Efficacy of erlotinib in patients with advanced non-small cell lung cancer: a pooled analysis of randomized trials

Hui Gao[a], Xin Ding[b], Dong Wei[a], Peng Cheng[a], Xiaomei Su[a], Huanyi Liu[a], Fahad Aziz[c], Daoyuan Wang[a] and Tao Zhang[a]

Erlotinib is a potent reversible HER1/epidermal growth factor receptor tyrosine kinase inhibitor with single-agent activity in patients with non-small cell lung cancer. The aim of this study was to evaluate the efficacy of erlotinib for treating advanced non-small cell lung cancer by carrying out a pooled analysis of randomized controlled trials that compared erlotinib-based regimens with other agent-based regimens between January 1997 and 2011. Outcomes analyzed were objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and adverse events. Fourteen trials including 7974 patients were identified. As first-line therapy was compared with chemotherapy, there was a similar ORR [OR: 0.33; 95% confidence interval (CI): 0.64–17.36; $P=0.15$], but decreased PFS [hazard ratio (HR): 1.55; 95% CI: 1.24–1.93; $P<0.01$] and OS (HR: 1.39; 95% CI: 0.99–1.94; $P=0.05$). As maintenance therapy was compared with placebo, erlotinib-based regimens significantly increased ORR (OR: 0.47; 95% CI: 0.31–0.70; $P<0.01$), prolonged PFS (HR: 0.71; 95% CI: 0.60–0.83; $P<0.01$), but did not improve OS (HR: 0.87; 95% CI: 0.68–1.11; $P=0.22$). As second/third-line therapy was compared with placebo, erlotinib-based regimens also significantly increased ORR (OR: 0.10; 95% CI: 0.02–0.41; $P<0.01$), prolonged PFS (HR: 0.61; 95% CI: 0.51–0.73; $P<0.01$), and improved OS (HR: 0.70; 95% CI: 0.58–0.84; $P<0.01$). However, as second/third-line therapy was compared with chemotherapy, the outcomes were similar between the two arms. When compared with PF299804, there was a decreased ORR (OR: 3.87; 95% CI: 1.27–11.81; $P=0.02$), and shortened PFS (HR: 0.58; 95% CI: 0.49–0.95; $P=0.02$). Meanwhile, erlotinib-based regimens showed no significant difference in adverse events, except for diarrhea, rash, and anemia. Erlotinib-based regimens significantly increased ORR and improved PFS as a first-line maintenance therapy or as a second/third-line therapy when compared with placebo. *Anti-Cancer Drugs* **22:842–852** © **2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2011, **22**:842–852

Keywords: advanced non-small cell lung cancer, erlotinib, pooled analysis

[a]Department of Oncology, [b]Department of Neurology, PLA General Hospital of Chengdu Military Region, Chengdu, People's Republic of China and [c]Department of Internal Medicine, Mount Sinai School of Medicine–Jersey City Campus, Jersey City, New Jersey, USA

Correspondence to Dr Tao Zhang, MD, Department of Oncology, PLA General Hospital of Chengdu Military Region, Tianhui Town, Jinniu District, Chengdu 610083, PR China
Tel: +86 028 86570500; fax: +86 028 83572211;
e-mail: drtao.zhang@gmail.com

Hui Gao and Xin Ding contributed equally to this study.

Received 26 October 2010 **Revised form accepted** 10 June 2011

Introduction

Lung cancer is the major cause of cancer deaths worldwide, and the majority of new cases belong to the advanced non-small cell lung cancer (NSCLC) catagory [1]. The standard first-line treatment for the advanced NSCLC is a platinum-based two-drug combination regimen [2]. However, no doublet regimen has been proved superior, and survival outcomes remained poor (median survival is 7.4–8.1 months; 1-year survival rate is 28–47%) [3–5]. Thus, the development of more effective therapy remains challenging. The development of agents that target the epidermal growth factor receptor (EGFR) signal transduction pathways has provided a class of novel targeted therapeutic agents.

The EGFRs have been shown to play a significant role in tumorigenesis, with up to 80% of NSCLC expressing EGFR [6,7]. Overexpression of EGFR is associated with advanced disease and poor survival [8]. Erlotinib (Tarceva, OSI Pharmaceuticals, Melville, New York, USA) is a highly potent reversible HER1/EGFR tyrosine kinase inhibitor that has shown significant antitumor activity in preclinical studies [9]. The antitumor activity with single-agent erlotinib has been proved by phase I/II studies in previously treated patients [10]. In a large randomized, double-blind, placebo-controlled phase III trial in previously treated patients with an advanced NSCLC, erlotinib significantly prolonged survival versus placebo [6.7 vs. 4.7 months; hazard ratio (HR): 0.70; $P<0.001$], delayed disease progression, and delayed worsening of disease-related symptoms [11]. The most common adverse events with single-agent erlotinib consisted of mild/moderate rash and diarrhea. However, this is the only phase III trial that has shown prolonged survival with an EGFR inhibitor in an advanced NSCLC. In other phase II and III trials, erlotinib-based regimens did not prove to be superior to other agent-based regimens.

Several randomized controlled clinical trials comparing erlotinib-based regimens with other agent-based

0959-4973 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CAD.0b013e328349c303

regimens in the treatment of advanced NSCLC have been proceeding, and nine of them have reported results. On the basis of these data, we conducted a pooled analysis to assess the efficacy and safety of erlotinib in patients with advanced NSCLC.

Materials and methods

Literature search

The aim of this pooled analysis was to review all published and reported randomized controlled trials (RCTs) comparing the erlotinib-based regimens with other agent-based regimens. Both published and unpublished trials reported between January 1997 and 2011 were identified through a computer-based search of the PubMed database and from abstracts from the past 12 conferences of the American Society of Clinical Oncology and from the past 12 conferences of the European Society for Medical Oncology. The search strategy included the following keywords variably combined: advanced or metastatic, non-small cell lung cancer or NSCLC, Erlotinib, or Tarceva. In addition, we searched trial registries and conference proceedings. We also examined reference lists of original articles, and contacted original trialists for possible unpublished trials. The deadline for trial inclusion was 31 January 2011.

Inclusion and exclusion criteria

The aim of this analysis was to evaluate objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and relevant grade 3/4 adverse events. If erlotinib alone or based combination therapy was included in a RCT, it was considered to be eligible. Inclusion criteria for the trails were as follows: (a) patients were randomly assigned to treatment; (b) erlotinib or based combination regimen was compared with other agent or based combination regimen without confounding by other agents or interventions; and (c) only patients with diagnosis of advanced NSCLC were included. Trials with missing adequate statistical analysis information were also excluded.

Validity assessment

Assessment of the trials was carried out openly with the instrument reported by Moher *et al.* [12], and there was no significant difference observed among the trials. Therefore, the result of the validity assessment was not considered in this pooled analysis.

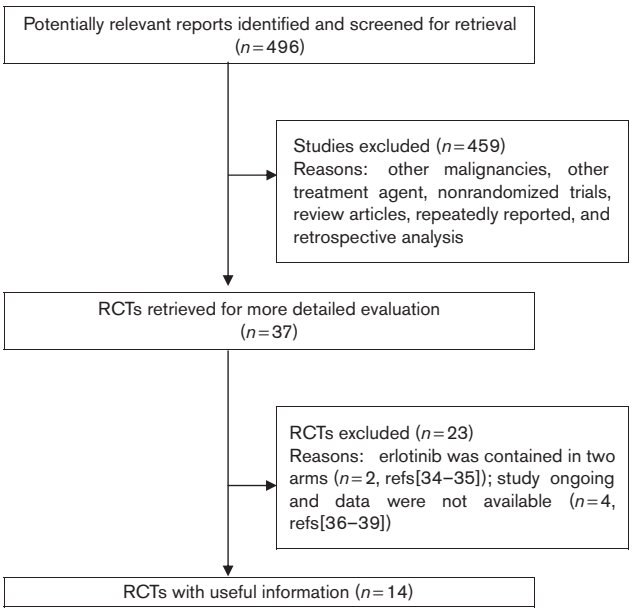
Data abstraction

The following information was extracted from each report: study design, regimen details, allocated patients, cause of disease, race or ethnic group, Eastern Cooperative Oncology Group performance status (PS), pathological subtype, earlier chemotherapy, smoking status, EGFR protein expression, median follow-up, HRs for the whole study populations, and the year of reporting. Data were independently extracted from each report by X. S. and H. L., who were blinded to each other, using a standardized data recording form. After extraction, data were reviewed and compared by T.Z. and P.C. All data were checked for internal consistency, and any disagreements were resolved by discussion among the investigators. We also tried to contact principal investigators of the trials to confirm or update both published and unpublished data.

Statistical analysis

The primary endpoints in the pooled analysis were OS and PFS. The secondary endpoints were ORR and adverse events. Except adverse events, all analyses were conducted on an intention-to-treat (ITT) basis, and all randomly assigned patients were included in the analyses according to the allocated treatment. We looked for heterogeneity among the trials based on standard methods [13]. The DerSimonian and Laird Q statistic (Q test) was used to test for heterogeneity among trials [14]. Begg's funnel plots [15] and Egger's test [16] were used to detect possible publication bias. On the basis of the results of the Q test, we applied a random-effects model (primarily) to estimate the summary HRs, ORs, and their 95% confidence intervals (CIs). If HRs or its 95% CIs could not be obtained from reports, crude logHR and its variance were calculated according to the method proposed by Parma *et al.* [17]. To reduce reading errors, original survival curves were digitalized and enlarged, and data extraction was based on reading off electronic coordinates for each point of interest.

Fig. 1



A flow chart showing the progress of trials through the review. RCTs, randomized controlled trials.

Table 1 Characteristics of the fourteen trials included in this pooled analysis

Author	Year	Publication form	Patients	Chemo/target therapy regimen	Sex (male, %)	PS 0–1 (%)	Age	Stage III/IV (%)	Adeno-carcinoma (%)	Smoking history (%)
Gatzemeier *et al.* [18]	2007	Full text	586	Erlotinib 150 mg/day, per oral + gemcitabine 1250 mg/m^2, days 1,8 + cisplatin 80 mg/m^2, day 1, 6 cycles	78.0	99.8	60.0	99.6	38.0	–
			586	Placebo + gemcitabine 1250 mg/m^2, days 1,8 + cisplatin 80 mg/m^2, day 1, 6 cycles	75.0	99.8	59.1	99.8	38.0	–
Herbst *et al.* [19]	2005	Full text	539	Erlotinib 150 mg/day, per oral + carboplatin AUC 6, day 1 + paclitaxel 200 mg/m^2, day 1, 6 cycles	61.6	100	62.7	100	59.9	86.6
			540	Placebo + carboplatin AUC 6, day 1 + paclitaxel 200 mg/m^2, day 1, 6 cycles	59.7	99.8	62.6	100	61.4	91.8
Lee *et al.* [20]	2010	Abstract	350	Erlotinib 150 mg/day, per oral	61.0	16	77.4	100	38	95.0
			320	Placebo	61.0	16	77.2	100	38	94.0
Lilenbaum *et al.* [21]	2008	Full text	52	Erlotinib 150 mg/day, per oral	44.0	0	51.0	100	50.0	88.0
			51	Carboplatin AUC 6, day 1 + paclitaxel 200 mg/m^2, day 1, 6 cycles	55.0	0	52.0	100	63.0	92.0
Reck *et al.* [22]	2010	Abstract	144	Erlotinib 150 mg/day, per oral	65.0	100	75.5	100	50.0	82.0
			140	Carboplatin AUC 5, day 1 + vinorelbine 25 mg/m^2, days 1,8, 6 cycles	71.0	100	76.1	99.0	49.0	86.0
Cappuzzo *et al.* [23]	2010	Full text	438	After CT, erlotinib 150 mg/day, per oral	73.0	31.0	60.0	100	47.0	82.0
			451	After CT, placebo	75.0	32.0	60.0	100	44.0	83.0
Miller *et al.* [11]	2009	Abstract	370	After CT, erlotinib 150 mg/day, per oral + bevacizumab 15 mg/kg, day 1, q3weeks	52.2	100	64.0	100	81.3	83.5
			373	After CT, placebo + bevacizumab 15 mg/kg, day 1, q3 weeks	52.3	99.7	64.0	100	82.5	82.3
Mok *et al.* [24]	2010	Full text	76	Erlotinib 150 mg/day, days 15–28 + gemcitabine 1250 mg /m^2, days 1, 8 + cisplatin 75 mg/m^2 (carboplatin AUC 5), day 1, 6 cycles	71.0	100	57.0	100	67.0	68.0
			78	Placebo + gemcitabine 1250 mg/m^2, days 1,8 + cisplatin 75 mg/m^2 (carboplatin AUC 5), day 1, 6 cycles	69.0	100	57.5	100	67.0	64.0
Perol *et al.* [25]	2010	Abstract	155	After CT, erlotinib 150 mg/day, per oral	73	100	56.4	100	63	–
			155	After CT, observation	73	100	59.8	100	67	–
Shepherd *et al.* [26]	2005	Full text	488	Erlotinib 150 mg/day, per oral	64.5	91.4	62.0	100	50.4	73.4
			243	Placebo	65.8	91.4	59.0	100	49.0	77.0
Herbst *et al.* [27]	2007	Full text	39	Erlotinib 150 mg/day, per oral + bevacizumab 15 mg/kg, day 1, q3 weeks	43.6	100	68.0	100	82.1	84.6
			40	Paclitaxel 75 mg/m^2, day 1/ pemetrexed 500 mg/m^2, day 1 + bevacizumab 15 mg/kg, day 1, q3 weeks	57.5	100	63.5	100	75.0	90.0
Vamvakas *et al.* [28]	2010	Abstract	166	Erlotinib 150 mg/day, per oral	81.3	79.2	65	100	53.6	–
			166	MTA 500 mg/m^2, d1, q3wks	82.5	81.3	66	100	56.6	–
Natale *et al.* [29]	2011	Full text	617	Erlotinib 150 mg/day, per oral	64.0	88.0	61.0	100	57.0	76.0
			623	Vandetanib 300 mg/day, per oral (a targeted drug)	61.0	99.0	60.0	100	63.0	79.0
Boyer *et al.* [30]	2010	Abstract	94	Erlotinib 150 mg/day, per oral	59.6	96.8	67.0	100	64.9	78.7
			94	PF299804 45 mg/day, per oral	58.5	81.9	69.0	100	66.0	79.8

All trials were randomized controlled phase III trials except for Lilenbaum *et al.* [21], Mok *et al.* [24], and Herbst *et al.* [27] trials, which were designed as randomized controlled phase II trials.
AUC, area under the serum concentration–time curve; CT, chemotherapy; PS, performance status.

All statistical analyses were conducted with Review Manager V. 5.0.23 (Nordic Cochran Centre, Copenhagen, Denmark). All statistical tests were two sided, and *P* values of 0.05 were considered to be statistically significant.

Results

Trial flow

The flow chart of our study is shown in Fig. 1. Ultimately, results of nine randomized phase II or III trials that had been published or presented at major international meetings were included in this analysis. Although we did not limit language in the process of searching, all the trials were published in English. All the 14 trials were RCTs and the results were based on ITT analysis except adverse events. There were three PIs who responded to our requests of confirming update of both published or unpublished data of the trials.

Characteristics of the fourteen trials

The characteristics of the 14 trials are listed in Table 1. They included three phase III RCTs comparing with placebo as first-line therapy [18–20], two phase II RCTs comparing with chemotherapy as first-line therapy [21,22], three phase III RCTs and one phase II RCT comparing with placebo as maintenance therapy [11,23–25], one phase III RCT comparing with placebo as second/third-line therapy [26], one phase III RCT and one phase II RCT comparing with chemotherapy as second/third-line therapy [27,28], one phase III RCT comparing with targeted drugs as second/third-line therapy [29], and one phase II RCT comparing with targeted drugs as second/

Table 2 Responses in thirteen trials

Author	Chemo/target therapy regimen	Patients with complete or partial response	Randomized patients	Objective response rate (%)
Gatzemeier *et al.* [18]	E+G+DDP	183	580	31.5
	P+G+DDP	173	579	29.9
Herbst *et al.* [19]	E+C+T	116	539	21.5
	P+C+T	104	540	19.3
Lilenbaum *et al.* [21]	E	2	52	4.0
	C+T	6	51	12.0
Reck *et al.* [22]	E	10	144	6.9
	C+NVB	32	140	22.9
Cappuzzo *et al.* [23]	After CT, E	52	438	11.9
	After CT, P	24	451	5.3
Mok *et al.* [24]	E+G+DDP (C)	27	76	35.5
	P+G+DDP (C)	19	78	24.4
Shepherd *et al.* [26]	E	38	488	7.8
	P	2	243	<1
Herbst *et al.* [27]	E+B	12	39	30.8
	T/M+B	16	40	40.0
Vamvakas *et al.* [28]	E	13	166	7.8
	MTA	19	166	11.4
Natale *et al.* [29]	E	74	617	12.0
	V (a targeted drug)	75	623	12.0
Boyer *et al.* [30]	E	4	94	4.3
	PF299804 (a targeted drug)	16	94	17.0

Response rate was not included in the objectives of the trials conducted by Lee *et al.* [20], Miller *et al.* [11], and Perol *et al.* [25] studies.
B, bevacizumab; C, carboplatin; D, docetaxel; DDP, cisplatin; E, erlotinib; G, gemcitabine; M, pemetrexed; NVB, vinorelbine; P, placebo; T, paclitaxel; V, vandetanib (a targeted drug).

third-line therapy [30]. In total, 7974 patients were randomized to receive erlotinib-based regimens (4114 patients) or other agent-based regimens (3860 patients). Thirteen patients enrolled in one trial were excluded after randomization [18]. Further information about unpublished data was obtained by contacting the principal investigators. No potential sources of heterogeneity including sex, age, Eastern Cooperative Oncology Group PS, pathological subtype, earlier chemotherapy, and smoking status were associated with significant differences in outcomes.

Objective response rate

Eleven trials except for the trials conducted by Lee *et al.* [20], Miller *et al.* [11], and Perol *et al.* [25] reported ORR. The response rates ranged from 4.0 to 31.5% for the erlotinib-based regimens and from less than 1.0 to 40.0% for the other agent-based regimens (Table 2). As a first-line therapy, including nine trials and 5404 patients (erlotinib, $n = 2710$; other agent, $n = 2694$), the random-effects model pooled estimate evaluated for ORR showed a similar ORR for erlotinib-based regimens (OR: 0.76; 95% CI: 0.53–1.08; $P = 0.12$). However, the test for heterogeneity shows a significant difference ($I^2 = 66\%$, $P = 0.02$), therefore we had to carry out subgroup analysis. The subgroup analysis showed a similar ORR comparing with placebo (OR: 0.90; 95% CI: 0.74–1.09; $P = 0.29$) or chemotherapy (OR: 0.33; 95% CI: 0.64–17.36; $P = 0.15$), but an increased ORR comparing with placebo as maintenance therapy (OR: 0.47; 95% CI: 0.31–0.70; $P < 0.01$).

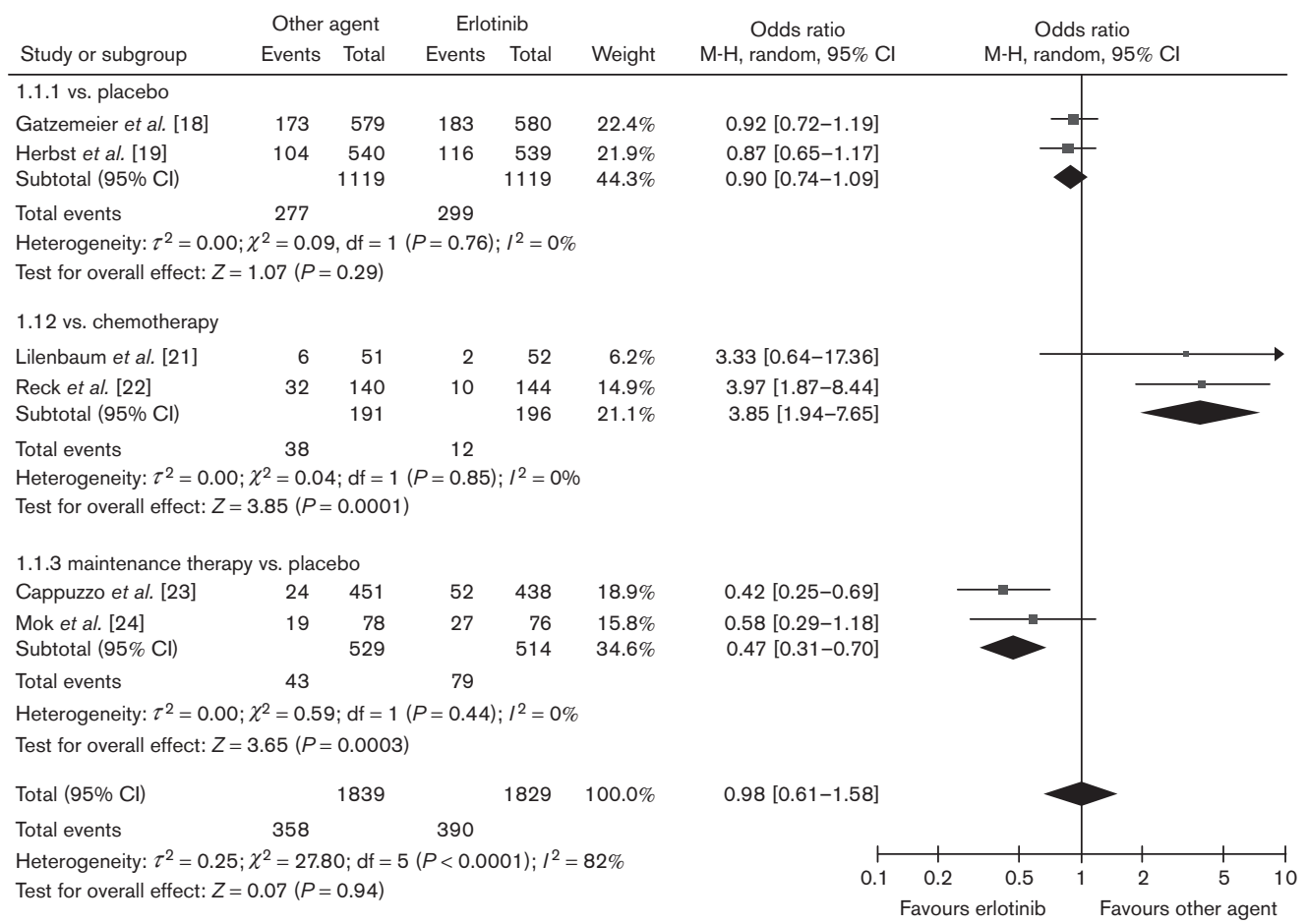
As second/third-line therapy including three trials and 1142 patients (erlotinib, $n = 693$; other agent, $n = 449$), the pooled estimate showed a similar ORR for erlotinib-based regimens (OR: 0.68; 95% CI: 0.15–3.10; $P = 0.62$). The test for heterogeneity also showed a significant difference ($I^2 = 86\%$, $P < 0.01$). When compared with placebo, the subgroup analysis showed an increased ORR (OR: 0.10; 95% CI: 0.02–0.41; $P < 0.01$). However, compared with chemotherapy, there was a similar ORR between two arms (OR: 1.51; 95% CI: 0.85–2.70; $P = 0.16$).

With respect to all efficacy outcomes, random-effects (Figs 2–7) and fixed-effects models (data not shown) yielded virtually identical results. Neither a Begg's funnel plot nor a rank correlation test regarding response rate indicated the existence of publication bias ($Z = -0.1$, $P = 1.00$). The results of Egger' test was similar.

Progression-free survival

All 14 trials reported PFS (Table 3). As a first-line therapy, the random-effects model pooled estimate evaluated for PFS showed a similar PFS for erlotinib-based regimens (HR: 0.88; 95% CI: 0.76–1.03; $P = 0.12$). However, the test for heterogeneity showed a significant difference ($I^2 = 85\%$, $P < 0.01$); therefore, we had to carry out subgroup analysis. The pooled estimate showed a similar PFS when compared with placebo (HR: 0.93; 95% CI: 0.85–1.01; $P = 0.09$), a decreased PFS compared with chemotherapy (HR: 1.55; 95% CI: 1.24–1.93; $P < 0.01$), but a prolonged PFS compared with placebo as maintenance therapy (HR: 0.71; 95% CI: 0.60–0.83; $P < 0.01$).

Fig. 2



Response to erlotinib-based regimens compared with other agent-based regimens as first-line therapy. The heterogeneity test yielded a significant result ($P<0.01$). CI, confidence interval.

As a second/third-line therapy including three trials, the pooled estimate showed a similar PFS for erlotinib-based regimens (HR: 0.75; 95% CI: 0.55–1.03; $P = 0.08$). The test for heterogeneity also showed a significant difference ($I^2 = 75\%$, $P = 0.02$). The subgroup analysis showed a prolonged PFS compared with placebo (HR: 0.61; 95% CI: 0.51–0.73; $P < 0.01$), but a similar PFS compared with chemotherapy (HR: 0.89; 95% CI: 0.73–1.09; $P = 0.26$).

Neither a Begg's funnel plot nor a rank correlation test regarding response rate indicated the existence of publication bias ($Z = 0.67$, $P = 0.50$). The results of Egger' test was similar.

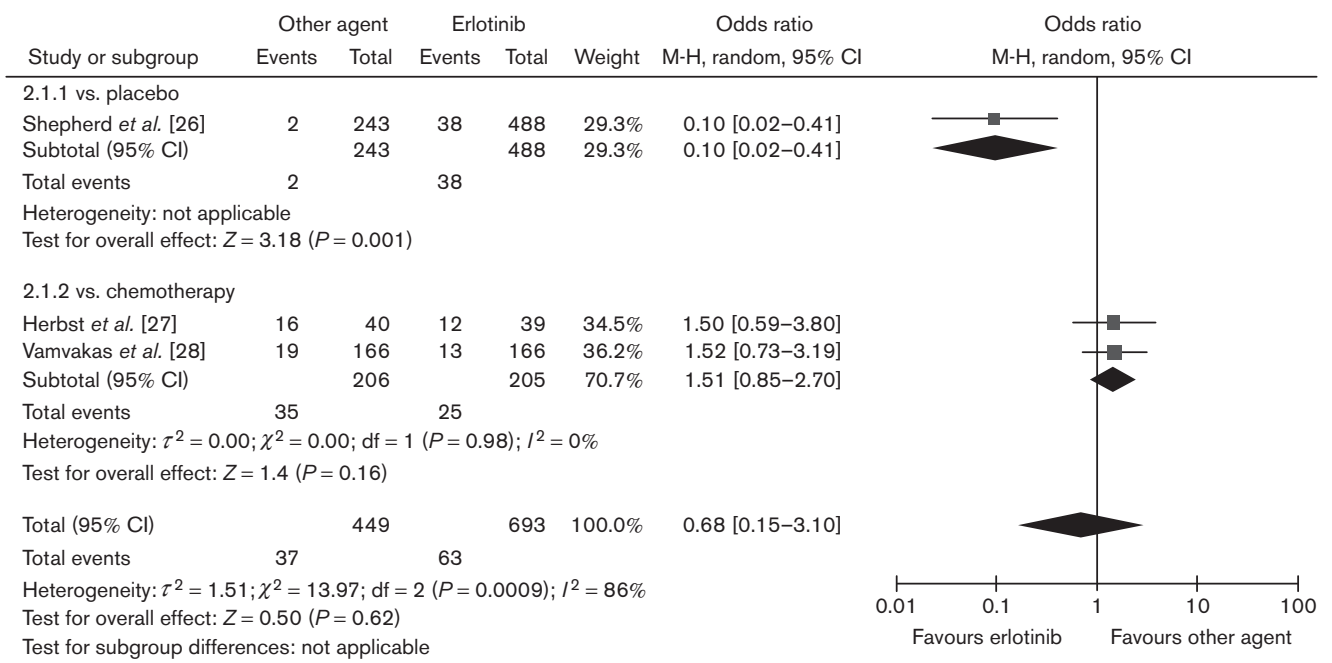
Overall survival

Eleven trials reported OS except for trials conducted by Miller *et al.* [11], Perol *et al.* [25], and Boyer *et al.* [30] (Table 3). As first-line therapy including four trials, the random-effects model pooled estimate evaluated for OS showed a similar OS for erlotinib-based regimens (HR: 1.04; 95% CI: 0.89–1.22; $P = 0.59$). The test for heterogeneity showed a significant difference ($I^2 = 65\%$, $P = 0.01$). The subgroup analysis showed a similar OS compared with placebo (HR: 1.02; 95% CI: 0.92–1.13; $P = 0.73$), or as maintenance therapy (HR: 0.87; 95% CI: 0.68–1.11; $P = 0.22$), but a decreased OS compared with chemotherapy (HR: 1.39; 95% CI: 0.99–1.94; $P = 0.05$).

As second/third-line therapy including three trials, the pooled estimate showed a similar OS for erlotinib-based regimens (HR: 0.88; 95% CI: 0.65–1.19; $P = 0.42$). The test for heterogeneity showed no significant difference ($I^2 = 83\%$, $P < 0.01$). The subgroup analysis showed a prolonged OS compared with placebo (HR: 0.70; 95% CI: 0.58–0.84; $P < 0.01$), but a similar OS compared with chemotherapy (HR: 1.01; 95% CI: 0.92–1.11; $P = 0.88$).

Neither a Begg's funnel plot nor a rank correlation test regarding response rate indicated the existence of publication bias ($Z = 0.73$, $P = 0.47$). The results of Egger' test was similar.

Fig. 3



Response to erlotinib-based regimens compared with other agent-based regimens as second/third-line therapy. The heterogeneity test yielded a significant result ($P<0.01$). CI, confidence interval.

Adverse events

All 14 trials including 7261 patients provided results of adverse events. Reported toxicities were analyzed in only 12 trials except for the targeted drugs containing trials [29,30] (Table 4). Grade 3/4 diarrhea (OR: 4.87; 95% CI: 3.19–7.44; $P < 0.01$), rash (OR: 28.94; 95% CI: 14.28–58.66; $P < 0.01$), and anemia (OR: 1.39; 95% CI: 1.06–1.82; $P = 0.02$) were significantly prominent in the erlotinib-based regimens, with all intertrial variability consistent with the play of chance. Compared with other agent-based regimens, erlotinib-based regimen did not increase the frequency of other adverse events. The heterogeneity test found no statistical significance for all adverse events.

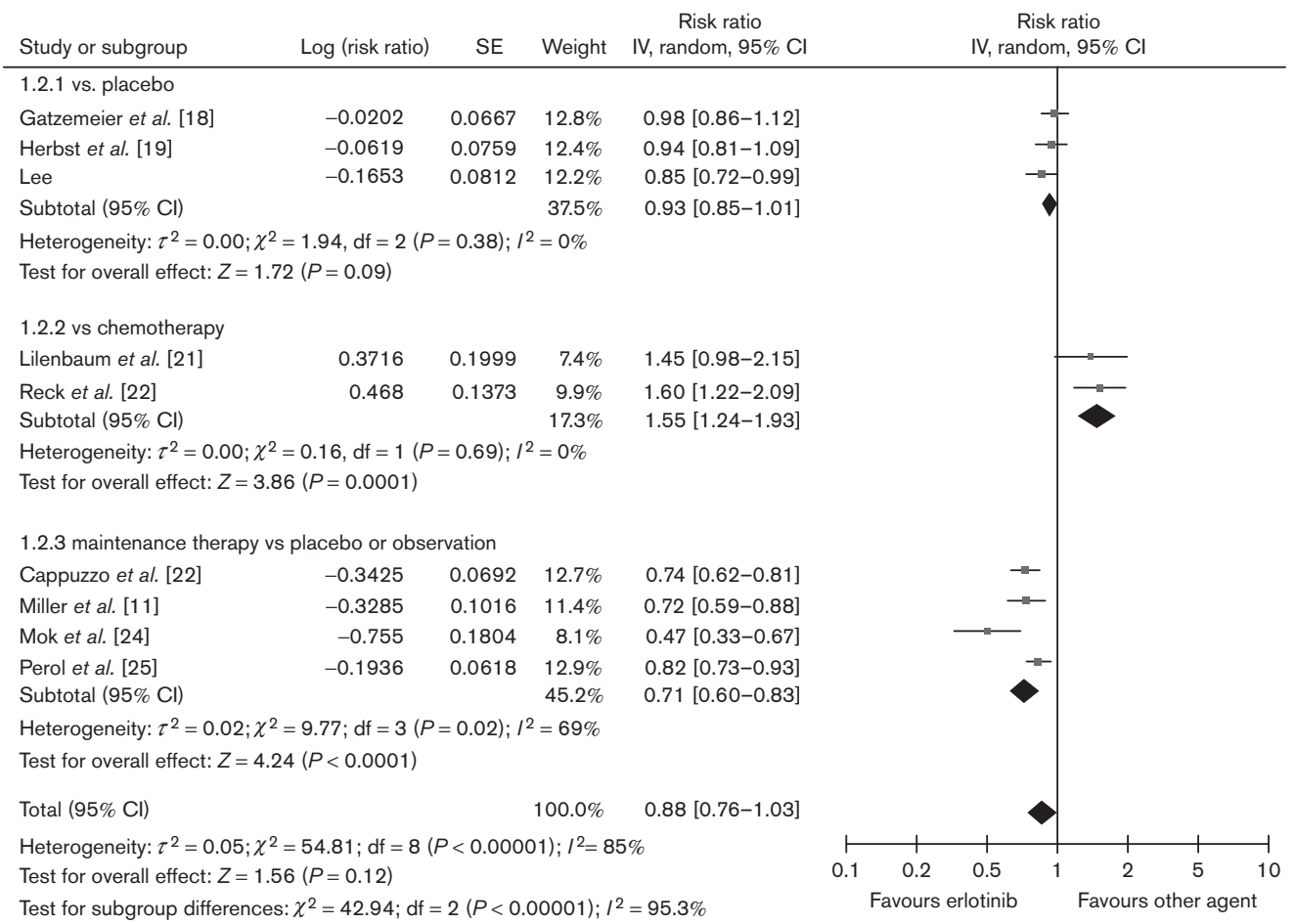
On account of the significant heterogeneity (data not shown), we had to compare erlotinib with other targeted drugs, respectively. Compared with vandetanib, there was a similar ORR (OR: 1.00; 95% CI: 0.71–1.40; $P = 0.98$), PFS (HR: 0.98; 95.22% CI: 0.87–1.10; $P = 0.72$), OS (HR: 1.01; 95.08% CI: 0.89–1.16; $P = 0.83$), and the frequency of grade 3/4 adverse events (data not shown). Compared with PF299804, there was a decreased ORR (OR: 3.87; 95% CI: 1.27–11.81; $P = 0.02$), and shortened PFS (HR: 0.58; 95% CI: 0.49–0.95; $P = 0.02$). At the same time, erlotinib did not increase the frequency of grade 3/4 adverse events, except for diarrhea (OR: 0.25; 95% CI: 0.07–0.91; $P = 0.04$).

Discussion

The EGFR family is part of a complicated signal-transduction network that is a key to several critical cellular processes [31]. Overexpression of EGFR is common in NSCLC and is associated with poor survival. During the last decade, the treatment for patients with advanced NSCLC has improved as a result of the invention of novel, effective, agents targeting the EGFR pathway, such as gefitinib and erlotinib. To date, the reports of several phase II/III trials showed inconsistent results on clinical outcomes with regard to ORR, PFS, and OS. Thus, the impact of erlotinib-based regimens on the survival of advanced NSCLC patients compared with other agent-based regimens remained undetermined.

In this pooled analysis, we identified 14 RCT trials including 7974 patients, and the largest accounted for 1240 randomly assigned patients. However, because of the difference of the schedule of treatment and controlled regimens, the heterogeneity between trials was statistically significant. Thus, we must explain the results with caution and we had to carry out subgroup analysis according to the schedule of treatment and controlled regimens. As first-line therapy was compared with chemotherapy, there was a decreased PFS (HR: 1.55; 95% CI: 1.24 to 1.93; $P < 0.01$) and OS (HR: 1.39; 95% CI: 0.99–1.94; $P = 0.05$). As maintenance therapy was compared with placebo, erlotinib-based regimens

Fig. 4

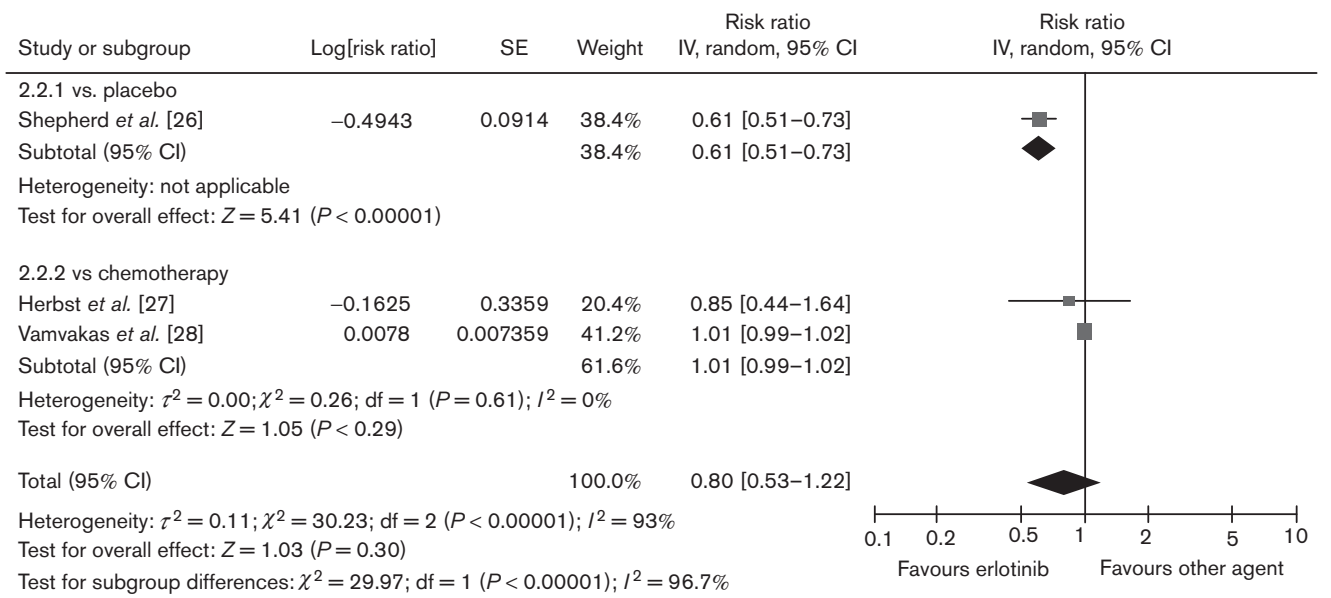


Progression-free survival with erlotinib-based regimens compared with other agent-based regimens as first-line therapy. The heterogeneity test yielded a significant result ($P<0.01$). CI, confidence interval.

significantly increased ORR (OR: 0.47; 95% CI: 0.31–0.70; $P < 0.01$), prolonged PFS (HR: 0.71; 95% CI: 0.60–0.83; $P < 0.01$), but did not improve OS (HR: 0.87; 95% CI: 0.68–1.11; $P = 0.22$). As second/third-line therapy was compared with placebo, erlotinib-based regimens also significantly increased ORR (OR: 0.10; 95% CI: 0.02–0.41; $P < 0.01$), prolonged PFS (HR: 0.61; 95% CI: 0.51–0.73; $P < 0.01$), and improved OS (HR: 0.70; 95% CI: 0.58–0.84; $P < 0.01$). However, as second/third-line therapy was compared with chemotherapy, the outcomes were similar between two arms. When compared with PF299804, there was a decreased ORR (OR: 3.87; 95% CI: 1.27–11.81; $P = 0.02$), and shortened PFS (HR: 0.58; 95% CI: 0.49–0.95; $P = 0.02$). Thus, we believe that as first-line therapy, we should prefer chemotherapy to erlotinib; as maintenance therapy, we should prefer erlotinib to placebo; as second/third-line therapy, we should prefer erlotinib or chemotherapy to best supportive care in some patients with good PS status. No matter compared with placebo or chemotherapy, the results did not show that erlotinib-based regimens could increase ORR and improve PFS and OS as first-line therapy.

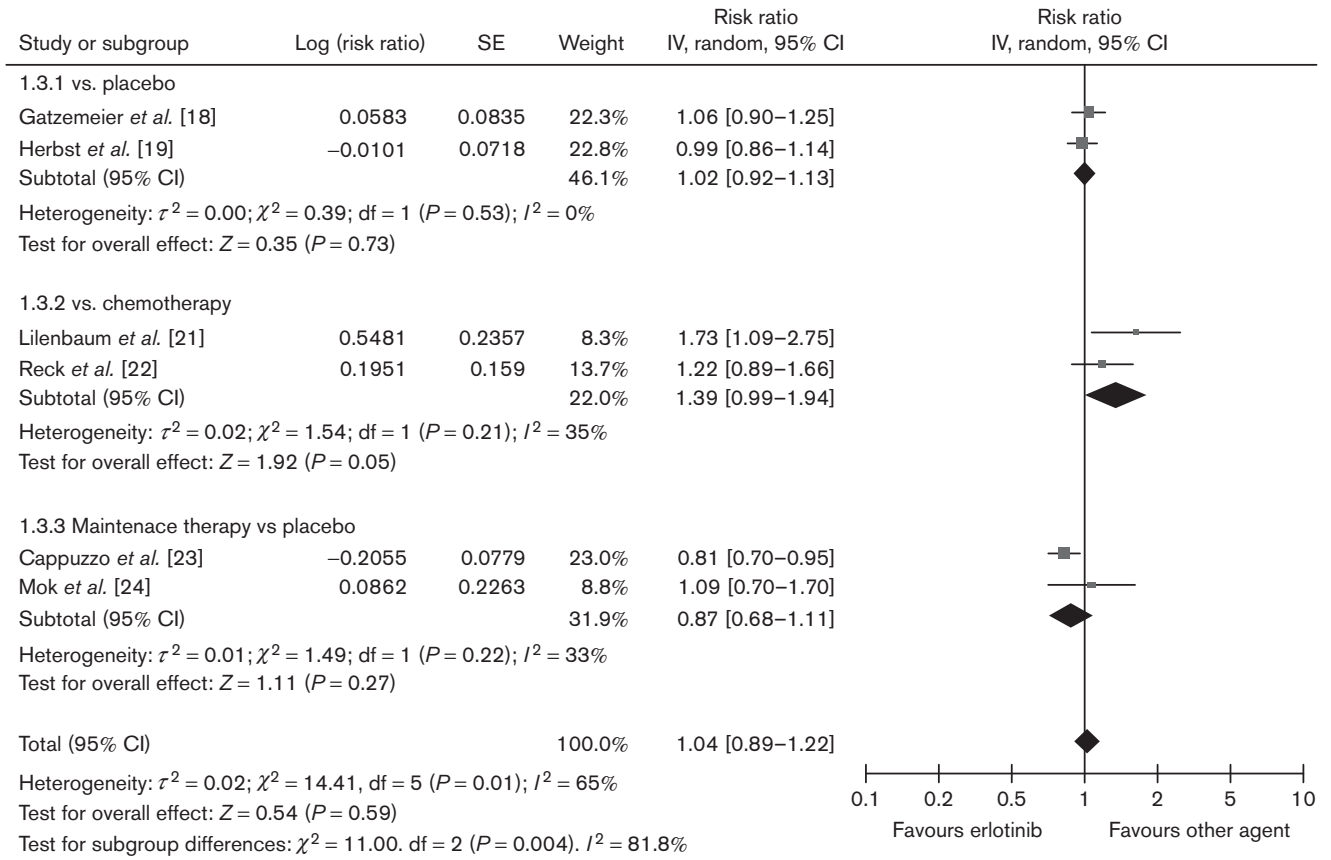
An unexpected finding was an increased incidence in anemia with the erlotinib combination. This increase was mostly due to the result reported during the trial conducted by Gatzemeier *et al.* [18]. The other four trials that reported the incidence of anemia did not show any difference between the two groups. As it is believed that erlotinib has no effect on bone marrow, and up to now, there is no experimental or clinical evidence of erlotinib inducing anemia, we believed the increased incidence reported by Gatzemeier *et al.* [18] was just an accident and pointless. Neither did the Begg's funnel plot for publication bias nor did the heterogeneity test yield a significant result. As the results based on the fixed-effect model were similar to the results based on the random-effect model, we did not show the results based on the fixed-effect model.

Fig. 5



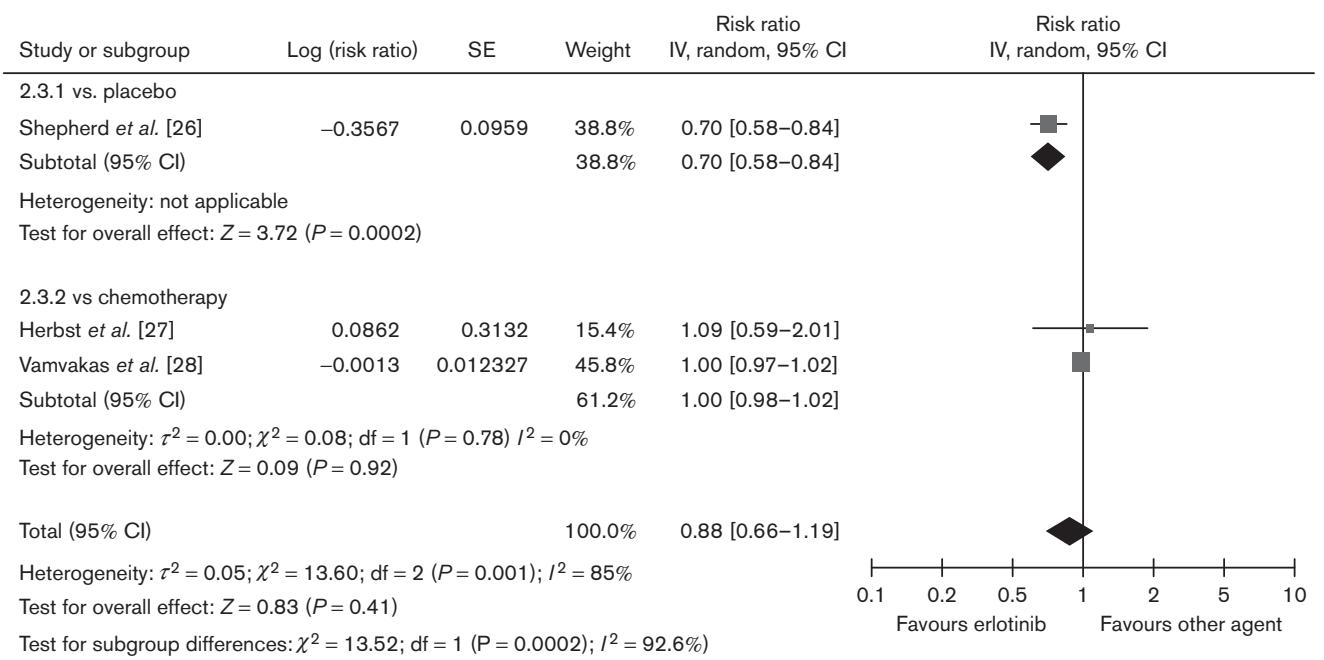
Progression-free survival with erlotinib-based regimens compared with other agent-based regimens as second/third-line therapy. The heterogeneity test yielded a significant result ($P<0.01$). CI, confidence interval.

Fig. 6



Overall survival with erlotinib-based regimens compared with other agent-based regimens as first-line therapy. The heterogeneity test did not yield a significant result ($P=0.01$). CI, confidence interval.

Fig. 7



Overall survival with erlotinib-based regimens compared with other agent-based regimens as second/third-line therapy. The heterogeneity test yielded a significant result (P=0.18). CI, confidence interval.

Table 3 Progression-free survival and overall survival in the fourteen trials

Author	Chemo/target therapy regimen	ITT analysis	Randomized patients	Median PFS (month)	*P* value	Median OS (month)	*P* value
Gatzemeier *et al.* [18]	E + G + DDP	Yes	586	5.50	0.74	10.00	0.49
	P + G + DDP		586	5.80		10.90	
Herbst *et al.* [19]	E + C + T	Yes	539	5.10	0.36	10.60	0.95
	P + C + T		540	4.90		10.50	
Lee *et al.* [20]	E	Yes	350	2.8	0.038	3.8	0.069
	P		320	2.7		3.6	
Lilenbaum *et al.* [21]	E	Yes	52	1.90	0.063	6.60	0.018
	C + T		51	3.50		9.70	
Reck *et al.* [22]	E	No	125	2.4	0.001	7.9	0.21
	C + NVB		113	4.6		8.4	
Cappuzzo *et al.* [23]	After CT, E	Yes	437	2.87	<0.01	12.0	0.009
	After CT, P		447	2.59		11.0	
Miller *et al.* [11]	After CT, E + B	Yes	373	4.76	0.001		–
	After CT, P + B		370	3.75			
Mok *et al.* [24]	E + G + DDP (C)	Yes	76	6.86	<0.01	17.29	0.72
	P + G + DDP (C)		78	5.46		17.67	
Perol *et al.* [25]	After CT, E	No	153	2.9	0.002		–
	After CT, Observation		152	1.9			
Shepherd *et al.* [26]	E	Yes	488	2.20	<0.01	6.70	<0.01
	P		243	1.80		4.70	
Herbst *et al.* [27]	E + B	Yes	39	4.40	>0.05	13.70	>0.05
	T/M + B		40	4.80		12.60	
Vamvakas *et al.* [28]	E	Yes	166	3.6	0.30	7.9	0.92
	MTA		166	2.7		8.9	
Natale *et al.* [29]	E	Yes	617	2.08	0.72	7.8	0.83
	V (a targeted drug)		623	2.64		6.9	
Boyer *et al.* [30]	E	Yes	94	1.94	0.019		–
	PF299804 (a targeted drug)		94	2.89			

B, bevacizumab; C, carboplatin; D, docetaxel; DDP, cisplatin; E, erlotinib; G, gemcitabine; ITT, intention to treat; M, pemetrexed; MTA, pemetrexed; P, placebo; PFS, progression-free survival; T, paclitaxel; V, vandetanib (a targeted drug).

Table 4 Adverse events in trials comparing erlotinib-based regimen with other agent-based regimen (grades III and IV)

Adverse events	Number of evaluable trials	Erlotinib-based therapy		Other agent-based therapy		OR (95% CI)	*P* value for Q test
		Patients with adverse events	Evaluable patients	Patients with adverse events	Evaluable patients		
Diarrhea[a]	12	134	3053	26	2784	4.87 (3.19–7.44)	<0.01
Rasha	12	235	3053	8	2784	28.94 (14.28–58.66)	<0.01
Anemia[a]	8	135	1418	99	1409	1.39 (1.06–1.82)	0.02
Neutropenia	8	173	1733	198	1726	0.86 (0.69–1.06)	0.16
Nausea/vomiting	8	110	1955	112	1684	0.84 (0.64–1.10)	0.33
Fatigue	7	96	1789	102	1518	0.79 (0.59–1.05)	0.17
Thrombocytopenia	7	116	1578	111	1571	1.04 (0.80–1.37)	0.09
Anorexia	7	43	1735	25	1465	1.46 (0.89–2.41)	0.13
Arthralgia/myalgia	5	56	1282	62	1285	2.18 (0.23–21.06)	0.50

Heterogeneity tests showed no significant results for all adverse events.
CI, confidence interval; OR, odds ratio.
[a]The result had a significant difference.

However, there were still several limitations in this pooled analysis. First, this analysis was based on literature abstract-based data, not individual patient data (IPD). An IPD meta-analysis would give a more robust estimate of the association but it would take a long time to obtain data [32]. However, the analysis based on published trials is an accepted method, and offers the most comprehensive insight into erlotinib-based regimens as soon as possible and may help physicians and their patients worldwide to make a better informed decision regarding the most appropriate therapy. A recently reported analysis confirmed that IPD and literature abstract-based meta-analyses did not differ substantially in their outcome [33]. Second, although we included 14 trials, there were only one to three trials in each subgroup [34–39]. However, all the 14 trials were RCTs, and all the results except for adverse events were based on ITT analysis. Therefore, we considered that our pooled analysis based on these trials is believable. Third, possible publication bias is also a potential threat in our study, although we did not detect it statistically.

In conclusion, this is the first published pooled analysis, to our knowledge, of randomized trials of erlotinib-based regimens versus other agent-based regimens in treating advanced NSCLC. Although there are some limitations, our findings demonstrate that erlotinib-based regimens significantly increase ORR and improve PFS as a first-line maintenance therapy or as a second/third-line therapy compared with placebo. Thus, the use of erlotinib may be a new effective therapy in treating advanced NSCLC as first-line maintenance therapy or second/third-line therapy compared with best supportive care.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, *et al.* Cancer statistics, 2008. *CA Cancer J Clin* 2008; **58**:71–96.

2 Hotta K, Matsuo K, Ueoka H, Kiura K, Tabata M, Tanimoto M, *et al.* Addition of platinum compounds to a new agent in patients with advanced non-small-cell lung cancer: a literature based meta-analysis of randomized trials. *Ann Oncol* 2004; **15**:1782–1789.

3 Korpanty G, Smyth E, Carney DN. Update on anti-angiogenic therapy in non-small cell lung cancer: are we making progress? *J Thorac Dis* 2011; **3**:19–29.

4 Shash E, Peccatori FA, Azim Jr HA. Optimizing the use of epidermal growth factor receptor inhibitors in advanced non-small-lung cancer (NSCLC). *J Thorac Dis* 2011; **3**:57–64.

5 Méndez M, Custodio A, Provencio M. New molecular targeted therapies for advanced non-small-cell lung cancer. *J Thorac Dis* 2011; **3**:30–56.

6 Fontanini G, De Laurentiis M, Vignati S, Chinè S, Lucchi M, Silvestri V, *et al.* Evaluation of epidermal growth factor-related growth factors and receptors and of neoangiogenesis in completely resected stage I–IIIA non-small-cell lung cancer: amphiregulin and microvessel count are independent prognostic indicators of survival. *Clin Cancer Res* 1998; **4**:241–249.

7 Grunwald V, Hidalgo M. Developing inhibitors of the epidermal growth factor receptor for cancer treatment. *J Natl Cancer Inst* 2003; **95**:851–867.

8 Douillard JY, Shepherd FA, Hirsh V, Mok T, Socinski MA, Gervais R, *et al.* Molecular predictors of outcome with gefitinib and docetaxel in previously treated non-small-cell lung cancer: data from the randomized phase III INTEREST trial. *J Clin Oncol* 2010; **28**:744–752.

9 Dai Q, Ling YH, Lia M, Zou YY, Kroog G, Iwata KK, *et al.* Enhanced sensitivity to the HER1/epidermal growth factor receptor tyrosine kinase inhibitor erlotinib hydrochloride in chemotherapy-resistant tumor cell lines. *Clin Cancer Res* 2005; **11**:1572–1578.

10 Perez-Soler R. Phase II clinical trial data with the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib (OSI-774) in non-small-cell lung cancer. *Clin Lung Cancer* 2004; **6**:s20–s23.

11 Miller VA, O'Connor P, Soh C, Kabbinavar F. A randomized, double-blind, placebo-controlled, phase IIIb trial (ATLAS) comparing bevacizumab (B) therapy with or without erlotinib (E) after completion of chemotherapy with B for first-line treatment of locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC). *J Clin Oncol* 2009; **27**:18s (suppl; abstr LBA8002).

12 Moher D, Jadad AR, Nichol G, Penman M, Tugwell P, Walsh S. Assessing the quality of randomized controlled trials: an annotated bibliography of scales and checklists. *Control Clin Trials* 1995; **16**:62–73.

13 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**:1539–1558.

14 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**:177–188.

15 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; **50**:1088–1101.

16 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**:629–634.

17 Parmar MB, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival end points. *Stat Med* 1998; **17**:2815–2834.

18 Gatzemeier U, Pluzanska A, Szczesna A, Kaukel E, Roubec J, De Rosa F, *et al.* Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: the Tarceva Lung Cancer Investigation Trial. *J Clin Oncol* 2007; **25**:1545–1552.

19 Herbst RS, Prager D, Hermann R, Fehrenbacher L, Johnson BE, Sandler A, *et al*. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol* 2005; **23**:5892–5899.

20 Lee S, Rudd R, Khan I, Upadhyay S, Lewanski CR, Falk. S, *et al*. TOPICAL: randomized phase III trial of erlotinib compared with placebo in chemotherapy-naive patients with advanced non-small cell lung cancer (NSCLC) and unsuitable for first-line chemotherapy. *J Clin Oncol* 2010; **28**:15s(suppl; abstr 7504).

21 Lilenbaum R, Axelrod R, Thomas S, Dowlati A, Seigel L, Albert D, *et al*. Randomized phase II trial of erlotinib or standard chemotherapy in patients with advanced non-small-cell lung cancer and a performance status of 2. *J Clin Oncol* 2008; **26**:863–869.

22 Reck M, Von Pawel J, Fischer JR, Kortsik C, Bohnet S, von Eiff M, *et al*. Erlotinib versus carboplatin/vinorelbine in elderly patients (age 70 or older) with advanced non-small cell lung carcinoma (NSCLC): a randomized phase II study of the German Thoracic Oncology Working Group. *J Clin Oncol* 2010; **28**:15s(suppl; abstr 7565).

23 Cappuzzo F, Coudert B, Wierzbicki R, Cicenas S, Szczésna A, Juhász E, *et al*. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol* 2010; **11**:521–529.

24 Mok TS, Wu YL, Yu CJ, Zhou C, Chen YM, Zhang L, *et al*. Randomized, placebo-controlled, phase II study of sequential erlotinib and chemotherapy as first-line treatment for advanced non-small-cell lung cancer. *J Clin Oncol* 2009; **27**:5080–5087.

25 Perol M, Chouaid C, Milleron BJ, Gervais R, Barlesi F, Westeel. V, *et al*. Maintenance with either gemcitabine or erlotinib versus observation with predefined second-line treatment after cisplatin-gemcitabine induction chemotherapy in advanced NSCLC: IFCT-GFPC 0502 phase III study. *J Clin Oncol* 2010; **28**:15s(suppl; abstr 7507).

26 Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, *et al*. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005; **353**:123–132.

27 Herbst RS, O'Neill VJ, Fehrenbacher L, Belani CP, Bonomi PD, Hart L, *et al*. Phase II study of efficacy and safety of bevacizumab in combination with chemotherapy or erlotinib compared with chemotherapy alone for treatment of recurrent or refractory non small-cell lung cancer. *J Clin Oncol* 2007; **25**:4743–4750.

28 Vamvakas L, Agelaki S, Kentepozidis NK, Karampeazis A, Pallis AG, Christophyllakis C, *et al*. Pemetrexed (MTA) compared with erlotinib (ERL) in pretreated patients with advanced non-small cell lung cancer (NSCLC): results of a randomized phase III Hellenic Oncology Research Group trial. *J Clin Oncol* 2010; **28**:15s(suppl; abstr 7519).

29 Natale RB, Thongprasert S, Greco FA, Thomas M, Tsai CM, Sunpaweravong P, *et al*. Phase III trial of vandetanib compared with erlotinib in patients with previously treated advanced non-small-cell lung cancer. *J Clin Oncol* 2011; **29**:1059–1066.

30 Boyer MJ, Blackhall FH, Park K, Barrios CH, Krzakowski MJ, Taylor I, *et al*. Efficacy and safety of PF299804 vs erlotinib (E): a global, randomized phase II trial in patients (pts) with advanced non-small cell lung cancer (NSCLC) after failure of chemotherapy (CT). *J Clin Oncol* 2010; **28**:18s(suppl; abstr LBA7523).

31 Brabender J, Danenberg KD, Metzger R, Schneider PM, Park J, Salonga D, *et al*. Epidermal growth factor receptor and HER2-neu mRNA expression in non-small cell lung cancer is correlated with survival. *Clin Cancer Res* 2001; **7**:1850–1855.

32 Clarke MJ, Stewart LA. . Obtaining individual patient data from randomized controlled trials. In: Egger M, Smith GD, Altman DG, editors. *Systematic Reviews in Health Care*. 2001; London: BMJ Publishing Group, pp. 109–121.

33 Bria E, Gralla RJ, Raftopoulos H, Giannarelli D. Comparing two methods of meta-analysis in clinical research – individual patient data-based (IPD) and literature-based abstracted data (AD) methods: analyzing five oncology issues involving more than 10 000 patients in randomized clinical trials (RCTs). *J Clin Oncol* 2007; **25**:s6512.

34 Riely GJ, Rizvi NA, Kris MG, Milton DT, Solit DB, Rosen N, *et al*. Randomized phase II study of pulse erlotinib before or after carboplatin and paclitaxel in current or former smokers with advanced non-small-cell lung cancer. *J Clin Oncol* 2009; **27**:264–270.

35 Gridelli C, Butts C, Ciardiello F, Feld R, Gallo C, Perrone F. An international, multicenter, randomized phase III study of first-line erlotinib followed by second-line cisplatin/gemcitabine versus first-line cisplatin/gemcitabine followed by second-line erlotinib in advanced non-small-cell lung cancer: treatment rationale and protocol dynamics of the TORCH trial. *Clin Lung Cancer* 2008; **9**:235–238.

36 Gridelli C, Rossi A, Mongillo F, Bareschino M, Maione P, Ciardiello F. A randomized phase II study of sorafenib/gemcitabine or sorafenib/erlotinib for advanced non-small-cell lung cancer in elderly patients or patients with a performance status of 2: treatment rationale and protocol dynamics. *Clin Lung Cancer* 2007; **8**:396–398.

37 Chen Y, Tsai C, Shih J, Perng R, Whang-Peng J. Phase II randomized trial of erlotinib versus vinorelbine in chemotherapy-naive patients with advanced non-small-cell lung cancer (NSCLC) aged $\geq$ 70 years in Taiwan. *J Clin Oncol* 2009; **27**:s8051.

38 Stinchcombe T, Bradford DS, Lee CB, Moore DT, Bakri KM, Taylor MA, *et al*. Preliminary results of a randomized phase II trial of first-line treatment of gemcitabine (G) versus erlotinib (E) versus gemcitabine and erlotinib (GE) in patients 70 years or older with advanced non-small cell lung cancer (NSCLC). *J Clin Oncol* 2010; **28**:15s(suppl; abstr 7576).

39 Ahn J, Kim S, Ahn M, Lee J, Uhm J, Sun J, *et al*. Randomized phase II study of gefitinib versus erlotinib in patients with advanced non-small cell lung cancer who failed previous chemotherapy. *J Clin Oncol* 2010; **28**:15s(suppl; abstr 7551).