized trial. Lung Cancer 34(Suppl 4):S47–S51
20. Georgoulias V, Papadakis E, Alexopoulos A et al (1999) Docetaxel plus cisplatin versus docetaxel plus gemcitabine chemotherapy in advanced non-small cell lung cancer: a preliminary analysis of a multicenter randomized phase II trial. ASCO annual meeting abstract 1999, Abstract No:1778
21. Novello S, Falcone A, Crino L et al (2009) Randomised multicenter phase II study of two schedules of docetaxel and gemcitabine or cisplatin/gemcitabine followed by docetaxel as first line treatment for advanced non-small cell lung cancer. Lung Cancer 66:327–332
22. Rubio JC, Vazquez S, Vazquez F et al (2009) A phase II randomized trial of gemcitabine-docetaxel versus gemcitabine-cisplatin in patients with advanced non-small cell lung carcinoma. Cancer Chemother Pharmacol 64:379–384
23. Rigas JR, Carey M, Dragnev KH et al (2008) Phase III multicenter web-based study demonstrating survival equivalents of nonplatinum-based chemotherapy for advanced non-small cell lung cancer (NSCLC): Subgroup analysis from D0112. J Clin Oncol 26: May 20 suppl, abstr 8100
24. Binder D, Schweisfurth H, Grah C et al (2007) Docetaxel/gemcitabine or cisplatin/gemcitabine followed by docetaxel in the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC): results of a multicentre randomized phase II trial. Cancer Chemother Pharmacol 60:143–150
25. Katakami N, Takiguchi Y, Yoshimori K et al (2006) Docetaxel in combination with either cisplatin or gemcitabine in unresectable non-small cell lung carcinoma: a randomized phase II study by the Japan lung cancer cooperative clinical study group. J Thorac Oncol 1:447–453
26. Gamaz M, Taright TMS (2006) Gemcitabine/docetaxel (GD) versus gemcitabine/cisplatin (GC) in stage III/IV non-small cell lung cancer (NSCLC): preliminary results. J Clin Oncol 2006 ASCO annual meeting proceedings part I, vol 24, no 18S (June 20 Supplement): 17116
27. Non-small Cell Lung Cancer Collaborative Group (1995) Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 311:899–909
28. Baggstrom MQ, Stinchcombe TE, Fried DB, Poole C, Hensing TA, Socinski MA (2007) Third-generation chemotherapy agents

in the treatment of advanced non-small cell lung cancer: a meta-analysis. J Thorac Oncol 2:845–853
29. D'Addario G, Fruh M, Reck M, Baumann P, Klepetko W, Felip E (2010) Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 21(Suppl 5):116–119
30. D'Addario G, Pintilie M, Leighl NB, Feld R, Cerny T, Shepherd FA (2005) Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. J Clin Oncol 23:2926–2936
31. Chen S, Zhang J, Wang R, Luo X, Chen H (2010) The platinum-based treatments for advanced non-small cell lung cancer, is low/negative ERCC1 expression better than high/positive ERCC1 expression? A meta-analysis. Lung Cancer 70:63–70