

# Targeted drugs for unselected patients with advanced non-small-cell lung cancer: a network meta-analysis

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**Background:** Currently, targeted therapy has shown encouraging treatment benefits in selected patients with advanced non-small cell lung cancer (NSCLC). However, the comparative benefits of targeted drugs and chemotherapy (CT) treatments in unselected patients are not clear. We therefore conduct a network meta-analysis to assess the relative efficacy and safety of these regimens.

**Methods:** PubMed, EMBASE, Cochrane Library and abstracts from major scientific meetings were searched for eligible literatures. The odds ratio (OR) for objective response rate (ORR) and safety was used for pooling effect sizes. Bayesian network meta-analysis was conducted to calculate the efficacy and safety of all included treatments. All tests of statistical significance were two sided.

**Results:** A total of 13,060 patients from 24 randomized controlled trials (RCT) were assessed. The targeted agents included bevacizumab (Bev), gefitinib (Gef), erlotinib (Erl) and cetuximab (Cet). Network meta-analysis showed that Bev + CT had a statistically significantly higher incidence of ORR relative to the other six different treatments, including placebo (OR =6.47; 95% CI, 3.85–10.29), Erl (OR =2.81; 95% CI, 2.08–3.70), CT (OR =1.92; 95% CI, 1.61–2.28), Gef (OR =1.40; 95% CI, 1.10–1.75), Erl + CT (OR =1.46; 95% CI, 1.17–1.80) and Gef + CT (OR =1.75; 95% CI, 1.36–2.22), whereas placebo and Erl were associated with statistically significantly lower incidence of ORR. Trend analyses of rank probability revealed that Bev + CT had the highest probability of being the best treatment arm in term of ORR, followed by Cet + CT. Meanwhile, Cet + CT showed significant severer rash and thrombocytopenia compared with Bev + CT. Gef was probable to be the rank 3 for ORR but was associated with relatively low risk for grade  $\geq 3$  toxicities.

**Conclusions:** Our study suggested that Bev + CT may offer better ORR in the treatment of unselected patients with advanced NSCLC. Future studies will be needed to investigate whether the increase of ORR with targeted drugs would be translated into survival benefits.

**Keywords:** Targeted drugs; efficacy; non-small cell lung cancer (NSCLC); network meta-analysis

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## Introduction

Lung cancer is the leading cause of cancer-related death, with nearly 1.6 million deaths annually worldwide, as of 2012 (1). Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer and more than 40% of NSCLCs are diagnosed at advanced stage (III or IV), the 5-year survival rate is extremely low, ranging from 5% to 15% (2). Platinum-based double chemotherapy is recommended as standard first-line treatment, however, the objective response rate (ORR) is modest and recurrence eventually occurs for most patients (3).

Over the past decade, the NSCLC therapeutics landscape has been dominated by the increasing focus on identification and validation of molecular targets (4). Several drugs were designed to interfere with specific aberrant biological pathways in NSCLC, for example, epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) (such as gefitinib and erlotinib) (5), monoclonal antibodies targeting EGFR (such as cetuximab) (6,7) and angiogenesis inhibitors (such as, bevacizumab) (8-10). In addition, other targeted agents were at varying stages of clinical development, panitumumab (anti-EGFR monoclonal antibodies) (4), ALK inhibitor (crizotinib and Ceritinib) (11,12), selumetinib (MEK1/MEK2 inhibitor) (13) and so on.

Similar to many other cancers, NSCLC is not a singular entity but is in fact multiple pathologies, it is initiated by activation of oncogenes or inactivation of tumor suppressor genes. Thus, the optimal management of NSCLC is to identify the driver mutations that help to predict sensitivity to targeted therapy and estimate prognosis respectively. For example, large randomized controlled trials and meta-analysis showed that TKI treatment was superior to conventional chemotherapy drugs in terms of progression-free survival (PFS) and ORR for patients harboring EGFR-mutation (14-19). Unfortunately, there are no reliable clinical phenotypes or characteristics that allow for accurate prediction of driver mutation, all tumours must undergo specific mutational testing. As we know, in routine clinical practice, obtaining information on driver gene mutational status is not always feasible, due to insufficient testing facilities and low-quality tumor samples, especially, in some advanced patients or postoperative recurrence cases. Even if we can obtain the driver mutations from the peripheral blood circulating tumor DNA (ctDNA) (20) or circulating tumor cells (CTC) (21), the existing methods have insufficient sensitivity, and the testing cost is expensive. At the same time, the occurrence and development of tumors

are a complicated process, and multiple signalling pathways have been identified in NSCLC that lead to malignant transformations, such as RAS-RAF-MEK-ERK or MAPK, PI3K-AKT-mTOR or JAK-STAT pathways (4). Single targeted therapy cannot obtain the expected effect and acquired resistance is frequently seen in clinical practice. So, the relative effects and safety of these targeted drugs compared with another in unselected patients with advanced NSCLC remains unclear.

Although many trials have been conducted to compare treatments, there is lack of integration information from head-to-head RCTs. Network meta-analysis provides a useful method for estimating the relative treatment effects of these agents (22). Unlike traditional meta-analysis, it enables us to synthesize data from both direct and indirect evidence of diverse regimens, and compare the results based on individual trial (23). Some previous researches reported that inferior response to EGFR-TKIs following treatment of chemotherapy (24,25). Therefore, we performed a systematic review and network meta-analysis of randomized controlled trials comparing the efficacy and safety of first-line chemotherapy and targeted therapy in unselected patients with advanced NSCLC and also estimated the rank probability of each treatment, expecting it will be helpful for making evidence-based clinical decision for physicians and patients.

## Methods

### *Search strategy*

We carried out a comprehensive systematic search for published articles from inception to 2015 using PubMed, EMBASE and Cochrane Library; the key words were as follows: NSCLC, bevacizumab, gefitinib, erlotinib, afatinib, cetuximab, and randomized controlled trial. No language limits were applied. At the same time, meeting abstracts and virtual presentations of American Society of Clinical Oncology (ASCO) annual meetings and European Society of Medical Oncology (ESMO) congresses were also searched to identify unpublished trials. Two authors (M.M.S and Y.G.Z) independently screened the selected eligible trials.

### *Selection criteria*

Eligible studies should meet the following criteria: (I) randomized controlled trial; (II) patients with confirmed

locally advanced or metastatic NSCLC were randomly assigned to first-line treatment; (III) at least two arms of different treatment regimens, chemotherapy, placebo or targeted therapy; (IV) studies with available data on patients' EGFR unselected status; (V) outcomes of interest were ORR and safety. Studies failed to meet the inclusion criteria will be excluded. If overlap reports were identified, we included only the most recent and informative publication.

### *Data extraction and quality assessment*

Two authors (M.M.S and Y.G.Z) independently extracted data according to a predefined information sheet, including first author, year of publication, number of patients, targeted treatment, chemotherapy regimens, patient characteristics (age, sex, ethnicity, histology and whether CT-native), and the outcomes of interest. The primary outcome in this study was ORR, it was defined as the proportion of complete response (CR) plus partial response (PR) among all evaluable patients, reflected the treatment by causing cancer cell death. For each trial, the OR with its 95% CI was directly extracted from research articles. Secondary outcome was the number of patients who had grade  $\geq 3$  adverse events, including rash, anemia, diarrhea, neutropenia and thrombocytopenia. Adverse events were graded according to National Cancer Institute Common Terminology Criteria (NCI-CTC) version 4.0.

Cochrane Collaboration's tool was used to evaluate the quality of each eligible trials (26). Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to rate the overall quality of each outcome (27). Discrepancies were resolved by two reviewers (Y.L and W.R.T) to reach consensus.

### *Statistical methods*

We first used random effects model to conduct direct meta-analysis, OR, 95% CI and P values were reported, two-side  $P < 0.05$  was considered statistically significant. If a direct comparison was based on two or more studies,  $I^2$  statistic was calculated to evaluate statistical heterogeneity.  $I^2$  values greater than 50% was considered high heterogeneity, 25–50% was indicative of modest heterogeneity, less than 25%, low heterogeneity (28).

Second, a Bayesian network meta-analysis was carried out to simultaneously compare the efficacy of all treatments which used in unselected patients with NSCLC. In the Bayesian framework, it incorporated both direct and

indirect evidence to obtain estimate of the relative treatment effects between all the comparisons (23). The posterior distributions for each parameter of interest were estimated using Markov Chain Monte Carlo by placing suitable prior distributions (29). Both random-effects and fixed-effects models were used, then we evaluated the overall fit of the selected models base on deviance information criterion (DIC) statistics and the total residual deviance, DIC was an estimate of expected predictive error (lower deviance was better) (30). In addition, Bayesian framework for network meta-analysis provided a ranking probability curve of each treatment, we can rank treatments by counting the proportion of iterations of Markov Chain in which each drug had the highest OR (30).

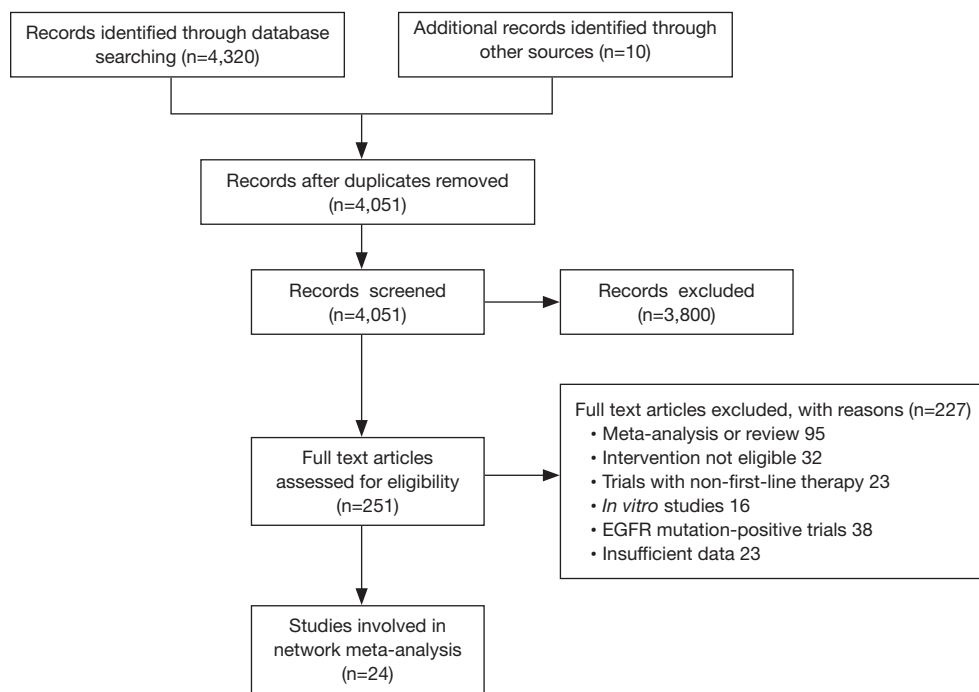
Pairwise comparisons and node-splitting method were performed by STATA version 12.0 (STATA Corporation, College Station, TX, USA). Bayesian network meta-analysis was calculated using R2OpenBUGS version 3.2.3 (MRC, UK, and Imperial College, UK). Diagrams were made by R version 3.1.3 (R Project for Statistical Computing, Vienna, Austria). This meta-analysis was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (31).

## **Results**

### *Description of eligible trials*

A total of 4,330 articles were identified according to the search strategy. Of these, 251 potentially eligible articles were evaluated in more detail, after review of full publications, 24 randomized clinical trials were finally selected for the study (*Figure 1*). Characteristics of the included trials were summarized in *Table 1*. Five trials applied bevacizumab (Bev) (9,10,32–34), seven trials applied gefitinib (Gef) (35–41), ten trials applied erlotinib (Erl) (24,42–50) and the other two trials applied cetuximab (Cet) (7,51). A total of 13,060 patients were enrolled, patients median age varied from 19–96; 38.2–100% of patients were adenocarcinoma; sixteen trials predominantly enrolled White patients (7,9,10,24,33,35–38,42,43,45,46,49–51) whereas other six had a majority of Asian patients (32,40,41,44,47,48) excluding the unreported data. For the outcomes of interest, eight different treatment arms were assessed: placebo, CT, Erl, Gef, Erl + CT, Gef + CT, Bev + CT, Cet + CT.

The quality of each eligible trial and other risks of bias were evaluated using Cochrane Collaboration's



**Figure 1** Trial selection process.

tool, 14/24 studies were reported as high quality and the remaining 10 studies as acceptable quality (*Table S1*). Based on the GRADE criteria, the overall quality of the evidence about ORR, neutropenia, rash and diarrhea were rated as moderate, and the quality of the evidence about thrombocytopenia and anemia were rated as low (*Table S2*).

### Direct comparisons

Pairwise comparisons were accomplished for the nine different comparisons. The number of patients who achieved ORR was reported in 24 studies. Grade  $\geq 3$  rash, anemia, diarrhea, neutropenia and thrombocytopenia were reported in 19 studies (7,10,24,34-46,48,49,51), 21 studies (7,9,10,24,33-45,48-51), 19 studies (7,24,34-46,48-51), 19 studies (7,9,10,24,32-36,38-42,44,45,48,49,51) and 16 studies (7,9,10,24,32-34,38,39,41,42,44,45,48,49,51) respectively. ORs and heterogeneity by  $I^2$  were listed in *Table 2*. For unselected patients, Bev + CT (OR =2.19; 95% CI, 1.55–3.11;  $P < 0.001$ ), Erl + CT (OR =1.64; 95% CI, 1.05–2.57;  $P = 0.031$ ) and Cet + CT (OR =1.68; 95% CI, 1.96–2.36;  $P = 0.003$ ) were associated with statistically significantly higher incidence of ORR than CT. The estimated OR for Gef + CT and Gef compared with CT showed a consistent trend for higher ORR, although they

did not reach statistical significance. However, Erl was associated with inferior efficacy compared with CT (OR =0.81; 95% CI, 0.23–2.78;  $P = 0.735$ ).

In terms of rash and diarrhea, Erl + CT, Gef + CT, Cet + CT and Gef were associated with significantly greater odds compared with CT. While CT showed statistically significantly more incidence of neutropenia and anemia compared to Gef and Erl. The risk of thrombocytopenia did not show any statistically significant difference among all the treatment arms except CT *vs.* Gef (OR =0.13; 95% CI, 0.03–0.61;  $P = 0.009$ ) (*Table 2*).

An estimate consistent with large heterogeneity ( $I^2 > 50\%$ ) was seen in three comparisons for ORR, two comparisons for rash, one comparison for neutropenia and one comparison for thrombocytopenia, while no large heterogeneity was seen in comparisons concerning anemia and diarrhea (*Table 2*).

### Network meta-analysis for efficacy and toxicities

From the eligible studies, 28 indirect comparisons were made, and the network geometry of ORR was described in *Figure 2*. ORs and credibility interval for all possible comparisons were calculated by Bayesian network meta-analysis (*Table 3*). According to the results, Bev + CT had a

Table 1 Characteristics of eligible studies included in the network meta-analysis

Study	No. of patients	Regimens arms 1	Regimens arms 2	Age, median [range], years	Female, N (%)	Ethnicity (%)	Smoking status: nonsmoker, N (%)	Adenocarcinoma, N (%)	CT-native
Sandler [2006] (10)	850	Paclitaxel + carboplatin + bevacizumab 15 mg/kg d1, iv, q3w	Paclitaxel 200 mg/m <sup>2</sup> d1 + carboplatin (AUC =6) d1, iv, q3w x6 cycles	NR	387 (45.5)	White (85.8)	NR	746 (87.7)	Yes
Reck [2010] (9)	1,043	Cisplatin + gemcitabine + bevacizumab 15 mg/kg d1, iv, q3w	Cisplatin 80 mg/m <sup>2</sup> d1 + gemcitabine 1,250 mg/m <sup>2</sup> d1,8, iv, q3w x6 cycles	57 [20–83]	378 (36.2)	White (91.2)	NR	876 (83.9)	Yes
Niho [2012] (32)	180	Paclitaxel + carboplatin + bevacizumab 15 mg/kg d1, iv, q3w	Paclitaxel 200mg/m <sup>2</sup> d1 + carboplatin (AUC =6) d1, iv, q3w x6 cycles	60 [34–74]	65 (36.1)	Asian (100.0)	57 (31.6)	166 (92.2)	Yes
Soria [2011] (33)	213	Paclitaxel + carboplatin + bevacizumab 15 mg/kg d1, iv, q3w	Paclitaxel 200 mg/m <sup>2</sup> d1 + carboplatin (AUC=6) d1, iv, q3w x6 cycles	57 [23–79]	78 (36.3)	White (98.6)	36 (16.9)	124 (58.2)	Yes
Boutsikou [2013] (34)	229	Docetaxel + carboplatin + bevacizumab 7.5 mg/kg d1, iv, q4w	Docetaxel 100 mg/m <sup>2</sup> d1 + carboplatin (AUC =5.5) d1, iv, q4w x6 cycles	NR	38 (16.5)	NR	27 (11.7)	206 (89.9)	Yes
		Docetaxel + carboplatin + erlotinib 150 mg/d d1, orally, 3 cycles	Docetaxel 100 mg/m <sup>2</sup> d1 + carboplatin (AUC =5.5) d1, iv, q4w x6 cycles						

Table 1 (continued)

Table 1 (continued)

Study	No. of patients	Regimens arms 1	Regimens arms 2	Age, median [range], years	Female, N (%)	Ethnicity (%)	Smoking status: nonsmoker, N (%)	Adenocarcinoma, N (%)	CT-native
Herbst [2004] (35)	1,037	Paclitaxel + carboplatin + gefitinib 250 mg/d orally, q3w	Paclitaxel 225 mg/m <sup>2</sup> d1 + carboplatin (AUC =6) d1, iv, q3w x6 cycles	61 [26–86]	418 (40.3)	White (90.2)	NR	572 (55.1)	Yes
Crinò [2008] (36)	196	Gefitinib 250 mg/d, orally	Vinorelbine 30 mg/m <sup>2</sup> d1,8, orally, q3w	74 [70–89]	48 (24.4)	White (82.6)	28 (14.2)	79 (40.3)	Yes
Goss [2009] (37)	201	Gefitinib 250 mg/d, orally	Placebo	74 [42–90]	79 (39.3)	White (96.0)	19 (9.4)	91 (45.2)	Yes
Giaccone [2004] (38)	1,093	Cisplatin + gemcitabine + gefitinib 250 mg/d orally	Cisplatin 80 mg/m <sup>2</sup> d1 + gemcitabine 1,250 mg/m <sup>2</sup> d1,8, iv, q3w x6 cycles	59 [31–85]	863 (79.0)	White (90.4)	NR	503 (46.1)	Yes
Morère [2010] (39)	127	Gefitinib 250 mg/d, orally	Docetaxel 75 mg/m <sup>2</sup> d1, q3w	70 [30–80]	22 (17.3)	White (NR)	8 (6.3)	62 (48.8)	Yes
Fukuoka [2011] (40)	1,217	Gefitinib 250 mg/d, orally	Paclitaxel 200 mg/m <sup>2</sup> d1 + carboplatin (AUC =5-6) d1, iv, q3w x≤6 cycle	57 [24–84]	965 (79.2)	Asian (99.8)	1140 (93.6)	1172 (96.3)	Yes
Han [2012] (41)	309	Gefitinib 250 mg/d, orally	Cisplatin 75 mg/m <sup>2</sup> d1 + gemcitabine 1,250 mg/m <sup>2</sup> d1,8, iv, q3w x9 cycles	57 [19–74]	274 (88.7)	Asian (100.0)	309 (100.0)	309 (100.0)	Yes

Table 1 (continued)

Table 1 (continued)

Study	No. of patients	Regimens arms 1	Regimens arms 2	Age, median [range], years	Female, N (%)	Ethnicity (%)	Smoking status: nonsmoker, N (%)	Adenocarcinoma, N (%)	CT-native
Herbst [2005] (42)	1,078	Paclitaxel + carboplatin + erlotinib 150 mg/d, orally	Paclitaxel 200 mg/m <sup>2</sup> d1 + carboplatin (AUC =6) d1, iv, q3w x6 cycles	63 [24-84]	424 (39.3)	White (86.6)	116 (10.7)	654 (60.6)	Yes
Lienbaum [2008] (43)	103	Erlotinib 150 mg/d, orally	Paclitaxel 200 mg/m <sup>2</sup> d1 + carboplatin (AUC =6) d1, iv, q3w x4 cycles	NR	52 (50.4)	White (66.0)	10 (9.7)	58 (56.3)	Yes
Mok [2009] (44)	154	Cisplatin/carboplatin + gemcitabine + erlotinib 150 mg/d, d15-28, orally	[Cisplatin 75 mg/m <sup>2</sup> d1 or carboplatin (AUC =5) d1] + gemcitabine 1,250 mg/m <sup>2</sup> d1,8, iv, q4w	57 [27-79]	46 (29.8)	Asian (94.1)	52 (33.7)	103 (66.8)	Yes
Gatzemeier [2007] (45)	1,159	Cisplatin + gemcitabine + erlotinib 150 mg/d, orally	Cisplatin 80 mg/m <sup>2</sup> d1 + gemcitabine 1,250 mg/m <sup>2</sup> d1,8, iv, q3w x6 cycles	60 [26-84]	267 (23.0)	White (91.8)	NR	445 (38.3)	Yes
Cappuzzo [2010] (46)	889	Erlotinib 150 mg/d, orally	Placebo	60 [30-83]	230 (25.8)	White (83.9)	152 (17.0)	403 (45.3)	No
Gridelli [2012] (24)	760	Erlotinib 150 mg/d, orally	Cisplatin 80 mg/m <sup>2</sup> d1 + gemcitabine 1,200 mg/m <sup>2</sup> d1,8, iv, q3w x6 cycles	62 [27-81]	256 (33.7)	White (100.0)	157 (20.7)	422 (55.5)	No

Table 1 (continued)

Table 1 (continued)

Study	No. of patients	Regimens arms 1	Regimens arms 2	Age, median [range], years	Female, N (%)	Ethnicity (%)	Smoking status: nonsmoker, N (%)	Adenocarcinoma, N (%)	CT-native
Chen [2012] (47)	113	Erlotinib 150 mg/d, orally	Vinorelbine 60 mg/m <sup>2</sup> d1,8, orally, q3w	77 [70-90]	21 (18.6)	Asian (100.0)	24 (19.5)	73 (64.6)	Yes
Wu [2013] (48)	451	Cisplatin/carboplatin + gemcitabine + erlotinib 150 mg/d, d15-28, orally	(Cisplatin 75 mg/m <sup>2</sup> d1 or carboplatin (AUC =5) d1) +Gemcitabine 1,250 mg/m <sup>2</sup> d1,8, iv, q4w x6 cycles	57 [31-96]	179 (39.7)	Asian (100.0)	219 (52.8)	342 (75.8)	Yes
Jänne [2012] (49)	181	Erlotinib 150 mg/d + paclitaxel 200 mg/m <sup>2</sup> d1 carboplatin (AUC =6) d1, iv, q3w x6 cycles	Erlotinib 150 mg/d, orally	59 [32-81]	107 (59.0)	White (80.0)	143 (79.0)	155 (86.0)	Yes
Lee [2012] (50)	670	Erlotinib 150 mg/d, orally	Placebo	77 [72-82]	261 (39.0)	White (97.0)	37 (5.5)	256 (38.2)	Yes
Butts [2007] (51)	131	Cisplatin/carboplatin + gemcitabine + cetuximab 400 mg/m <sup>2</sup> on day 1, 250 mg/m <sup>2</sup> weekly	Cisplatin 75 mg/m <sup>2</sup> d1 + gemcitabine 1,250 mg/m <sup>2</sup> d1,8 or carboplatin (AUC =5) d1+ gemcitabine 1,000 mg/m <sup>2</sup> d1,8, iv, q3w x6 cycles	64 [35-84]	73 (55.7)	White (83.2)	19 (14.5)	61 (46.6)	Yes
Lynch [2010] (7)	676	Paclitaxel/docetaxel + carboplatin + cetuximab 400 mg/m <sup>2</sup> on day 1, 250 mg/m <sup>2</sup> weekly	(Paclitaxel 225 mg/m <sup>2</sup> or docetaxel 75 mg/m <sup>2</sup> ) + carboplatin (AUC =5) d1, iv, q3w x≤6 cycle	64 [34-87]	280 (41.4)	White (88.1)	53 (7.8)	354 (52.4)	Yes

d1, day 1; iv, intravenously; q3w, every 3 weeks; AUC, area under the curve. NR, not reported; CT, chemotherapy.



**Table 2** The odds ratios and heterogeneity for direct comparisons

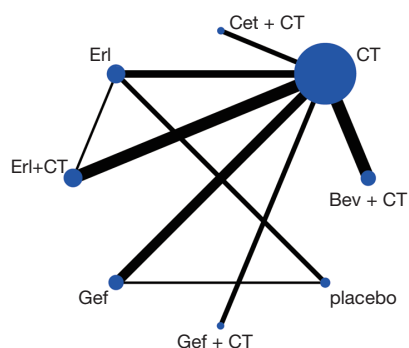
Outcome	No. of studies	Events/total	OR (95% CI)	P	I <sup>2</sup> (%)
CT vs. Bev + CT					
ORR	5	181/896 vs. 355/949	2.19 (1.55–3.11)	<0.001	52.7
Neutropenia	5	235/927 vs. 349/973	1.53 (0.95–2.47)	0.082	62.4
Rash	1	2/440 vs. 10/427	5.25 (1.14–24.11)	0.033	–
Thrombocytopenia	5	82/927 vs. 96/973	1.15 (0.83–1.60)	0.390	55.8
Anemia	4	52/869 vs. 40/854	0.67 (0.17–2.64)	0.577	49.7
CT vs. Erl + CT					
ORR	5	355/1,478 vs. 446/1,469	1.64 (1.05–2.57)	0.031	82.5
Neutropenia	5	234/1,149 vs. 229/1,141	0.98 (0.78–1.24)	0.903	10.1
Rash	5	15/1,149 vs. 105/1,141	7.64 (2.64–22.08)	<0.001	56.2
Diarrhea	5	10/1,149 vs. 55/1,141	5.33 (2.78–10.21)	<0.001	26.4
Thrombocytopenia	4	126/1,088 vs. 142/1,089	1.43 (0.88–1.47)	0.310	0.0
Anemia	5	116/1,149 vs. 150/1,141	1.35 (1.04–1.75)	0.023	0.0
CT vs. Gef + CT					
ORR	2	252/669 vs. 277/681	1.13 (0.91–1.41)	0.277	0.0
Neutropenia	2	37/696 vs. 44/704	1.19 (0.76–1.87)	0.453	0.0
Rash	2	9/696 vs. 24/704	2.67 (1.23–5.81)	0.013	0.0
Diarrhea	2	18/696 vs. 47/704	2.71 (1.56–4.71)	<0.001	48.6
Thrombocytopenia	1	20/355 vs. 21/362	1.03 (0.55–1.94)	0.923	–
Anemia	2	8/696 vs. 9/704	1.11 (0.42–2.90)	0.832	0.0
CT vs. Gef					
ORR	4	273/898 vs. 353/908	1.41 (0.99–2.01)	0.055	31.5
Neutropenia	4	518/864 vs. 28/895	0.02 (0.01–0.05)	<0.001	38.6
Rash	4	10/876 vs. 69/903	4.56 (1.05–19.75)	0.042	68.1
Diarrhea	4	15/876 vs. 33/903	2.19 (1.18–4.07)	0.013	0.0
Thrombocytopenia	1	13/150 vs. 2/159	0.13 (0.03–0.61)	0.009	–
Anemia	4	86/864 vs. 16/895	0.17 (0.10–0.29)	<0.001	0.0
Placebo vs. Gef					
ORR	1	1/101 vs. 6/100	6.38 (0.75–54.02)	0.089	–
Diarrhea	1	3/101 vs. 3/100	1.01 (0.20–5.13)	0.990	–
Anemia	1	0/101 vs. 3/100	7.28 (0.37–143.92)	0.191	–
Placebo vs. Erl					
ORR	2	31/765 vs. 67/788	2.27 (1.46–3.53)	<0.001	0.0
Rash	1	0/445 vs. 37/433	84.27 (5.16–1,376.79)	0.002	–
Diarrhea	2	4/758 vs. 35/767	8.04 (2.98–21.65)	<0.001	0.0
Anemia	1	3/313 vs. 6/334	1.89 (0.47–7.62)	0.371	–

**Table 2** (continued)

Table 2 (continued)

Outcome	No. of studies	Events/total	OR (95% CI)	P	I <sup>2</sup> (%)
CT vs. Erl					
ORR	3	135/487 vs. 92/489	0.81 (0.23–2.78)	0.735	78.9
Neutropenia	1	79/368 vs. 42/372	0.47 (0.31–0.70)	<0.001	–
Rash	2	26/419 vs. 44/424	2.13 (0.57–8.01)	0.26	29.0
Diarrhea	2	2/419 vs. 23/424	9.78 (2.63–36.30)	0.001	0.0
Thrombocytopenia	1	44/368 vs. 39/372	0.86 (0.55–1.36)	0.526	–
Anemia	2	34/419 vs. 19/424	0.53 (0.29–0.95)	0.032	0.0
Erl vs. Erl + CT					
ORR	1	28/81 vs. 46/100	1.61 (0.88–2.95)	0.121	–
Neutropenia	1	0/81 vs. 41/100	113.7 (6.86–1,885.30)	0.001	–
Rash	1	6/81 vs. 10/100	1.39 (0.48–4.00)	0.543	–
Diarrhea	1	4/81 vs. 7/100	1.45 (0.41–5.13)	0.566	–
Thrombocytopenia	1	0/81 vs. 5/100	9.38 (0.51–172.34)	0.131	–
Anemia	1	1/81 vs. 7/100	6.02 (0.72–50.00)	0.096	–
CT vs. Cet + CT					
ORR	2	70/404 vs. 105/403	1.68 (1.96–2.36)	0.003	0.0
Neutropenia	2	209/386 vs. 229/389	1.21 (0.91–1.61)	0.190	0.0
Rash	2	0/386 vs. 43/389	42.18 (5.70–312.13)	<0.001	0.0
Diarrhea	2	8/386 vs. 20/389	2.46 (1.09–5.55)	0.029	0.0
Thrombocytopenia	2	58/386 vs. 70/389	1.32 (0.87–2.02)	0.184	0.0
Anemia	2	28/386 vs. 34/389	1.26 (0.74–2.16)	0.397	0.0

The reference of OR is treatment arm in the left column. ORR, objective response rate; Bev, bevacizumab; Gef, gefitinib; Erl, erlotinib; Cet, cetuximab; CT, chemotherapy.



**Figure 2** Network of studies comparing objective response rate of different agents for unselected patients with advanced non-small cell lung cancer. Each link represents at least one study, width of each link is number of trials per comparison, size of each node is proportional to the total sample size. CT, chemotherapy; Bev, bevacizumab; Gef, gefitinib; Erl, erlotinib; Cet, cetuximab.

statistically significantly higher incidence of ORR relative to the other six difference treatments, including placebo, Erl, CT, Gef, Erl + CT and Gef + CT, in contrast, placebo and Erl were associated with inferior ORR. Although no significant differences were observed among Bev + CT vs. Cet + CT and Erl + CT vs. Gef + CT, Bev + CT showed a trend of higher ORR than Cet + CT and Erl + CT showed a trend of higher ORR than Gef + CT.

We selected rash, anemia, diarrhea, neutropenia and thrombocytopenia, which were the most common toxicities, as the representative of targeted drugs-related toxicities. The results showed that patients who received Cet + CT experienced more severe rash compared with the other seven treatments. Significantly increased odds for anemia observed in patients treated with Erl + CT compared to those treated with placebo, CT, Erl, Gef and Bev + CT. Erl had greater odds of diarrhea over four other agents:

Table 3 Multiple treatment comparison for efficacy based on network meta-analysis

Treatment	Comparator							
	Placebo	CT	Erl	Gef	Erl + CT	Gef + CT	Bev + CT	Cet + CT
ORR								
Placebo	1	3.36 (2.07–5.25)	2.30 (1.51–3.43)	4.66 (2.80–7.38)	4.46 (2.72–7.04)	3.72 (2.22–5.99)	6.47 (3.85–10.29)	5.42 (3.01–9.13)
CT	0.31 (0.19–0.48)	1	0.69 (0.54–0.87)	1.39 (1.18–1.62)	1.33 (1.16–1.52)	1.11 (0.93–1.31)	1.92 (1.61–2.28)	1.61 (1.18–2.16)
Erl	0.45 (0.29–0.67)	1.46 (1.15–1.84)	1	2.03 (1.51–2.66)	1.94 (1.49–2.48)	1.62 (1.20–2.15)	2.81 (2.08–3.70)	2.35 (1.59–3.39)
Gef	0.23 (0.13–0.36)	0.73 (0.62–0.85)	0.50 (0.38–0.66)	1	0.96 (0.78–1.18)	0.80 (0.63–1.01)	1.40 (1.10–1.75)	1.17 (0.82–1.63)
Erl + CT	0.24 (0.14–0.37)	0.76 (0.66–0.86)	0.52 (0.40–0.67)	1.05 (0.85–1.28)	1	0.84 (0.67–1.04)	1.46 (1.17–1.80)	1.22 (0.86–1.68)
Gef + CT	0.28 (0.16–0.45)	0.91 (0.76–1.08)	0.63 (0.46–0.83)	1.26 (0.99–1.59)	1.21 (0.96–1.50)	1	1.75 (1.36–2.22)	1.46 (1.01–2.05)
Bev + CT	0.17 (0.10–0.26)	0.53 (0.44–0.62)	0.37 (0.27–0.48)	0.73 (0.57–0.91)	0.70 (0.56–0.86)	0.58 (0.45–0.74)	1	0.85 (0.59–1.18)
Cet + CT	0.20 (0.11–0.33)	0.64 (0.47–0.86)	0.44 (0.30–0.64)	0.89 (0.62–1.23)	0.85 (0.60–1.17)	0.71 (0.50–0.99)	1.23 (0.86–1.72)	1
Rash								
Placebo	1	1.3E7 (44.15–1.2E8)	2.7E7 (94.78–2.3E8)	1.1E8 (321.59–9.9E8)	9.1E7 (292.3–7.6E8)	3.8E7 (116.3–3.5E8)	3.9E7 (127.2–3.7E8)	1.9E28 (1.2E5–3.9E28)
CT	3E–4 (0.00–1.4E–3)	1	2.09 (1.29–3.26)	8.15 (4.06–15.73)	7.06 (4.29–11.43)	3.00 (1.30–6.30)	3.37 (1.02–8.96)	2.2E33 (1.2E9–3.5E33)
Erl	8E–4 (0.00–7.5E–3)	0.50 (0.30–0.78)	1	4.11 (1.69–8.94)	3.54 (1.83–6.39)	1.52 (0.56–3.48)	1.69 (0.44–4.68)	2.7E21 (37.43–3.4E21)
Gef	4E–4 (0.00–3.6E–3)	0.14 (0.06–0.25)	0.29 (0.11–0.60)	1	0.98 (0.36–2.05)	0.41 (0.12–1.03)	0.46 (0.10–1.39)	3.4E32 (1.94–9.9E32)
Erl + CT	3E–4 (0.00–3.0E–3)	0.15 (0.09–0.24)	0.32 (0.16–0.56)	1.25 (0.51–2.69)	1	0.46 (0.17–1.05)	0.51 (0.14–1.41)	2.5E22 (50.35–1.9E23)
Gef + CT	1.8E–3 (0.00–0.02)	0.39 (0.16–0.76)	0.82 (0.29–1.82)	3.10 (0.96–7.57)	2.76 (0.97–6.12)	1	1.30 (0.27–3.95)	2.6E23 (24.16–1.8E24)
Bev + CT	1.2E–3 (0.00–0.01)	0.44 (0.12–1.11)	0.93 (0.22–2.48)	3.53 (0.76–10.52)	3.04 (0.76–8.28)	1.31 (0.26–4.08)	1	1.9E16 (63.44–1.3E17)
Cet + CT	0.00 (0.00–0.00)	0.00 (0.00–0.03)	0.01 (0.00–0.07)	0.03 (0.00–0.27)	0.03 (0.00–0.23)	0.01 (0.00–0.10)	0.01 (0.00–0.11)	1
Anemia								
Placebo	1	13.03 (2.44–46.19)	5.83 (1.16–20.16)	2.38 (0.42–8.52)	17.49 (3.17–62.92)	16.53 (1.96–67.28)	10.17 (1.75–36.80)	16.89 (2.80–63.12)
CT	0.14 (0.02–0.43)	1	0.47 (0.26–0.77)	0.19 (0.11–0.30)	1.34 (1.05–1.70)	1.26 (0.42–2.98)	0.78 (0.51–1.15)	1.30 (0.76–2.09)
Erl	0.30 (0.05–0.89)	2.28 (1.29–3.79)	1	0.42 (0.19–0.82)	3.05 (1.65–5.28)	2.88 (0.80–7.56)	1.78 (0.86–3.34)	2.95 (1.33–5.76)
Gef	0.77 (0.11–2.39)	5.74 (3.39–9.46)	2.69 (1.20–5.27)	1	7.71 (4.30–13.22)	7.34 (2.08–19.23)	4.50 (2.22–8.34)	7.45 (3.44–14.48)
Erl + CT	0.10 (0.02–0.32)	0.76 (0.59–0.95)	0.35 (0.19–0.60)	0.14 (0.08–0.24)	1	0.96 (0.31–2.33)	0.59 (0.36–0.91)	0.98 (0.54–1.65)
Gef + CT	0.14 (0.01–0.53)	1.03 (0.33–2.42)	0.48 (0.13–1.25)	0.19 (0.05–0.49)	1.38 (0.43–3.31)	1	0.80 (0.23–2.00)	1.33 (0.37–3.38)
Bev + CT	0.18 (0.03–0.59)	1.34 (0.87–1.97)	0.63 (0.30–1.15)	0.25 (0.12–0.45)	1.79 (1.08–2.79)	1.70 (0.51–4.27)	1	1.73 (0.86–3.14)
Cet + CT	0.11 (0.02–0.37)	0.83 (0.48–1.33)	0.39 (0.17–0.76)	0.15 (0.07–0.29)	1.11 (0.61–1.87)	1.05 (0.30–2.72)	0.65 (0.32–1.17)	1

Table 3 (continued)

Table 3 (continued)

Treatment	Comparator							
	Placebo	CT	Erl	Gef	Erl + CT	Gef + CT	Bev + CT	Cet + CT
<b>Diarrhea</b>								
Placebo	1	1.02 (0.30-2.70)	8.35 (3.33-19.93)	2.11 (0.59-5.68)	7.47 (1.99-20.92)	2.88 (0.70-8.22)	-	2.93 (0.59-9.29)
CT	1.35 (0.38-3.40)	1	9.77 (3.88-21.52)	2.14 (1.15-3.72)	7.57 (3.76-14.34)	2.81 (1.59-4.77)	-	2.86 (1.17-6.25)
Erl	0.15 (0.05-0.30)	0.13 (0.05-0.26)	1	0.26 (0.09-0.62)	0.90 (0.33-1.97)	0.36 (0.11-0.85)	-	0.36 (0.09-1.00)
Gef	0.67 (0.18-1.75)	0.51 (0.27-0.88)	4.92 (1.64-11.92)	1	3.91 (1.50-8.51)	1.45 (0.59-2.99)	-	1.47 (0.47-3.61)
Erl + CT	0.19 (0.05-0.50)	0.15 (0.07-0.26)	1.37 (0.52-3.01)	0.32 (0.12-0.68)	1	0.42 (0.16-0.89)	-	0.43 (0.13-1.10)
Gef + CT	0.52 (0.12-1.44)	0.38 (0.21-0.63)	3.71 (1.16-9.27)	0.82 (0.33-1.70)	2.92 (1.10-6.44)	1	-	1.10 (0.35-2.70)
Cet + CT	0.55 (0.11-1.63)	0.42 (0.16-0.86)	4.04 (0.97-10.96)	0.90 (0.28-2.13)	3.16 (0.92-7.73)	1.19 (0.38-2.80)	-	1
<b>Neutropenia</b>								
CT	-	1	0.34 (0.23-0.47)	0.03 (0.02-0.05)	1.07 (0.89-1.28)	1.22 (0.76-1.85)	1.35 (1.14-1.60)	1.15 (0.94-1.38)
Erl	-	3.05 (2.13-4.31)	1	0.10 (0.06-0.16)	3.26 (2.22-4.70)	3.71 (2.02-6.29)	4.13 (2.75-6.03)	3.50 (2.30-5.16)
Gef	-	32.20 (21.85-46.71)	10.84 (6.22-17.66)	1	34.51 (22.41-51.74)	39.12 (21.18-67.37)	43.61 (28.34-65.27)	36.90 (23.70-55.70)
Erl + CT	-	0.94 (0.78-1.12)	0.32 (0.21-0.45)	0.03 (0.02-0.04)	1	1.14 (0.69-1.79)	1.28 (0.99-1.62)	1.08 (0.82-1.39)
Gef + CT	-	0.86 (0.54-1.32)	0.29 (0.16-0.49)	0.03 (0.01-0.05)	0.93 (0.56-1.45)	1	1.17 (0.71-1.83)	0.99 (0.59-1.57)
Bev + CT	-	0.74 (0.62-0.88)	0.25 (0.16-0.36)	0.02 (0.01-0.04)	0.80 (0.62-1.01)	0.90 (0.55-1.41)	1	0.85 (0.66-1.10)
Cet + CT	-	0.88 (0.72-1.06)	0.30 (0.19-0.43)	0.03 (0.02-0.04)	0.94 (0.72-1.22)	1.07 (0.64-1.68)	1.19 (0.91-1.53)	1
<b>Thrombocytopenia</b>								
CT	-	1	0.81 (0.52-1.21)	0.15 (0.02-0.46)	1.16 (0.91-1.46)	1.09 (0.55-1.92)	1.16 (0.85-1.55)	1.32 (0.91-1.86)
Erl	-	1.29 (0.82-1.92)	1	0.19 (0.02-0.63)	1.50 (0.89-2.34)	1.40 (0.62-2.74)	1.49 (0.86-2.41)	1.70 (0.94-2.84)
Gef	-	21.20 (2.23-101.60)	17.33 (1.65-81.56)	1	24.59 (2.49-119.80)	22.98 (2.01-114.30)	24.73 (2.41-119.70)	28.00(2.78-134.60)
Erl + CT	-	0.88 (0.69-1.10)	0.71 (0.43-1.11)	0.13 (0.01-0.41)	1	0.95 (0.46-1.74)	1.02 (0.68-1.46)	1.16 (0.74-1.73)
Gef + CT	-	1.01 (0.52-1.77)	0.82 (0.36-1.61)	0.15 (0.01-0.52)	1.17 (0.58-2.13)	1	1.17 (0.56-2.19)	1.33 (0.62-2.53)
Bev + CT	-	0.88 (0.65-1.17)	0.72 (0.41-1.16)	0.13 (0.01-0.42)	1.02 (0.69-1.46)	0.96 (0.46-1.78)	1	1.16 (0.72-1.79)
Cet + CT	-	0.78 (0.54-1.09)	0.63 (0.35-1.05)	0.12 (0.01-0.37)	0.90 (0.58-1.35)	0.84 (0.39-1.60)	0.90 (0.55-1.39)	1

ORR, objective response rate; Bev, bevacizumab; Gef, gefitinib; Erl, erlotinib; Cet, cetuximab; CT, chemotherapy.

placebo, CT, Gef, Gef + CT. Bev + CT was associated with significantly greater odds for neutropenia compared to CT, Erl and Gef. In terms of thrombocytopenia, Cet + CT, Bev + CT, Gef + CT, Erl + CT, Erl and CT were significant severer than Gef while no other significant differences were observed among the rest comparisons (Table 3).

### Ranking of treatment arms

Table 4 showed the rank probabilities among all the treatments, agents with greater value in the histogram were associated with greater probabilities for higher rank. This analysis indicated that Bev + CT had the highest probability of being the best treatment arm for ORR, followed by Cet + CT and Gef. In contrast, CT, Erl and placebo were associated with relatively inferior ORR rankings compared with other agents. Meanwhile, we could see that Bev + CT was associated with the highest risk for neutropenia and second risk for thrombocytopenia. Cet + CT was most probable to be the rank 1 for rash and thrombocytopenia, and the rank 2 for anemia. Gef was found to be associated with relatively low risk for grade  $\geq 3$  toxicities.

### Discussion

During the past few years, therapies for advanced NSCLC have significantly changed due to the development of molecular targeted drugs, either receptor monoclonal antibodies (mAb) or small molecule TKI (4). Through the identification of epigenetic mutations, tumour suppressor gene inactivation as well as oncogene driver mutations, they can provide more accurate therapeutic targets. Selection of driver genes is essential in targeted therapy, however, in routine clinical practice, a considerable number of patients are unable to provide adequate tissue samples for accurate genotyping. Although ctDNA or CTC would be a reliable method to detect mutations, its specificity, sensitivity and costs still need to be assessed (20,21). For the vast majority at present, no known drivers were detected and such patients were still empirically treated with standard cytotoxic chemotherapy. This network meta-analysis showed that Bev + CT offered superior ORR compared with other included regimens in treating patients with locally advanced or metastatic NSCLC without a known driver mutation.

Although other systematic reviews and meta-analysis have been conducted to evaluate the benefits of chemotherapy and targeted therapy in advanced NSCLC (52,53), direct

head to head comparisons between these agents have not been well established, especially in unselected patients with advanced NSCLC. Unique to this analysis, multiple-treatments comparisons were used to accomplish a mixed-treatments analysis and obtained the information on the effectiveness of each agents. Our findings were similar to previous publications (44,53). A recent pooled analysis of available studies was performed to evaluate the efficacy of bevacizumab compared with other targeted drugs in patients with advanced NSCLC, they demonstrated that bevacizumab with chemotherapy significantly improved patients' ORR among chemotherapy-native patients compared with other targeted drugs, which was consistent with our direct and indirect comparisons (52). However, it did not compare effect among other targeted drugs, nor did it explore the toxicity. In addition, treatment-line might affect the efficacy of TKIs, some previous studies found inferior response to EGFR-TKIs following chemotherapy exposure (24,25). Therefore, in order to minimize the crossover effects, we conducted a systematic review and network meta-analysis to assess the substantial differences among these first-line treatments in unselected patients with advanced NSCLC.

Moreover, Bayesian statistical model could also help us rank these regimens to determine which one is most likely to be the best or the worst, especially when the relative values fail to reach statistical significance (30). In this study, although no statistically significant differences between Bev + CT and Cet + CT in terms of ORR, Bev + CT arm had the greatest probability to rank the first, followed by Cet + CT. The formation of new blood vessels played an important role in the growth and invasiveness of primary tumors, vascular endothelial growth factor (VEGF) was a key potential target for the pharmacological inhibition of tumour angiogenesis, which may explain the relative good efficacy of bevacizumab (anti-VEGF monoclonal antibody) in the treatment of unselected patients with advanced NSCLC, in some ways. In regards to safety, although Bev + CT and Cet + CT presented potentially better efficacy, they were associated with severer rash, thrombocytopenia and neutropenia. Gef was probable to be the rank 3 for ORR and was associated with relatively low risk for grade  $\geq 3$  toxicities. Therefore, Gef therapy may remain as one of the options for patients with unknown driver mutation, particularly considering the rising cost of targeted drugs and limited medical resources.

The conclusion of this study will lead us to the argument about whether the targeted drugs should be used in clinical

**Table 4** Rank probabilities of each drug for different outcomes based on network meta-analysis

Treatment	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7	Rank 8
<b>ORR</b>								
Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00
CT	0.00	0.00	0.00	0.00	0.13	0.86	0.00	0.00
Erl	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00
Gef	0.00	0.17	0.51	0.29	0.02	0.00	0.00	0.00
Erl + CT	0.00	0.07	0.34	0.55	0.04	0.00	0.00	0.00
Gef + CT	0.00	0.00	0.01	0.07	0.78	0.13	0.00	0.00
Bev + CT	0.85	0.15	0.00	0.00	0.00	0.00	0.00	0.00
Cet + CT	0.15	0.61	0.14	0.09	0.02	0.00	0.00	0.00
<b>Rash</b>								
Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00
CT	0.00	0.00	0.00	0.00	0.00	0.04	0.96	0.00
Erl	0.00	0.00	0.00	0.11	0.36	0.53	0.00	0.00
Gef	0.00	0.58	0.35	0.06	0.00	0.00	0.00	0.00
Erl + CT	0.00	0.38	0.55	0.07	0.00	0.00	0.00	0.00
Gef + CT	0.00	0.01	0.03	0.38	0.37	0.20	0.00	0.00
Bev + CT	0.00	0.03	0.06	0.38	0.26	0.22	0.03	0.00
Cet + CT	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
<b>Anemia</b>								
Placebo	0.00	0.00	0.00	0.00	0.00	0.01	0.23	0.76
CT	0.00	0.07	0.41	0.47	0.05	0.00	0.00	0.00
Erl	0.00	0.00	0.00	0.01	0.10	0.87	0.02	0.00
Gef	0.00	0.00	0.00	0.00	0.00	0.01	0.75	0.24
Erl + CT	0.44	0.39	0.17	0.01	0.00	0.00	0.00	0.00
Gef + CT	0.15	0.14	0.31	0.17	0.18	0.05	0.00	0.00
Bev + CT	0.00	0.02	0.06	0.23	0.63	0.06	0.00	0.00
<b>Diarrhea</b>								
Placebo	0.00	0.00	0.04	0.06	0.12	0.39	0.40	–
CT	0.00	0.00	0.00	0.00	0.01	0.40	0.59	–
Erl	0.67	0.30	0.02	0.00	0.00	0.00	0.00	–
Gef	0.00	0.00	0.12	0.28	0.49	0.11	0.00	–
Erl + CT	0.32	0.64	0.04	0.00	0.00	0.00	0.00	–
Gef + CT	0.00	0.02	0.42	0.37	0.16	0.03	0.00	–
Cet + CT	0.01	0.04	0.36	0.29	0.22	0.08	0.01	–

**Table 4** (continued)

Table 4 (continued)

Treatment	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7	Rank 8
Neutropenia								
CT	0.00	0.00	0.08	0.38	0.54	0.00	0.00	–
Erl	0.00	0.00	0.00	0.00	0.00	1.00	0.00	–
Gef	0.00	0.00	0.00	0.00	0.00	0.00	1.00	–
Erl + CT	0.01	0.13	0.32	0.34	0.19	0.00	0.00	–
Gef + CT	0.28	0.25	0.16	0.10	0.21	0.00	0.00	–
Bev + CT	0.64	0.30	0.05	0.01	0.00	0.00	0.00	–
Cet + CT	0.06	0.31	0.39	0.17	0.07	0.00	0.00	–
Thrombocytopenia								
CT	0.00	0.02	0.14	0.42	0.37	0.05	0.00	–
Erl	0.01	0.02	0.04	0.06	0.19	0.67	0.00	–
Gef	0.00	0.00	0.00	0.00	0.00	0.00	1.00	–
Erl + CT	0.14	0.30	0.30	0.17	0.07	0.01	0.00	–
Gef + CT	0.19	0.14	0.12	0.11	0.22	0.22	0.00	–
Bev + CT	0.17	0.27	0.26	0.17	0.10	0.03	0.00	–
Cet + CT	0.49	0.25	0.14	0.07	0.04	0.01	0.00	–

ORR, objective response rate; Bev, bevacizumab; Gef, gefitinib; Erl, erlotinib; Cet, cetuximab; CT, chemotherapy.

practice to have the best outcome as a whole. Several points needed to be considered. Firstly, cetuximab was not licensed in other countries except for the US. National Comprehensive Cancer Network (NCCN)-NSCLC guidelines showed that EGFR TKIs should be employed only in patients harboring EGFR-activating mutations. Bevacizumab was indicated as treatment for naïve patients. Secondly, in this study, we only analyzed ORR and toxicity as an efficacy, whether the increase of ORR with drugs would be translated into survival benefit was still not clear. A recent pooled analysis showed that a strong correlation between ORR and improved PFS and overall survival (OS) in chemotherapy-naïve patients treated with bevacizumab (52). In contrast, Boutsikou *et al.* (34) reported that administration of bevacizumab was associated with higher ORR compared with chemotherapy, but it did not translate into longer OS. This conflicting result indicated that data regarding ORR should be interpreted with caution, the surrogacy relation of ORR with survival data would be confirmed. We are currently planning to collect all relevant PFS and OS data to make up for our shortcomings.

Nevertheless, our network meta-analysis showed the different efficacy and safety of these included regimens

from the available evidence. At the same time, several limitations needed to be considered. First, the number of studies included was relatively small. The indirect estimates were often very similar to the direct comparisons due to only single comparison was available. For example, the informative value of the direct comparison Cet + CT arms was limited by low number of events. Additionally, the established networks lacked sufficient direct comparisons between combination therapies. These resulted in trials' heterogeneity. Second, given the retrospective nature of meta-analysis, publication bias and selection bias cannot be excluded. And many potentially important differences among these studies, including different dosage and administration schedules of targeted drugs and chemotherapy. Moreover, the treatment designs were not same in all arms. All of these would increase the clinical heterogeneity among included trials. Third, different baselines of trial populations, such as age, gender, ethnicity, interventions, comorbidities, and differences in other possible prognostic factors, these may introduce potential confounding and bias to the analysis. Fourth, due to a large proportion of trials were open label, an inherent risk of bias in the individual trial was introduced. Finally, this

study only analyzed ORR and adverse events as an efficacy, progression free survival and OS data needed to be assessed in the future study.

In summary, our study suggested that the use of bevacizumab in combination with chemotherapy in the treatment of unselected patients with advanced NSCLC may offer a greater ORR and moderate toxicity. We hope this network meta-analysis may guide physicians in the therapeutic decision-making.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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**Table S1** Quality assessment: risk of bias by Cochrane collaboration's tool

Trial	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other source of bias
Sandler [2006] (10)	Adequate	Inadequate	Unclear	Adequate	Adequate	-
Reck [2010] (9)	Adequate	Adequate	Adequate	Adequate	Adequate	-
Niho [2012] (32)	Adequate	Adequate	Unclear	Adequate	Adequate	-
Soria [2011] (33)	Adequate	Adequate	Adequate	Adequate	Adequate	-
Boutsikou [2013] (34)	Adequate	Inadequate	Unclear	Adequate	Unclear	-
Herbst [2004] (35)	Adequate	Inadequate	Unclear	Inadequate	Adequate	-
Crinò [2008] (36)	Adequate	Adequate	Inadequate	Adequate	Adequate	Vinorelbine is a less potent comparator; included only elderly patients
Goss [2009] (37)	Adequate	Adequate	Adequate	Adequate	Adequate	-
Giaccone [2004] (38)	Adequate	Adequate	Adequate	Adequate	Adequate	-
Morère [2010] (39)	Adequate	Inadequate	Unclear	Adequate	Adequate	Biased baseline characteristic: docetaxel arm had more never-smokers (14.3% vs. 4.7%)
Fukuoka [2011] (40)	Adequate	Adequate	Inadequate	Adequate	Adequate	-
Han [2012] (41)	Adequate	Adequate	Adequate	Adequate	Adequate	-
Herbst [2005] (42)	Adequate	Inadequate	Unclear	Adequate	Adequate	-
Lilenbaum [2008] (43)	Adequate	Adequate	Unclear	Adequate	Adequate	-
Mok [2009] (44)	Adequate	Adequate	Adequate	Adequate	Adequate	-
Gatzemeier [2007] (45)	Adequate	Adequate	Inadequate	Adequate	Adequate	-
Cappuzzo [2010] (46)	Adequate	Adequate	Adequate	Adequate	Adequate	-
Gridelli [2012] (24)	Adequate	Adequate	Unclear	Adequate	Adequate	-
Chen [2012] (47)	Adequate	Adequate	Adequate	Adequate	Unclear	Vinorelbine is a less potent comparator; included only elderly patients
Wu [2013] (48)	Adequate	Adequate	Adequate	Adequate	Adequate	-
Jänne [2012] (49)	Adequate	Adequate	Unclear	Adequate	Adequate	-
Lee [2012] (50)	Adequate	Adequate	Adequate	Adequate	Adequate	-
Butts [2007] (51)	Adequate	Inadequate	Unclear	Adequate	Adequate	-
Lynch [2010] (7)	Adequate	Inadequate	Unclear	Adequate	Adequate	-

**Table S2** GRADE summary of findings

Outcomes	No. of participants (studies) follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control	Risk difference with experiment (95% CI)
Objective response rate	11,666 (24 studies)	⊕⊕⊕⊖; moderate (due to inconsistency)	RR 1.554 (1.259–1.918)	229 per 1,000	127 more per 1,000 (from 59 more to 211 more)
Neutropenia	9,045 (19 studies)	⊕⊕⊕⊖; moderate (due to risk of bias, inconsistency, publication bias, plausible confounding would change the effect)	RR 0.644 (0.35–1.185)	70 per 1,000	25 fewer per 1,000 (from 45 fewer to 13 more)
Rash	9,331 (19 studies)	⊕⊕⊕⊖; moderate (due to inconsistency, publication bias, plausible confounding would change the effect)	RR 5.292 (2.89–9.691)	15 per 1,000	63 more per 1,000 (from 28 more to 127 more)
Diarrhea	9,111 (19 studies)	⊕⊕⊕⊖; moderate (due to risk of bias)	RR 3.453 (2.617–4.554)	14 per 1,000	35 more per 1,000 (from 23 more to 50 more)
Thrombocytopenia	6,996 (16 studies)	⊕⊕⊖⊖; low (due to risk of bias, inconsistency)	RR 1.093 (0.931–1.283)	99 per 1,000	9 more per 1,000 (from 7 fewer to 28 more)
Anemia	9,819 (21 studies)	⊕⊕⊖⊖; low (due to risk of bias, inconsistency)	RR 0.811 (0.542–1.212)	67 per 1,000	13 fewer per 1,000 (from 31 fewer to 14 more)

The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). GRADE working group grades of evidence: high quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality, we are very uncertain about the estimate. CI, confidence interval; RR, risk ratio.