Original Article

Erlotinib in patients with advanced non-small-cell lung cancer: a meta-analysis

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Abstract: Erlotinib is a potent reversible HER1/epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor with single-agent activity in patients with non–small-cell lung cancer (NSCLC). In this article, we updated the evidence of erlotinib in treating advanced NSCLC by adding new results of RCTs published between January 2011 and May 2012 into a pooled analysis which had been published in 2011. Outcomes analyzed were objective response rate (ORR), progression free survival (PFS), overall survival (OS) and adverse events. Twenty trials including 9,005 patients were identified, and six of them were recently published. As first-line therapy compared to placebo or chemotherapy, there was a similar ORR (P=0.29 and 0.42), PFS (P=0.09 and 0.25) and OS (P=0.73 and 0.49). However, for the patients with EGFR mutations, erlotinib based regimens could significantly improve ORR (P<0.01), prolong PFS (P<0.0), but did not prolong OS (P=0.22). As maintenance therapy compared with placebo, erlotinib based regimens significantly increased ORR (P<0.01), prolonged PFS (P<0.01), but did not improve OS (P=0.22). As second/third-line therapy comparing with placebo, erlotinib based regimens also significantly increased ORR (P<0.01), prolonged PFS (P<0.01), and improved OS (P<0.01). As second/third-line therapy compared with chemotherapy, gefitinib, or vandetanib, the outcomes were similar between two arms. However, compared with PF299804, there was a decreased ORR (P=0.02), and shorten PFS (P=0.02). Meanwhile, The patients treated with erlotinib based regimens suffered from more diarrhea, rash, and less fatigue, neutropenia, and thrombocytopenia than other agent based regimens. Our meta analysis showed that erlotinib based regimens could significantly increase ORR, improve PFS as first-line maintenance therapy or second/third-line therapy comparing with placebo or PF299804.

Key Words: Erlotinib; advanced non-small-cell lung cancer; meta analysis

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Introduction

Lung cancer is the major cause of cancer deaths worldwide, and the majority of new cases belong to advanced non small cell lung cancer (NSCLC) catagory (1). The standard first-line treatment for 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 to 8.1 months; 1-year survival rate is 28% to 47%) (3-5). Thus the development of more effective therapy remains challenging. The development of agents that target the epidermal growth factor receptor signal transduction pathways has provided a class of novel targeted therapeutic agents.

The epidermal growth factor receptors (EGFR) have 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) is a highly potent reversible HER1/EGFR tyrosine kinase inhibitor (EGFR-TKI) 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 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 which have shown prolonged survival with an EGFR inhibitor in advanced NSCLC. In other phase II and III trials, erlotinib based regimens did not show superior to other agent based regimens.

In 2011, We had carried out a pooled analysis of randomized controlled trials (RCTs) that compared erlotinib based regimens with other agent based regimens between January 1997 and 2011 (12). In this article, we added the results of RCTs which were recently published between January 2011 and May 2012 into the meta analysis, and updated the evidence.

Materials and methods

Literature search

The aim of this meta analysis was to review all published and reported randomized controlled trials comparing the erlotinib based regimens with other agent based regimens. Both published and unpublished trials reported between January 1997 and May 2012 were identified through a computer-based search of the PubMed database and abstracts from the past 13 conferences of the American Society of Clinical Oncology and the past 13 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 May 1, 2012.

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 (E) alone or based combination therapy was included in a randomized controlled trial (RCT), it was considered to be eligible. Inclusion criteria for the trails included: (I) patients were randomly assigned to treatment; (II) erlotinib or based combination regimen was compared to other agent or based combination regimen without confounding by other agents or interventions; and (III) 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*. (13), and there was no significant difference observed among the trials. Therefore, the result of the validity assessment was not considered in this meta analysis.

Data abstraction

The following information was extracted from each report: study design, regimen details, allocated patients, cause of disease, race or ethnic group, ECOG performance status, pathological subtype, prior chemotherapy, smoking status, EGFR protein expression, median follow-up, HRs for the whole study populations, and the year of reporting. Data was independently extracted from each report by XM. Su and HY. Liu, who were blinded to each other, using a standardized data recording form. After extraction, data was reviewed and compared by T. Zhang and P. Cheng 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 meta 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

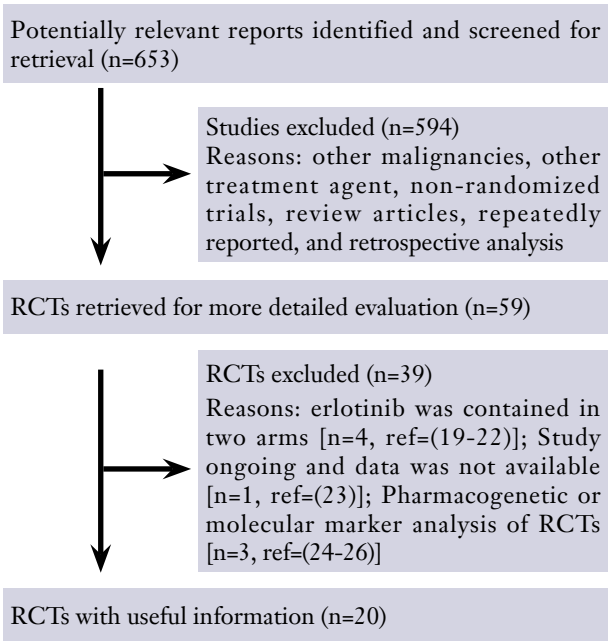

Figure 1 A flow chart showing the progress of trials through the review RCT, randomized controlled trials

to the allocated treatment. We looked for heterogeneity among the trials based on standard methods (14). The DerSimonian and Laird Q statistic (Q test) was used to test for the heterogeneity among trials (15). Begg's funnel plots (16) and Egger's test (17) were used to detect possible publication bias. Based on 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.* (18). 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.

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 *Figure 1* (19-26). Ultimately, results of twenty randomized phase II or III trials 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 twenty trials were randomized controlled trials and the results were almost based on intention to treat analysis except adverse events. There were three PIs responded to our requests of confirming update both published or unpublished data of the trials.

Characteristics of the twenty trials

The characteristics of the twenty trials are listed in *Table 1*. Three phase III RCTs comparing with placebo as first-line therapy (27-29), two phase III and four phase II RCT comparing with chemotherapy as first-line therapy (30-35), three phase III and one phase II RCTs comparing with placebo as maintenance therapy (36-39); one phase III RCT comparing with placebo as second/third-line therapy (11), one phase III and one phase II RCTs comparing with chemotherapy as second/third-line therapy (40,41), one phase III RCT comparing with vandetanib as second/third-line therapy (42), one phase II RCT comparing with PF299804 as second/third-line therapy (43), and one ohase II RCT comparing with Gefitinib as second/third-line therapy (44). In total, 9,005 patients were randomized to receive erlotinib based regimens (4,620 patients) or other agent based regimens (4,385 patients). 13 patients enrolled in one trial were excluded after randomization (27). Further information about unpublished data was obtained by contacting the principal authors. No potential sources of heterogeneity including sex, age, ECOG performance status, pathological subtype, prior chemotherapy, smoking status were associated with significant differences in outcomes.

Objective response rate

Seventeen trials except for Lee's, Miller's, and Perol's trials reported ORR (29,37,39). The response rates ranged from 4.0% to 82.9% for the erlotinib based regimens and from <1.0% to 47.9% for the other agent based regimens (*Table 2*). As first-line therapy, including ten trials and 4,168 patients (erlotinib, n=2,083; other agent, n=2,058), the random-effects model pooled estimate evaluated for ORR showed a similar ORR for erlotinib based regimens (OR, 0.58; 95% CI, 0.33 to 1.01; P=0.06). However, the test for heterogeneity showed a significant difference (I^2=89%, P<0.01), so we had to carry out subgroup analysis. The subgroup analysis showed a similar ORR comparing

Table 1 Characteristics of the twenty trials included in this meta analysis

Author	Year	Publication form	Design of studys	Pts	Chemo/Target therapy regimen	Sex (male, %)	PS 0-1(%)	Age	Stage III/IV (%)	Adeno-carcinoma (%)	Smoking History (%)
Gatzemeier	2007	Full text	Phase III Bouble-blind	586	E 150 mg/d, per oral + G 1,250 mg/m^2, d1,8 + DDP 80 mg/m^2, d1, 6 cycles	78.0	99.8	60.0	99.6	38.0	-
				586	Placebo + G 1,250 mg/m^2, d1,8 + DDP 80 mg/m^2, d1, 6 cycles	75.0	99.8	59.1	99.8	38.0	-
Herbst	2005	Full text	Phase III	539	E 150 mg/d, per oral + C AUC 6, d1 + T 200 mg/m^2, d1, 6 cycles	61.6	100	62.7	100	59.9	86.6
			-	540	Placebo + C AUC 6, d1 + T 200 mg/m^2, d1, 6 cycles	59.7	99.8	62.6	100	61.4	91.8
Lee	2010	Abstract	Phase III	350	E 150 mg/d, per oral	61.0	16	77.4	100	38	95.0
			-	320	Placebo	61.0	16	77.2	100	38	94.0
Rosell	2012	Full text	Phase III	86	E 150 mg/d, per oral G 1,	67.0	86.0	65.0	98.0	95.0	34.0
			Open-label	87	250 mg/m^2, d1,8 (D 75 mg/m^2, d1) + DDP 75 mg/m^2 (C AUC 5), d1, 3 cycles	78.0	86.0	65.0	100	90.0	28.0
Zhou	2011	Full text	Phase III	83	E 150 mg/d, per oral	41.0	91.0	57.0	100	88.0	28.0
			Open-label	82	G 1,000 mg/m^2, d1,8 + C AUC 5, d1, 4 cycles	40.0	96.0	59.0	100	86.0	31.0
Gridelli	2011	Full etxt	Phase II	29	E 150 mg/d, per oral + S 400mg/d, per oral, bid	59.0	100	76.0	100	86.0	93.0
			Open-label	31	G 1,250 mg/m^2, d1,8, 6 cycles + S 400 mg/d, per oral, bid	65.0	94.0	74.0	100	81.0	90.0
Lilenbaum	2008	Full text	Phase II	52	E 150 mg/d, per oral	44.0	0	51.0	100	50.0	88.0
			Open-label	51	C AUC 6, d1 + T 200 mg/m^2, d1, 6 cycles	55.0	0	52.0	100	63.0	92.0
Reck	2010	Abstract	Phase II	144	E 150 mg/d, per oral	65.0	100	75.5	100	50.0	82.0
			Open-label	140	C AUC 5, d1 + NVB 25 mg/m^2, d1,8, 6 cycles	71.0	100	76.1	99.0	49.0	86.0
Chen	2012	Full text	Phase II	57	E 150 mg/d, per oral	82.5	80.7	78.1	100	63.2	79.0
			Open-label	56	NVB 60 mg/m^2, d1,8, 6 cycles	80.4	73.2	77.8	100	66.1	78.6
Cappuzzo	2010	Full text	Phase III	438	After CT, E 150 mg/d, per	73.0	31.0	60.0	100	47.0	82.0
			Double-blind	451	oral, After CT, Placebo	75.0	32.0	60.0	100	44.0	83.0

Table 1 *(continued)*

Table 1 (continued)

Author	Year	Publication form	Design of studys	Pts	Chemo/Target therapy regimen	Sex (male,%)	PS 0-1(%)	Age	Stage III/IV (%)	Adeno-carcinoma (%)	Smoking History (%)
Miller	2009	Abstract	Phase III Bouble-blind	370	After CT, E 150 mg/d, per oral + B 15 mg/kg, d1, q3 wks	52.2	100	64.0	100	81.3	83.5
				373	After CT, Placebo + B 15 mg/kg, d1, q3 wks	52.3	99.7	64.0	100	82.5	82.3
Mok	2010	Full text	Phase II Bouble-blind	76	E 150 mg/d, per oral, d15-28 + G 1,250 mg /m^2, d1, 8 + DDP 75 mg/m^2 (C AUC 5), d1, 6 cycles	71.0	100	57.0	100	67.0	68.0
				78	Placebo+G 1,250 mg/m^2, d1,8 + DDP 75 mg/m^2 (C AUC 5), d1, 6 cycles	69.0	100	57.5	100	67.0	64.0
Perol	2010	Abstract	Phase III	155	After CT, E 150 mg/d, per oral	73	100	56.4	100	63	-
			Open-label	155	After CT, Observation	73	100	59.8	100	67	-
Shepherd	2005	Full text	Phase III	488	E 150 mg/d, per oral	64.5	91.4	62.0	100	50.4	73.4
			Bouble-blind	243	Placebo	65.8	91.4	59.0	100	49.0	77.0
Ciuleanu	2012	Full text	Phase III	203	E 150 mg/d, per oral	79.0	81.0	59.0	100	47.0	85.0
			Open-label	221	D or M	72.0	79.0	59.0	100	52.0	80.0
Herbst	2007	Full text	Phase II	39	E 150 mg/d, per oral+B 15 mg/kg, d1, q3 wks	43.6	100	68.0	100	82.1	84.6
			Open-label	40	T 75 mg/m^2, d1/M 500 mg/m^2, d1+B 15 mg/kg, d1, q3 wks	57.5	100	63.5	100	75.0	90.0
Vamvakas	2010	Abstract	Phase III	166	E 150 mg/d, per oral	81.3	79.2	65	100	53.6	-
			Open-label	166	MTA 500 mg/m^2, d1, q3 wks	82.5	81.3	66	100	56.6	-
Natale	2011	Full text	Phase III	617	E 150 mg/d, per oral	64.0	88.0	61.0	100	57.0	76.0
			Bouble-blind	623	V 300 mg/d, per oral	61.0	99.0	60.0	100	63.0	79.0
Boyer	2010	Abstract	Phase II	94	E 150 mg/d, per oral	59.6	96.8	67.0	100	64.9	78.7
			Open-label	94	PF299804 45 mg/do, per oral	58.5	81.9	69.0	100	66.0	79.8
Kim	2011	Full text	Phase II	48	E 150 mg/d, per oral	14.6	85.4	56.0	83.4	89.6	4.2
			Open-label	48	Gefitinib 250 mg/d, per oral	14.6	85.4	60.0	87.5	91.7	8.3

All trials were phase III trials except for Gridelli's, Lilenbaum's, Reck's, Mok's, and Herbst's trials which were designed as phase II trials.
A, abstract; AUC, area under the serum concentration-time curve; B, bevacizumab; C, carboplatin; CT, chemotherapy; D, docetaxel; DDP, cisplatin; E, erlotinib; F, full text; G, gemcitabine; M, pemetrexed; NVB, vinorelbine; Pts, patients; PS, performance status; S, Sorafenib; T, paclitaxel; V, vandetanib (a targeted drug); d, day; po, per oral; wks, weeks

Table 2 Responses in the seventeen trials

Author	Chemo/Targeted therapy regimen	Pts with complete or partial response	Randomized Pts	Objective response rate (%)
Gatzemeier *et al*.	E+G+DDP	183	580	31.5
	P+G+DDP	173	579	29.9
Herbst *et al*.	E+C+T	116	539	21.5
	P+C+T	104	540	19.3
Rosell zffigure.	E	50	86	58.1
	G (D) + DDP (C)	13	87	14.9
Zhou *et al*.	E	68	82	82.9
	G + C	26	72	36.1
Gridelli *et al*.	E + S	3	29	10.3
	G + S	2	31	6.5
Lilenbaum *et al*.	E	2	52	4.0
	C+T	6	51	12.0
Reck *et al*.	E	10	144	6.9
	C+NVB	32	140	22.9
Chen *et al*.	E	13	57	22.8
	NVB	5	56	8.9
Cappuzzo *et al.*	After CT, E	52	438	11.9
	After CT, P	24	451	5.3
Mok *et al*.	E+G+DDP (C)	27	76	35.5
	P+G+DDP (C)	19	78	24.4
Shepherd *et al*.	E	38	488	7.8
	P	2	243	<1
Ciuleanu *et al*.	E	16	203	7.9
	D or M	14	221	6.3
Herbst *et al*.	E+B	12	39	30.8
	T/M+B	16	40	40.0
Vamvakas *et al.*	E	13	166	7.8
	MTA	19	166	11.4
Natale *et al*.	E	74	617	12.0
	V	75	623	12.0
Boyer *et al*.	E	4	94	4.3
	PF299804	16	94	17.0
Kim *et al*.	E	19	48	39.6
	Gefitinib	23	48	47.9

B, bevacizumab; C, carboplatin; D, docetaxel; DDP, cisplatin; E, erlotinib; G, gemcitabine; M, pemetrexed; NVB, vinorelbine; P, Placebo; Pts, patients; S, Sorafenib; T, paclitaxel; V, vandetanib (a targeted drug). Response Rate was not included in the objectives of Lee's, Miller's, and Perol's studys

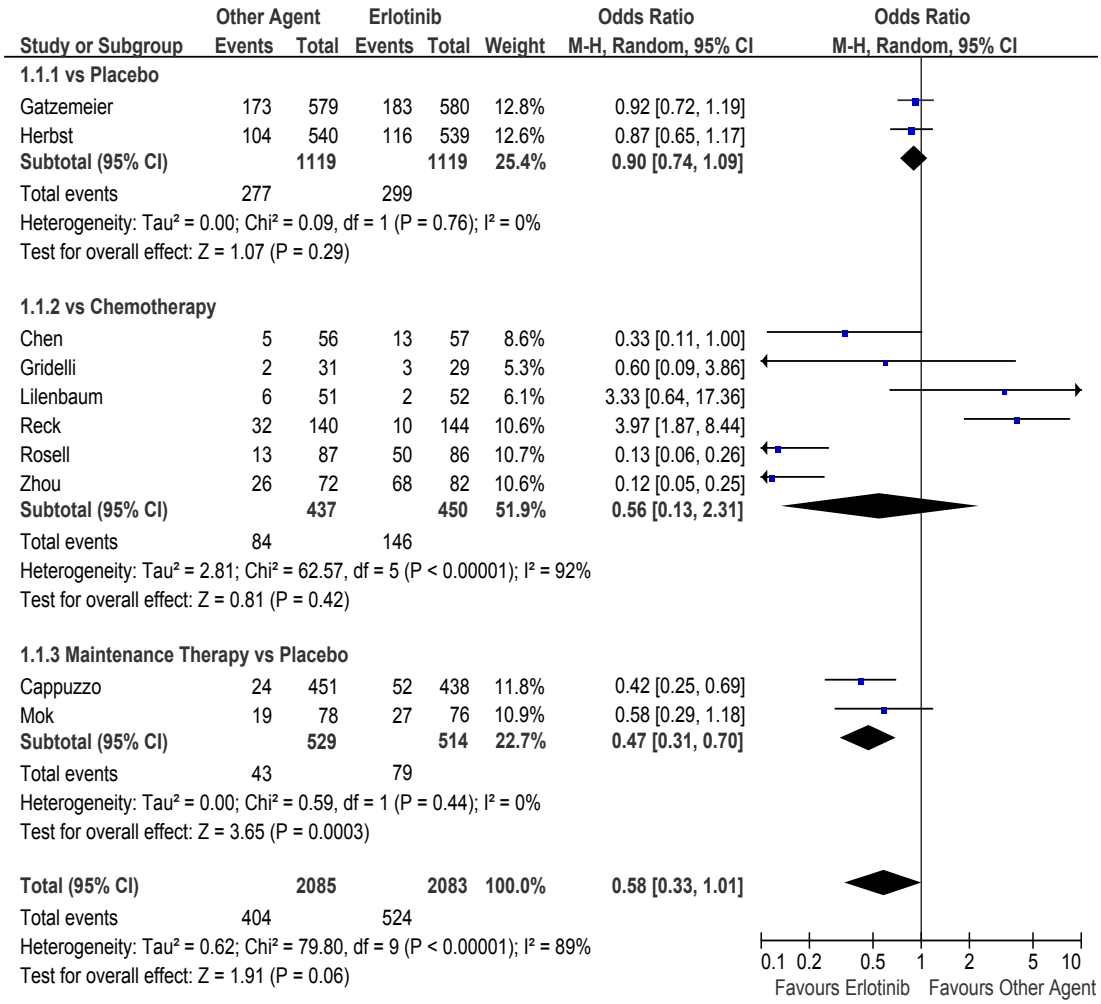

Figure 2 Response to erlotinib based regimens compared with other agent based regimens as first-line therapy. The heterogeneity test yielded a significant result (P<0.01)

with placebo (OR, 0.90; 95% CI, 0.74 to 1.09; P=0.29), or chemotherapy (OR, 0.56; 95% CI, 0.13 to 2.31; P=0.42), but an increased ORR comparing with placebo as maintenance therapy (OR, 0.47; 95% CI, 0.31 to 0.70; P<0.01; *Figure 2*).

Two of the six trials comparing with chemotherapy as first line therapy only enrolled the patients with EGFR mutations (32,33). So, there was a significant heterogeneity in this subgroup (I^2=92%, P<0.01). For these patients, erlotinib based regimens could significantly improve the ORR than chemotherapy (OR, 0.12; 95% CI, 0.07 to 0.20; P<0.01; data not shown).

As second/third-line therapy including seven trials and 3,090 patients (erlotinib, n=1,655; other agent, n=1,435), the pooled estimate showed a similar ORR for erlotinib based regimens (OR, 1.11; 95% CI, 0.65 to 1.90; P=0.70). The test for heterogeneity also showed a significant difference (I^2=70%, P<0.01). When compared with placebo, the subgroup analysis showed an increased ORR (OR, 0.10; 95% CI, 0.02 to 0.41; P<0.01). However, compared with chemotherapy, there was a similar ORR between two arms (OR, 1.18; 95% CI, 0.75 to 1.87; P=0.47; *Figure 3*).

With respect to all efficacy outcomes, random-effect (*Figures 2*,*3*,*4*,*5*,*6*,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=0.21, P=0.84). The results of Egger' test was similar.

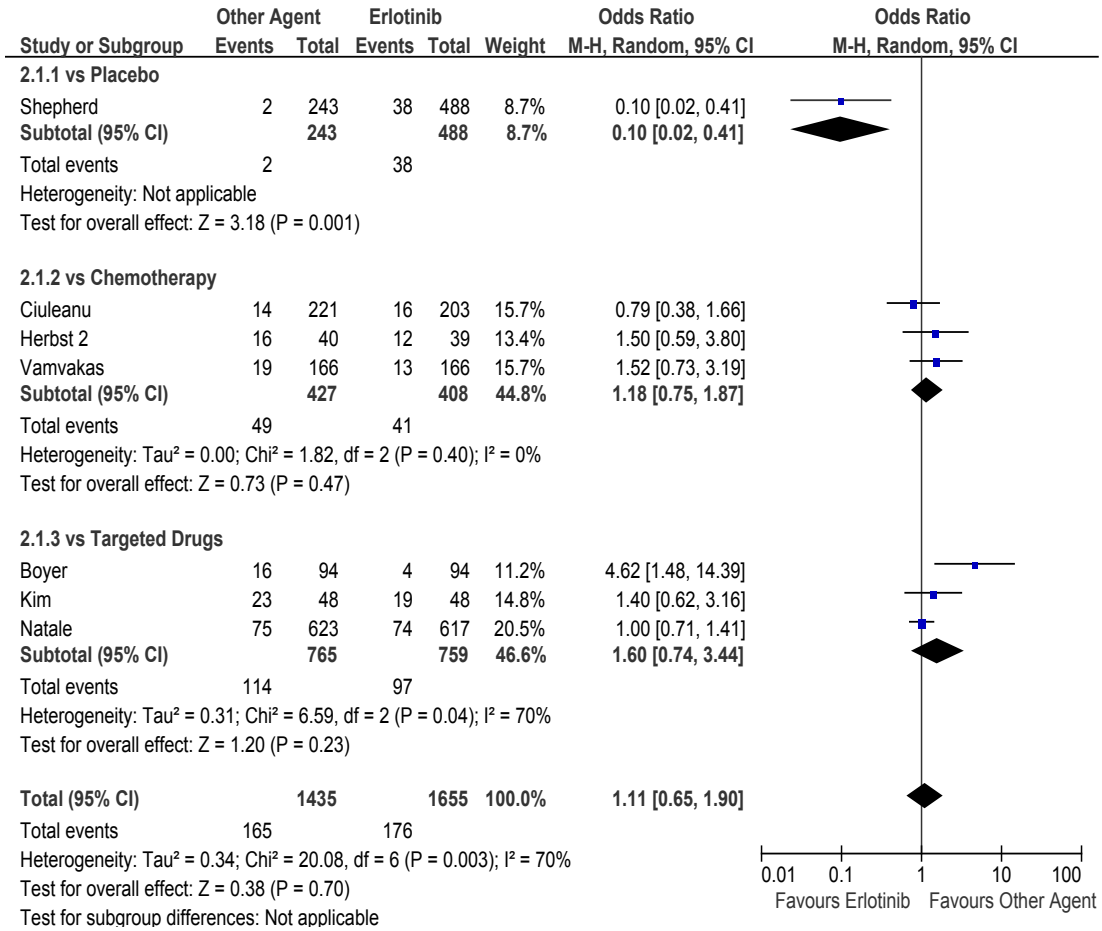

Figure 3 Response to erlotinib based regimens compared with other agent based regimens as second/third-line therapy. The heterogeneity test yielded a significant result (P<0.01)

Progression free survival

Ninteen trials except for Gridelli's trial reported PFS (*Table 3*) (34). As first-line therapy, the random-effects model pooled estimate evaluated for PFS showed a improved PFS for erlotinib based regimens (HR, 0.73; 95% CI, 0.60 to 0.89; P<0.01). However, the test for heterogeneity showed a significant difference (I^2=91%, P<0.01), so we had to carry out subgroup analysis. The pooled estimate showed a similar PFS comparing with placebo (HR, 0.93; 95% CI, 0.85 to 1.01; P=0.09), and chemotherapy (HR, 0.62; 95% CI, 0.28 to 1.40; P=0.25), but a prolonged PFS comparing with placebo as maintenance therapy (HR, 0.71; 95% CI, 0.60 to 0.83; P<0.01; *Figure 4*).

For the patients with EGFR mutations (32,33), our analysis showed that erlotinib based regimens could significantly improve the PFS than chemotherapy (HR, 0.25; 95% CI, 0.11 to 0.56; P<0.01; data not shown).

As second/third-line therapy including seven trials, the pooled estimate showed a similar PFS for erlotinib based regimens (HR, 0.91; 95% CI, 0.77 to 1.07; P=0.25). The test for heterogeneity also showed a significant difference (I^2=85%, P<0.01). The subgroup analysis showed a prolonged PFS compared with placebo (HR, 0.61; 95% CI, 0.51 to 0.73; P<0.01), but a similar PFS compared with chemotherapy (HR, 1.04; 95% CI, 0.93 to 1.16; P=0.50; *Figure 5*).

Neither a Begg's funnel plot nor a rank correlation test regarding response rate indicated the existence of publication bias (Z=0.70, P=0.48). The results of Egger' test was similar.

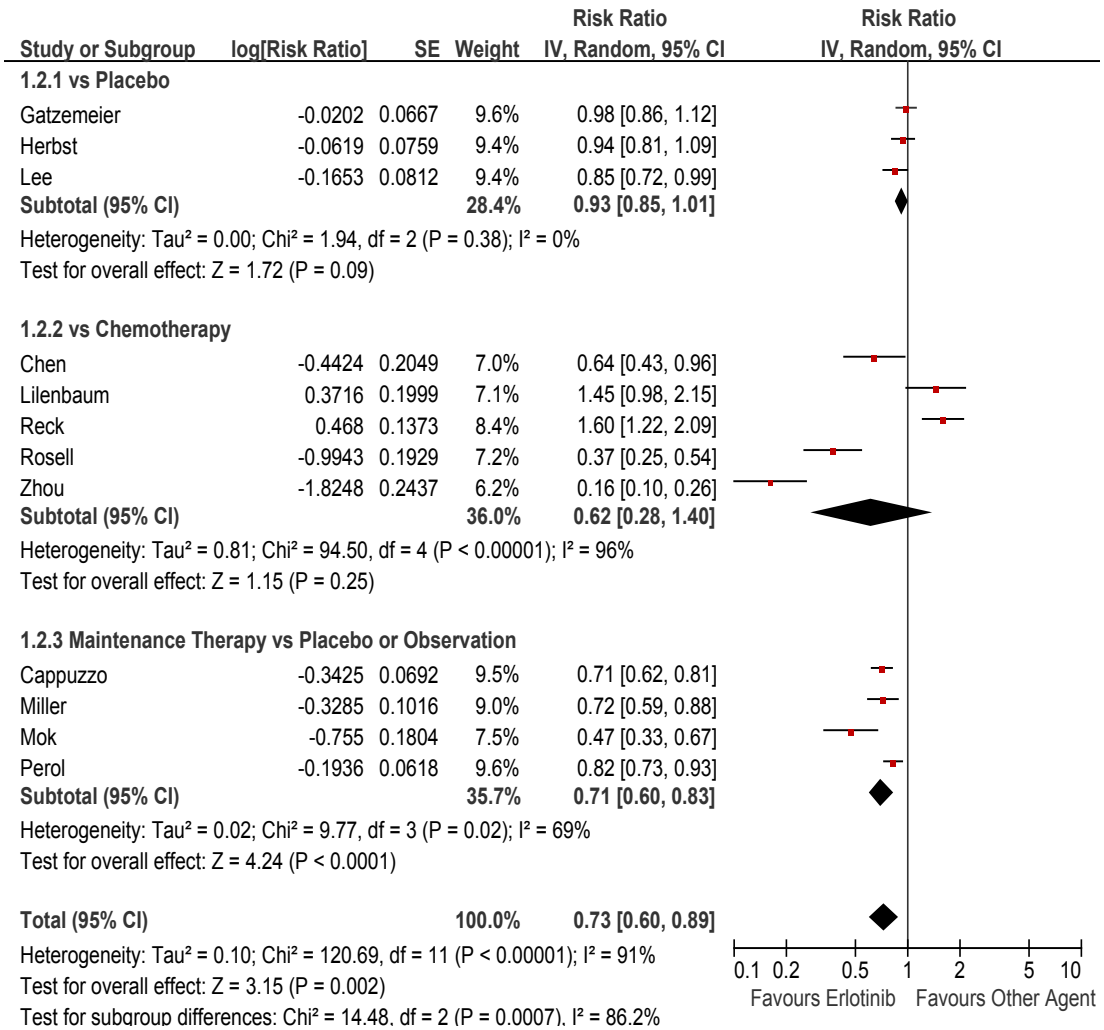

Figure 4 Progression-free survival with erlotinib based regimens compared to other agent based regimens as first-line therapy. The heterogeneity test yielded a significant result (P<0.01)

Overall survival

Only thirteen trials reported OS (*Table 3*). As first-line therapy including eight trials, the random-effects model pooled estimate evaluated for OS showed a similar OS for erlotinib based regimens (HR, 0.99; 95% CI, 0.89 to 1.22; P=0.93). The test for heterogeneity showed a significant difference (I^2=57%, P=0.02). The subgroup analysis showed a similar OS compared with placebo (HR, 1.02; 95% CI, 0.92 to 1.13; P=0.73), or with chemotherapy (HR, 1.11; 95% CI, 0.82 to 1.51; P=0.49), or as maintenance therapy (HR, 0.87; 95% CI, 0.68 to 1.11; P=0.22; *Figure 6*).

Only one trial reported OS for the patients with EGFR mutations (32). Our analysis showed that there was a similar OS between erlotinib based regimens and chemotherapy (HR, 1.22; 95% CI, 0.89 to 1.66; P=0.22; data not shown).

As second/third-line therapy including five trials, the pooled estimate showed a similar OS for erlotinib based regimens (HR, 0.92; 95% CI, 0.78 to 1.08; P=0.31). The test for heterogeneity showed a significant difference (I^2=64%, P=0.02). The subgroup analysis showed a prolonged OS compared with placebo (HR, 0.70; 95% CI, 0.58 to 0.84; P<0.01), but a similar OS compared with chemotherapy (HR, 0.99; 95% CI, 0.85 to 1.14; P=0.85). Erlotinib could also not improve OS of the patients compared with vandetanib (HR, 1.01; 95% CI, 0.89 to 1.16; P=0.85; *Figure 7*).

Neither a Begg's funnel plot nor a rank correlation

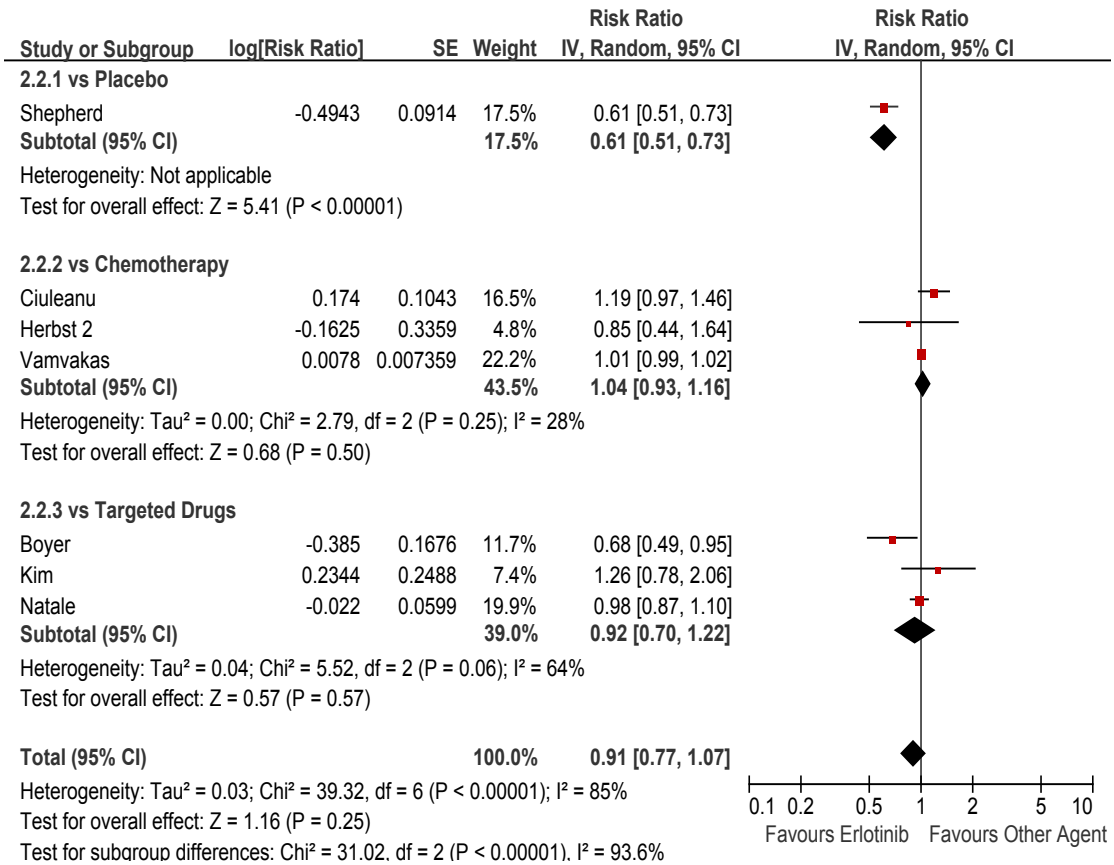

Figure 5 Progression-free survival with erlotinib based regimens compared to other agent based regimens as second/third-line therapy. The heterogeneity test yielded a significant result (P<0.01)

test regarding response rate indicated the existence of publication bias (Z=0.43, P=0.70). The results of Egger' test was similar.

Adverse events

Ninteen trials including 8,147 patients, except Chen' trial, provided results of adverse events (35). Reported toxicities were analyzed in only sixteen trials except for the targeted drugs containing trials (37,38) (*Table 4*). Grade 3/4 diarrhea (OR, 5.08; 95% CI, 3.43 to 7.52; P<0.01) and rash (OR, 19.37; 95% CI, 11.40 to 32.92; P<0.01) were significantly prominent in the erlotinib based regimens, with all intertrial variability consistent with the play of chance. However, fatigue (OR, 0.72; 95% CI, 0.55 to 0.94; P=0.02), neutropenia (OR, 0.74; 95% CI, 0.59 to 0.92; P<0.01) and thrombocytopenia (OR, 0.73; 95% CI, 0.57 to 0.93; P=0.01) were significantly decreased in the erlotinib based regimens. Compared to other agent based regimens, erlotinib based regimen did not increase the frequency of other adverse events. The heterogeneity test found no statistical significance except for thrombocytopenia.

Because of the significant heterogeneity (data not showen), we had to compare erlotinib with other targeted drugs respectively (*Figures 5*,*6*,7). Compared with gefitinib, there was a similar ORR (OR, 1.40; 95% CI, 0.62 to 3.61; P=0.41), PFS (HR, 1.26; 95% CI, 0.78 to 2.06; P=0.35), and the frequency of grade 3/4 adverse events (data not showen). Compared with vandetanib, there was a similar ORR (OR, 1.00; 95% CI, 0.71 to 1.40; P=0.98), PFS (HR, 0.98; 95.22% CI, 0.87 to 1.10; P=0.72), OS (HR, 1.01; 95.08% CI, 0.89 to 1.16; P=0.83), and the frequency of grade 3/4 adverse events (data not showen). Compared with PF299804, there was a decreased ORR (OR, 3.87; 95% CI, 1.27 to 11.81; P=0.02), and shorten PFS (HR, 0.58; 95% CI, 0.49 to 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 to 0.91; P=0.04).

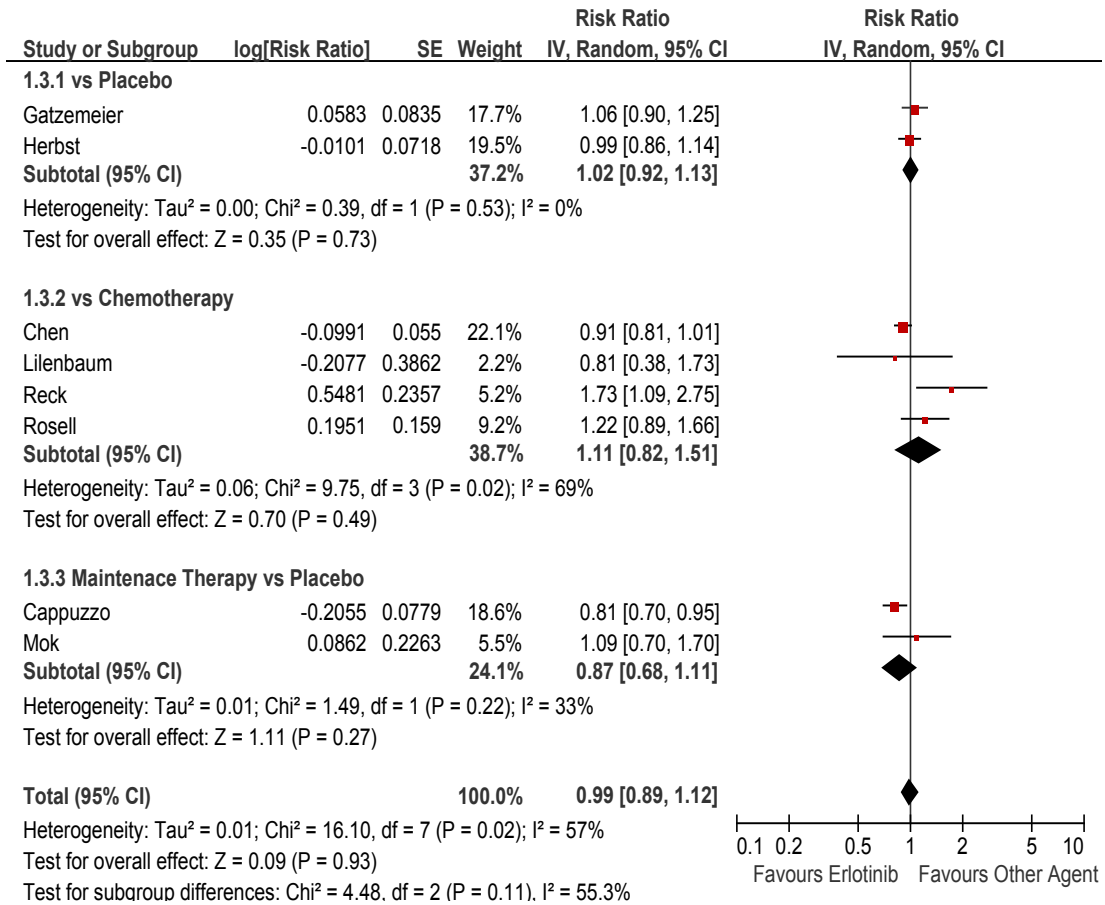

Figure 6 Overall survival with erlotinib based regimens compared to other agent based regimens as first-line therapy. The heterogeneity test did not yield a significant result (P=0.02)

Discussion

The epidermal growth factor receptor (EGFR) family is part of a complicated signal-transduction network that is a key to several critical cellular processes (39). Overexpression of EGFR is common in non small cell lung cancer (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, targeting the EGFR pathway agents such as gefitinib and erlotinib. Up to now, 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 meta analysis, we identified twenty RCT trials including 9,005 patients, and the largest accounted for 1,240 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 compared to placebo or chemotherapy, there were similar PFS (P=0.09 and 0.25) and OS (P=0.73 and 0.49). However, for the patients with EGFR mutations, erlotinib based regimens could significantly improve ORR (OR, 0.12; 95% CI, 0.07 to 0.20; P<0.01), prolong PFS (HR, 0.25; 95% CI, 0.11 to 0.56; P<0.0), but not OS (HR, 1.22; 95% CI, 0.89 to 1.66; P=0.22). As maintenance therapy compared with placebo, erlotinib based regimens significantly increased ORR (OR, 0.47; 95% CI, 0.31 to 0.70; P<0.01), prolonged PFS (HR, 0.71; 95% CI, 0.60 to 0.83; P<0.01), but did not

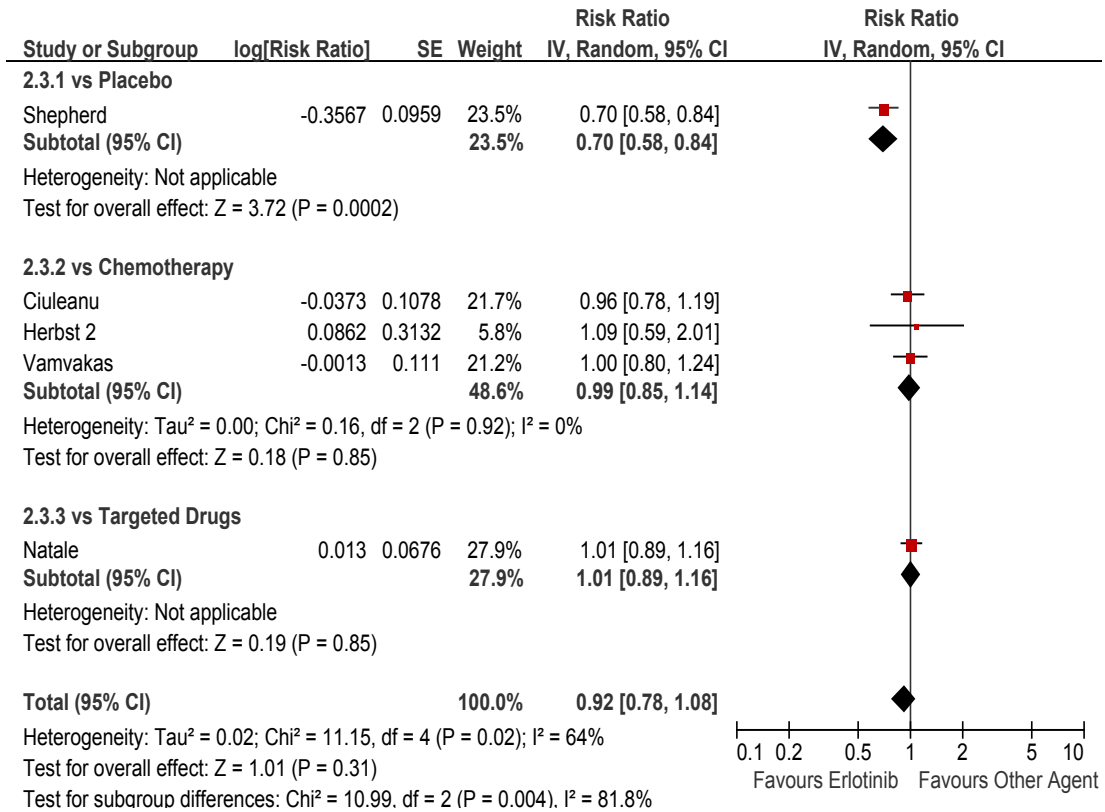

Figure 7 Overall survival with erlotinib based regimens compared to other agent based regimens as second/third-line therapy. The heterogeneity test yielded a significant result (P<0.01)

improve OS (HR, 0.87; 95% CI, 0.68 to 1.11; P=0.22). As second/third-line therapy comparing with placebo, erlotinib based regimens also significantly increased ORR (OR, 0.10; 95% CI, 0.02 to 0.41; P<0.01), prolonged PFS (HR, 0.61; 95% CI, 0.51 to 0.73; P<0.01), and improved OS (HR, 0.70; 95% CI, 0.58 to 0.84; P<0.01). However, as second/third-line therapy compared with chemotherapy, the outcomes were similar between two arms.

As first-line therapy, from the results of this meta analysis, we found that no matter compared with placebo or chemotherapy, for the patients we did not know their status of EGFR mutations, erlotinib based regimens could not increase ORR, improve PFS and OS. However, For the patients with EGFR mutations, erlotinib based regimens could significantly improve ORR, prolong PFS, but not OS. As first line maintenance therapy, we should prefer erlotinib to placebo.

As second/third-line therapy, we should prefer erlotinib or chemotherapy to best supportive care (BSC) in some patients with good PS status. Compared with molecular targeted drugs such as gefitinib or vandetanib, there was no significant difference between two arms. However, compared with PF299804, there was a decreased ORR (OR, 3.87; 95% CI, 1.27 to 11.81; P=0.02), and shorten PFS (HR, 0.58; 95% CI, 0.49 to 0.95; P=0.02).

In the pooled analysis published in 2011, an unexpected finding was an increased incidence in anemia with the erlotinib combination (12). At that time, we found that this increase was mostly due to the result reported by Gatzemeier's trial (27), and believed this increased incidence was just an accident and pointless. In this analysis, there was not significant difference in the incidence of anemia between erlotinib based regimens and other agent based regimens. Neither the Begg's funnel plot for publication bias nor did the heterogeneity test yield a significant result. Because the results based on fixed effect model were similar to the results based on random effect model, we did not show the results based on fixed effect model.

However, there were still several limitations in this meta analysis. First, this analysis was based on literature abstract-

Table 3 Progression free survival and overall survival in the twenty trials

Author	Chemo/Target therapy regimen	ITT analysis	Randomized Pts	Median PFS (month)	P Value	Median OS (month)	P Value
Gatzemeier *et al*.	E+G+DDP	Yes	586	5.50	0.74	10.00	0.49
	P+G+DDP		586	5.80		10.90	
Herbst *et al*.	E+C+T	Yes	539	5.10	0.36	10.60	0.95
	P+C+T		540	4.90		10.50	
Lee *et al*.	E	Yes	350	2.8	0.038	3.8	0.069
	P		320	2.7		3.6	
Rosell *et al*.	E	Yes	86	9.7	<0.0001	19.3	0.87
	G (D) + DDP (C)		87	5.2		19.5	
Zhou *et al*.	E	No	83	13.1	<0.0001	-	-
	G + C		82	4.6			
Gridelli *et al*.	E + S	Yes	29	3.0	-	12.6	-
	G + S		31	2.0		6.6	
Lilenbaum *et al*.	E	Yes	52	1.90	0.063	6.60	0.018
	C+T		51	3.50		9.70	
Reck *et al*.	E	No	125	2.4	0.001	7.9	0.21
	C+NVB		113	4.6		8.4	
Chen *et al*.	E	Yes	57	4.57	0.029	11.67	0.698
	NVB		56	2.53		9.3	
Cappuzzo *et al*.	After CT, E	Yes	437	2.87	<0.01	12.0	0.009
	After CT, P		447	2.59		11.0	
Miller *et al*.	After CT, E+B	Yes	373	4.76	0.001		-
	After CT, P+B		370	3.75			
Mok *et al*.	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*.	After CT, E	No	153	2.9	0.002		-
	After CT, Observation		152	1.9			
Shepherd *et al*.	E	Yes	488	2.20	<0.01	6.70	<0.01
	P		243	1.80		4.70	
Ciuleanu *et al*.	E	Yes	203	1.47	0.089	5.3	0.55
	D or M		221	2.01		5.3	
Herbst *et al*.	E+B	Yes	39	4.40	>0.05	13.70	>0.05
	T/M+B		40	4.80		12.60	
Vamvakas *et al*.	E	Yes	166	3.6	0.30	7.9	0.92
	MTA		166	2.7		8.9	
Natale *et al*.	E	Yes	617	2.08	0.72	7.8	0.83
	V		623	2.64		6.9	
Boyer *et al*.	E	Yes	94	1.94	0.019	-	-
	PF299804		94	2.89			
Kim *et al*.	E	Yes	48	3.1	0.336	-	-
	Gefitinib		48	4.9			

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; Pts, patients; S, Sorafenib; T, paclitaxel; V, vandetanib

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

Adverse events	No. of evaluable trials	Erlotinib based therapy		Other agent based therapy		OR (95% CI)	P Value for Q Test
		Pts with adverse events	Evaluable Pts	Pts with adverse events	Evaluable Pts		
Diarrhea[a]	16	149	3445	27	3182	5.08 (3.43-7.52)	<0.01
Rash[a]	16	261	3445	8	3182	19.37 (11.40-32.92)	<0.01
Fatigue[a]	11	105	2181	124	1916	0.72(0.55-0.94)	0.02
Neutropenia[a]	11	174	2042	225	2052	0.74(0.59-0.92)	<0.01
Thrombocytopenia[a]	10	116	1774	153	1756	0.73(0.57-0.93)	0.01
Anemia	12	137	1810	115	1807	1.21(0.93-1.57)	0.15
Nausea/vomiting	11	112	2263	113	2000	0.96(0.73-1.26)	0.76
Anorexia	10	44	2044	31	1791	1.24 (0.78-1.97)	0.36
Arthralgia/myalgia	4	7	541	11	554	0.64(0.25-1.62)	0.35

Heterogeneity tests showed no significant results except for thrombocytopenia. OR, odds ratio; CI, confidence interval; [a]the result had a significant difference

based (AD) data, not individual patient data (IPD). An IPD meta-analysis would give a more robust estimate of the association but have to take a long time to obtain data (45). But the analysis based on published trials is an accepted method, 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 individual patient-based (IPD) and literature abstract-based (AD) meta-analyses did not differ substantially in their outcome (46). Second, although we included twenty trials, there were only one to six trials in each subgroup. However, all the twenty trials were randomized controlled trials, and all the results except for adverse events were based on intention to treat analysis. Therefore we considered our meta analysis based on these trials is believable. Third, possible publication bias is also a potential threat in our study, though we did not detect it statistically.

In conclusion, we updated the evidence 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, improve PFS as first-line maintenance therapy or second/third line therapy comparing with placebo. Thus, the use of erlotinib may be a new effective therapy of treating advanced NSCLC as first-line maintenance therapy, or second/third line therapy compared with best supportive care (BSC).

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