ejpmr, 2016,3(6), 31-44

SJIF Impact Factor 3.628

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

EFFICACY OF TARGETED THERAPY IN UNSELECTED PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER: A NETWORK META-ANALYSIS

Miaomiao Sheng[1], Fang Wang[1], Yueguang Zhao[1], Shanshan Li[1], Xiaojie Wang[2], Tao Shou[2], Ying Luo[1], Wenru Tang[1*]

[1]Laboratory of Molecular Genetics of Aging & Tumor, Medical Faculty, Kunming University of Science and Technology, Chenggong Campus, Kunming, Yunnan, 650500, China.
[2]First People's Hospital of Yunnan Province, Kunming, Yunnan, 650032, China.

***Corresponding Author: Wenru Tang**
Laboratory of Molecular Genetics of Aging & Tumor, Medical Faculty, Kunming University of Science and Technology, Chenggong Campus, Kunming, Yunnan, 650500, China.

Article Received on 28/03/2016 **Article Revised on 17/04/2016** **Article Accepted on 06/05/2016**

ABSTRACT

Objective: 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 treatments in unselected patients are not clear. We therefore conducted a network meta-analysis to assess the relative efficacy of these regimens. **Methods:** We searched Pubmed, EMBASE, Cochrane Library and abstracts from major scientific meetings for eligible literatures. The hazard ratio (HR) for progression-free survival (PFS) and overall survival (OS) was used for pooling effect sizes. Bayesian network meta-analysis was conducted to calculate the efficacy of all included treatments. All tests of statistical significance were two sided. **Results:** A total of 18476 patients from 32 randomized controlled trials (RCT) were assessed. The targeted therapy included bevacizumab (Bev), gefitinib (Gef), erlotinib (Erl) and cetuximab (Cet). Network meta-analysis showed that Bev+chemotherapy (CT) was associated with statistically significant hazard ratio for PFS relative to Gef (HR, 0.73; 95% CI, 0.55-0.96), Erl (HR, 0.64; 95% CI, 0.47-0.83), CT (HR, 0.69; 95% CI, 0.55-0.84) and placebo (HR, 0.49; 95% CI, 0.34-0.67). No statistically significant differences were observed for combination therapy treatments, including Erl+CT, Gef+CT, Bev+CT, Cet+CT and Bev+Erl. Trend analyses of rank probability revealed that Bev+CT and Bev+Erl were among the top ranked for PFS, Cet+CT was most probable to be the rank 1 in terms of OS and followed by Bev+CT. **Conclusions:** Our study suggested that Bev+CT may offer greater benefits in the treatment of unselected patients with advanced NSCLC. Cet+CT presented the best survival but inferior PFS compared with Bev+CT.

KEYWORDS: non-small-cell lung cancer, targeted drugs, efficacy, network meta-analysis.

INTRODUCTION

Lung cancer is the most common cause of cancer-related death in men and women, 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 approximately 75% of the patients have been in advanced stage (Ⅲ or Ⅳ) at diagnosis, the 5-year survival rate is extremely low, ranging from 5% to 15%.[2] Palliative care, surgery, chemotherapy and radiation therapy remain the standard care, however, the efficacy of chemo-radiation therapy is limited and the side effect is very large, there is a considerable part of the patients could not bear.[3]

In the recent years, molecular translational research advances have brought major breakthroughs in the management of non-small cell lung.[4] Several drugs that target molecular pathways in NSCLC are available, especially for the treatment of advanced disease, for example, epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (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 are at varying stages of clinical development, panitumumab (Anti-EGFR monoclonal antibodies)[4], selumetinib (MEK1/MEK2 inhibitor)[11] 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 showed that TKI treatment was superior to conventional chemotherapy drugs in terms of progression-free survival

(PFS) and objective response rate for patients harboring EGFR-mutation.[12-15]

Unfortunately, there are no reliable clinical phenotypes or characteristics that allow for accurate prediction of driver mutation, all tumors 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) or circulating tumor cells (CTC), the existing methods have insufficient sensitivity, and the testing cost is expensive.

At the same time, the occurance and development of tumors are a complicated process, 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.

Single targeted therapy can not obtain the expected effect and acquired resistance is frequently seen in clinical practice. However, the relative efficacy 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 were lack of integration information on the relative efficacy of all regimens. Network meta-analysis provides a useful method for estimating the relative treatment effects of these agents.[16] Unlike traditional meta-analysis, it enable us to synthesize data from both direct and indirect evidence of diverse regimens, and compare the results based on individual trials.[17]

Therefore, we performed a systematic review and network meta-anaysis of randomized controlled trials comparing the relative efficacy of chemotherapy and targeted therapy in unselected patients with advanced NSCLC and also estimated the rank probability of each treatments, expecting it will be helpful for making evidence-based clinical decision for physicians and patients.

MATERIALS AND 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: non-small cell lung cancer, 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 F.W) independently screened the selected eligible trials.

Selection Criteria

Studies meeting the following inclusion criteria were involved: (1) randomized controlled trial; (2) patients with locally advanced or metastatic NSCLC; (3) at least two arms of different treatment regimens, chemtherapy, placebo or targeted therapy; (4) studies with available data on patients' EGFR unselected status; (5) outcomes of interest were progression free survival (PFS), time to progression (TTP) and overall survival (OS). 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 F.W) independently extracted data according to a predefined information sheet, including first author, year of publication, line of treatment (first vs second or later), number of patients, targeted treatment, chemotherapy regimens, patient characteristics (age, sex, ethnicity, histology and whether CT-native), and the outcomes. PFS, TTP, OS and their 95% confidence intervals (CI) were collected. If the HRs were not reports in the selected papers, we used the graphic software package Engauge to estimate HRs and its condifence intervals.

JADAD score was used to evaluate the quality of each eligible trials[18], it assesses the quality of published clinical trials based methods relevant to random assignment (0-2 points), double blinding (0-2 points), and withdrawals and dropouts (0-1 points), the range of possible scores is 0 (bad) to 5 (good). 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, HRs, 95% confidence intervals and *P* values were reported, two-side $P<0.05$ were considered statistically significant. If a direct comparison was based on two or more studies, I^2 statistic were 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.[19]

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.[17]

For example, a trial compares treatment A to C while another compares B to C, an indirect estimate of the relative effect on A versus B can be achieved.[20]

The network-analysis was based on the assumption that the difference in effect between treatments A & B (dAB) was equal to the difference in effects between treatments A & C and B & C (dAB = dAC - dBC). Firstly, the derived estimates of the mean log hazard ratio and it's standard error were estimated using formulae (1) and (2):

$$\frac{\ln(HR_{uci})+\ln(HR_{lci})}{2} \quad (1); \quad se = \frac{\ln(HR_{uci})-\ln(HR_{lci})}{2\times 1.96} \quad (2).$$

Then, the analyses were conducted using R2OpenBUGS, the R2OpenBUGS code for fixed or random effects analyses were presented as previously reported.[18]

Two chains were fit in R2OpenBUGS for each analysis, with at least 240000 interations and at least 40000 burn-in. We evaluated the overall fit of the selected models base on deviance informaton criterion (DIC) statistics and the total residual deviance, DIC was an estimate of expected predictive error (lower deviance was better).[21]

In addition, Bayesion 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 HR.[22]

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.[23]

RESULTS

Description of eligible trials

A total of 4828 articles were identified according to the search strategy. After removal of duplicates and title/abstract screening, 358 trials were assessed for eligiblity. After review of full publications, 32 randomized clinical trials were finally selected for the study (Fig. 1). Among them, 31 studies were published in peer-reviewed journal, one studies was published as an abstract in ASCO annual meeting.[24]

All trials except five provided PFS outcomes, these trials reported the time to progression (TTP) instead.[25-29] Characteristics of the included trials were summaried in Table 1. Eight trials applied bevacizumab (Bev)[9, 10, 24, 25, 30-33], twelve trials applied gefitinib (Gef)[26, 34-44], ten trials applied erlotinib (Erl)[27-29, 45-51] and the other two trials applied cetuximab (Cet).[7, 52] 17 studies were performed as first-line treatment[7, 9, 10, 26-28, 32-34, 38, 40, 43, 46-48, 50, 52], 12 studies as second or third-line treatment.[29-31, 35-37, 39, 42, 44, 45, 49, 51]

Total of 18476 patients were enrolled, patients median age varied from 20-90; 38.3%-96.3% of patients were adenocarcinoma; patients of 18 studies had not received any chemotherapy[7, 9, 10, 24-28, 30, 32-34, 38, 40, 41, 46, 47, 52]; seventeen trials predominantly enrolled White patients[7, 9, 10, 26-28, 30, 31, 34, 35, 38, 44, 46, 48-50, 52] whereas other eight had a majority of Asian patients[24, 32, 37, 39, 41, 43, 47, 51] excluding the unreported data.

For the outcomes of interest, nine different treatment arms were assessed: placebo, chemotherapy (CT), Erl, Gef, Erl+CT, Gef+CT, Bev+CT, Cet+CT, Bev+Erl. The resluting network geometry was described in Fig.2.

The quality of each eligible trials and other risks of bias were evaluated using JADAD score (Supplementary Table 1). The method of randomisation was appropriatley described in most of the trials, 9 trials were double-blinded[9, 29, 31, 32, 34, 35, 38, 42, 45] and 30 described the reasons of withdrawals and dropouts.[7, 9, 10, 24, 25, 27-33, 35-52] Thus, 15/32 studies were reported as high quility and the remaning 17 studies as acceptable quality.

Direct comparisons

Among the 32 clinical trials, 30 studies reported hazard ratios for PFS and OS[7, 9, 10, 25-32, 34-52], for other two trials, one reported PFS directly[24] and one reported OS directly[33] (Supplementary Table 2). Pairwise comparisons were accomplished for the 12 different comparisons. Hazard ratios and heterogeneity by I^2 were listed in Table 2.

For unselected patients, Bev+CT was associated with statistically significant hazard ratio for PFS over CT (HR, 0.70; 95% CI, 0.60-0.81; *P* <0.001), the estimated HR for Bev+Erl (HR, 0.72; 95% CI, 0.42-1.23), Gef+CT (HR, 0.92; 95% CI, 0.69-1.22), Erl+CT (HR, 0.82; 95% CI, 0.64-1.05) and Cet+CT (HR, 0.88; 95% CI, 0.76-1.01) compared with CT showed a consistent trend for better PFS, although they did not reach statistical significant. Bev+Erl had improved PFS over Erl alone (HR, 0.62; 95% CI, 0.52-0.75; *P* <0.001). Erl was associated with statistically worse PFS in comparison to CT (HR,1.22; 95% CI,1.10-1.36; *P* <0.001).

Inconsistent with the reslut of PFS, Bev+CT, Gef+CT, Erl+CT and Cet+CT were not associated with statistically significant hazard ratio for OS comapred with CT. Either, there was no significant difference between Bev+Erl and Erl (HR, 0.97; 95% CI, 0.80-1.18; *P*=0.759) or CT (HR, 0.78; 95% CI, 0.46-1.31; *P*=0.352) with respect to OS. Both Gef and Erl had improved PFS and OS over placebo.

An estimate consistent with large heterogeneity (I^2>50%) was seen in three comparisons for PFS and two comparisons for OS. The I^2 values were 0% for the

comparison of CT *versus* Gef and Cet+CT *versus* CT with regard to both PFS and OS.

Network meta-analysis for PFS

Hazard ratios for PFS and credibility interval obtained from all possible compasrisons were calculated by Beyesian network meta-analysis (Fig.3). According to the results, CT, Erl, Gef, Erl+CT, Gef+CT, Bev+CT, Cet+CT and Bev+Erl had statistically improved PFS in comparison to placebo. No significant differences were observed for combination therapy treatments, including Erl+CT, Gef+CT, Bev+CT, Cet+CT and Bev+Erl. Bev+CT was associated with statistically significant hazard ratio for PFS relative to four different treatments (placebo, CT, Erl and Gef), wherase CT, Erl and Gef had a trend for worse PFS compared with combination therapies.

Fig.4 shown the ranking probablities among all the treatments, agents with greater value in the histogram were associated with greater probablities for higher rank. This analysis indicated that Bev+CT and Bev+Erl ranked best for PFS, followed by Erl+CT and Cet+CT, they shared similar rankings and were probable to be the rank 3. CT, Erl and placebo were associated with relatively inferior PFS rankings compared with other agents.

Network meta-analysis for OS

Results of the multiple-treatments meta-analysis for OS were displayed in Fig.5. CT, Erl, Gef, Bev+CT and Cet+CT had statistically longer survival than placebo. Howerver, there were no significant differences among all the treatment arms except placebo. Cet+CT showed a trend for improved survival compared with other agents. Using the mean rank scale, Cet+CT was most probable to be the rank 1, Bev+CT to be the rank 2, both Erl + CT and Gef+ CT were ranked 8, and the last one was placebo (Fig.6).

Table 1: Characterstics of eligible studies included in the network meta-analysis.

Study	Line of Treatment	No. of patients	Experiment Drugs	Age, Median (Range), y	Female NO.(%)	Ethnicity NO.(%)	Smoking status: nonsmoker NO.(%)	Adenocarci-noma NO.(%)	CT-native
Sandler A(2006) [10]	First	850	Bev+PCp vs PCp	NR	387(45.5)	White(85.8)	NR	746(87.7)	Yes
Herbst RS(2007) [30]	Second	120	Bev+D/P vs D/P Bev+Erl vs D/P	63.5(40-88)	55(45.8)	White(78.3)	16(13.3)	95(79.1)	Yes
Reck M(2010) [9]	First	1043	Bev+CG vs CG	57(20-83)	378(36.2)	White(91.2)	NR	876(83.9)	Yes
Nishio M(2009) [24]	NR	180	Bev+PCp vs PCp	NR	NR	Asian(100)	NR	NR	Yes
Herbst RS(2011) [31]	Second	636	Bev+Erl vs Erl	NR	295(46.3)	White(81.9)	67(10.5)	477(75.0)	No
Johnson DH(2004) [25]	NR	99	Bev+PCp vs PCp	NR	39(39.3)	NR	NR	60(62.5)	Yes
Niho S(2012) [32]	First	180	Bev+PCp vs PCp	60(34-74)	65(36.1)	Asian(100)	57(31.6)	166(92.2)	Yes
Boutsikou E(2013) [33]	First	229	Bev+DC vs DC	NR	38(16.5)	NR	27(11.7)	206(89.9)	Yes
Herbst RS(2004) [26]	First	1037	Gef+Pcp vs Pcp	61(26-86)	418(40.3)	White(90.2)	NR	572(55.1)	Yes
Lee DH(2010) [39]	Second	161	Gef vs Docetaxel	57(20-74)	61(37.8)	Asian(100)	66(40.9)	109(67.7)	No
Cufer T(2006) [36]	Second	141	Gef vs Docetaxel	59.5(29-85)	43(30.4)	White(42.5)	36(25.5)	NR	No
Goss G(2009) [38]	First	201	Gef vs Placebo	74(42-90)	79(39.3)	White(96.0)	19(9.4)	91(45.2)	Yes
Giaccone G(2004) [34]	First	1093	Gef+CG vs CG	59(31-85)	863(79.0)	White(90.4)	NR	503(46.1)	Yes
Takeda K(2010) [41]	NR	604	Gef+Platinum vs Platinum	62(25-74)	215(35.6)	Asian(100)	186(30.8)	469(77.6)	Yes
Morere JF(2010) [40]	First	127	Docetaxel vs Gef Gemcitabine vs Gef	70(30-80)	22(17.3)	White(NR)	8(6.3)	62(48.8)	Yes
Gaafar RM(2011) [42]	Second	173	Gef vs Placebo	61(28-80)	40(23.1)	White(NR)	38(21.9)	89(51.4)	No
(Table continues)									
Table 1 (contiuned)									
Study	**Line of Treatment**	**No. of patients**	**Experiment Drugs**	**Age, Median (Range), y**	**Female NO.(%)**	**Ethnicity NO.(%)**	**Smoking status: nonsmoker NO.(%)**	**Adenocarci-noma NO.(%)**	**CT-native**
Thatcher N(2005) [35]	Second or Third	1692	Gef vs Placebo	61(28-90)	553(32.6)	White(75.2)	375(22.1)	767(45.3)	No
Maruyama R(2008) [37]	Second	489	Gef vs Docetaxel	NR	187(38.2)	Asian(100)	158(32.3)	380(77.7)	No
Fukuoka M(2011) [43]	First	1217	Gef vs PCp	57(24-84)	965(79.2)	Asian(99.8)	1140(93.6)	1172(96.3)	No
Douillard JY(2010) [44]	Second	1466	Gef vs Docetaxel	60(20-84)	512(34.9)	White(78.0)	298(20.3)	830(56.6)	No
Shepherd FA(2005) [45]	Second or Third	731	Erl vs Placebo	59(32-89)	256(35.0)	Asian(12.6)	146(19.9)	365(49.9)	No
Herbst RS(2005) [27]	First	1078	Erl+PCp vs PCp	63(24-84)	424(39.3)	White(86.6)	116(10.7)	654(60.6)	Yes
Lilenbaum R(2008) [46]	First	103	Erl vs PCp	NR	52(50.4)	White(66.0)	10(9.7)	58(56.3)	Yes
MoK T(2009) [47]	First	154	Erl+GP vs GP	57(27-79)	46(29.8)	Asian(94.1)	52(33.7)	103(66.8)	Yes
Gatzemeier U(2007) [28]	First	1159	Erl+CG vs CG	60(26-84)	267(23.0)	White(91.8)	NR	445(38.3)	Yes

Cappuzzo F(2010) [48]	First	889	Erl vs Placebo	60(30-83)	230(25.8)	White(83.9)	152(17.0)	403(45.3)	No
Ciuleanu T(2012) [49]	Second	424	Erl vs D/P	59(22-80)	103(24.2)	White(85.4)	74(17.4)	210(49.5)	No
Karampeazis A(2013) [29]	Second or Third	332	Pemetrexed vs Erl	65(37-86)	59(17.7)	NR	53(15.9)	NR	No
Kawaguchi T(2014) [51]	Second or Third	301	Erl vs Docetaxel	67(31-85)	86(28.5)	Asian(100)	76(25.2)	207(68.8)	No
Gridelli C(2012) [50]	First	760	Erl vs CG	62(27-81)	256(33.7)	White(100)	157(20.7)	422(55.5)	No
Butts CA(2007) [52]	First	131	Cet+GP vs GP	64(35-84)	73(55.7)	White(83.2)	19(14.5)	61(46.6)	Yes
Lynch TJ(2010) [7]	First	676	Cet+TC vs TC	64(34-87)	280(41.4)	White(88.1)	53(7.8)	324(47.9)	Yes

NR: not reported; Bev: Bevacizumab; Gef: Gefitinib; Erl: Erlotinib; Cet: Cetuximab; PCp: Paclitaxel+Carboplatin; D/P: Docetaxel/Pemetrexed; CG: Cisplatin+Gemcitabine; DC: Docetaxel+carboplatin; GP: Gemcitabine/platinum; TC: Taxane+Carboplatin.

Table 2. Hazard ratios and heterogeneity for direct comoparisons

Outcome	No. of studies	Treatment	HR (95% CI)	*P*	I^2
PFS	6	Bev+CT vs CT	0.70 (0.60-0.81)	<0.001	41%
OS	6		0.88 (0.78-1.01)	0.063	14%
PFS	1	Bev+Erl vs CT	0.72 (0.42-1.23)	0.231	–
OS	1		0.78 (0.46-1.31)	0.352	–
PFS	1	Bev+Erl vs Erl	0.62 (0.52-0.75)	<0.001	–
OS	1		0.97 (0.80-1.18)	0.759	–
PFS	3	Gef+CT vs CT	0.92 (0.69-1.22)	0.543	89%
OS	3		1.03 (0.87-1.22)	0.723	67%
PFS	5	Gef vs CT	0.87 (0.73-1.04)	0.126	73%
OS	5		0.97 (0.90-1.05)	0.465	0%
PFS	3	Gef vs placebo	0.77 (0.65-0.91)	0.002	37%
OS	3		0.87 (0.77-0.98)	0.023	0%
PFS	2	CT vs Gef	0.71 (0.52-0.97)	0.029	0%
OS	2		0.72 (0.52-1.00)	0.049	0%
PFS	2	Erl vs placebo	0.67 (0.58-0.78)	<0.001	39%
OS	2		0.76 (0.66-0.88)	<0.001	27%
PFS	3	Erl+CT vs CT	0.82 (0.64-1.05)	0.114	86%
OS	3		1.03 (0.93-1.15)	0.56	0%
PFS	4	Erl vs CT	1.22 (1.10-1.36)	<0.001	0%
OS	4		1.12 (0.90-1.40)	0.304	66%
PFS	1	CT vs Erl	1.17 (0.93-1.47)	0.191	–
OS	1		1.00 (0.78-1.29)	0.988	–
PFS	2	Cet+CT vs CT	0.88 (0.76-1.01)	0.073	0%
OS	2		0.87 (0.74-1.01)	0.065	0%

CT: chemotherapy; Bev: Bevacizumab; Gef: Gefitinib; Erl: Erlotinib; Cet: Cetuximab. The estimated HRs for PFS and OS using random-effects model.

Figure captions:
Fig.1. Trial selection process.

Fig.2. Network of eligible trials. Each link represents at least 1 study, widths 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.

Fig.3. Multiple treatment comparison for PFS based on Bayesian network meta-analysis. HR<1 indicates PFS benefit. CT=chemotherapy, Bev=Bevacizumab, Gef=Gefitinib, Erl=Erlotinib, Cet=Cetuximab.

Fig.4. Rank probabilities of each treatments for PFS based on Bayesian network meta-analysis. A. Ranking for PFS. Each value represents the probablity of each treatment to be a specific rank. B. Distribution of probablities of each treatment being ranked at each of the possible positions. CT=chemotherapy, Bev=Bevacizumab, Gef=Gefitinib, Erl=Erlotinib, Cet=Cetuximab.

Fig.5. Multiple treatment comparison for OS based on Bayesian network meta-analysis. HR<1 indicates OS benefit. CT=chemotherapy, Bev=Bevacizumab, Gef=Gefitinib, Erl=Erlotinib, Cet=Cetuximab.

Fig.6. Rank probabilities of each treatments for OS based on Bayesian network meta-analysis. A. Ranking for OS. Each value represents the probablity of each treatment to be a specific rank. B. Distribution of probablities of each treatment being ranked at each of the possible positions. CT=chemotherapy, Bev=Bevacizumab, Gef=Gefitinib, Erl=Erlotinib, Cet=Cetuximab.

Fig. 1

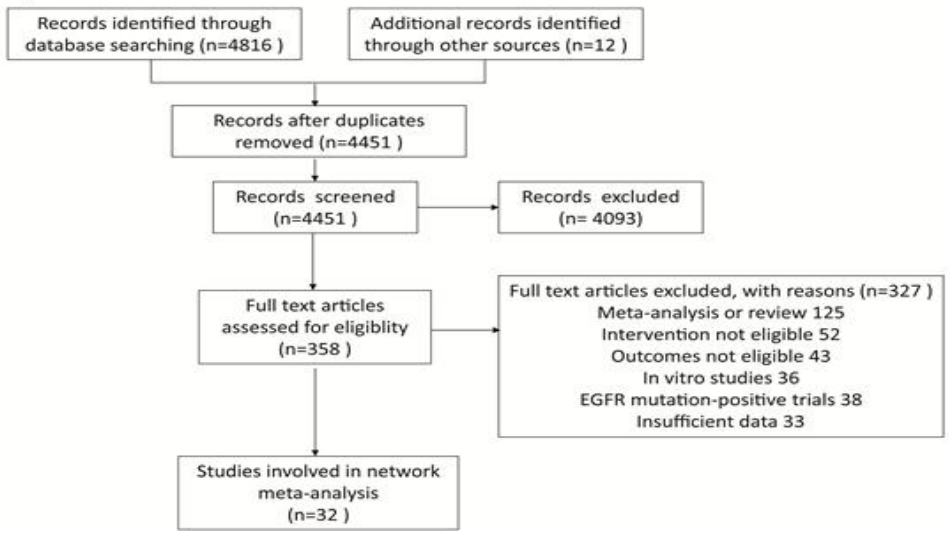


Fig. 2

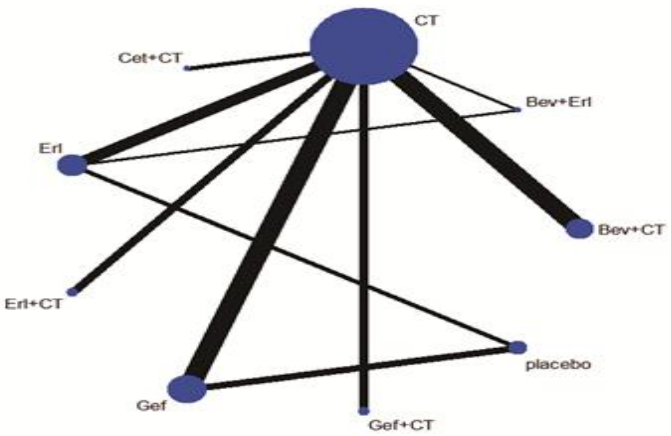


Fig. 3

Treatment	placebo	CT	Erl	Gef	Erl+CT	Gef+CT	Bev+CT	Cet+CT	Bev+Erl
placebo		1.41 (1.09-1.79)	1.31 (1.02-1.64)	1.51 (1.20-1.87)	1.73 (1.22-2.45)	1.56 (1.08-2.18)	2.08 (1.49-2.84)	1.64 (1.08-2.40)	2.08 (1.30-3.31)
CT	0.72 (0.56-0.91)		0.93 (0.77-1.11)	1.07 (0.89-1.29)	1.23 (0.96-1.58)	1.10 (0.86-1.40)	1.48 (1.19-1.83)	1.17 (0.84-1.58)	1.48 (0.97-2.16)
Erl	0.78 (0.61-0.98)	1.09 (0.90-1.30)		1.16 (0.92-1.46)	1.33 (0.98-1.82)	1.20 (0.87-1.62)	1.60 (1.20-2.10)	1.27 (0.87-1.79)	1.59 (1.07-2.28)
Gef	0.67 (0.53-0.84)	0.94 (0.78-1.13)	0.87 (0.69-1.09)		1.16 (0.84-1.57)	1.04 (0.75-1.40)	1.39 (1.04-1.83)	1.10 (0.75-1.55)	1.39 (0.87-2.07)
Erl+CT	0.60 (0.41-0.83)	0.83 (0.63-1.05)	0.77 (0.55-1.03)	0.89 (0.64-1.19)		0.91 (0.62-1.27)	1.22 (0.86-1.67)	0.96 (0.63-1.40)	1.22 (0.73-1.90)
Gef+CT	0.66 (0.46-0.93)	0.92 (0.72-1.17)	0.86 (0.62-1.15)	0.99 (0.72-1.33)	1.13 (0.79-1.60)		1.36 (0.97-1.87)	1.07 (0.70-1.57)	1.36 (0.82-2.12)
Bev+CT	0.49 (0.34-0.67)	0.69 (0.55-0.84)	0.64 (0.47-0.83)	0.73 (0.55-0.96)	0.84 (0.60-1.16)	0.76 (0.53-1.03)		0.80 (0.53-1.14)	1.01 (0.63-1.51)
Cet+CT	0.63 (0.42-0.93)	0.88 (0.63-1.19)	0.82 (0.56-1.15)	0.94 (0.64-1.33)	1.08 (0.71-1.59)	0.97 (0.64-1.42)	1.30 (0.88-1.87)		1.30 (0.75-2.09)
Bev+Erl	0.50 (0.31-0.77)	0.70 (0.45-1.04)	0.65 (0.43-0.93)	0.75 (0.47-1.14)	0.86 (0.52-1.37)	0.77 (0.46-1.23)	1.03 (0.65-1.57)	0.82 (0.47-1.33)	

Fig. 4

A

Treatment	Rank1	Rank2	Rank3	Rank4	Rank5	Rank6	Rank7	Rank8	Rank9
placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.03	0.96
CT	0.00	0.00	0.00	0.02	0.11	0.34	0.42	0.10	0.00
Erl	0.00	0.00	0.00	0.02	0.05	0.10	0.19	0.63	0.01
Gef	0.00	0.02	0.08	0.20	0.28	0.23	0.14	0.06	0.00
Erl+CT	0.06	0.15	0.32	0.23	0.13	0.06	0.03	0.02	0.00
Gef+CT	0.01	0.04	0.14	0.22	0.23	0.16	0.11	0.08	0.01
Bev+CT	0.43	0.42	0.11	0.03	0.01	0.00	0.00	0.00	0.00
Cet+CT	0.05	0.10	0.22	0.22	0.16	0.10	0.08	0.07	0.01
Bev+Erl	0.46	0.26	0.13	0.07	0.04	0.02	0.02	0.01	0.00

B

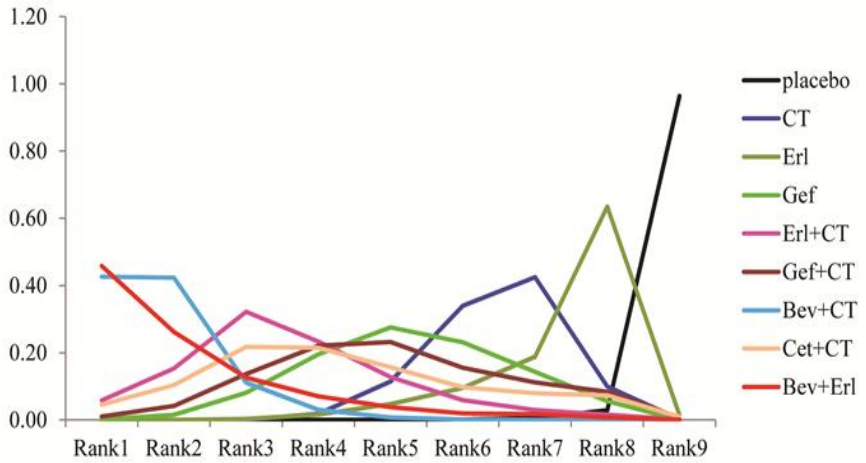


Fig. 5

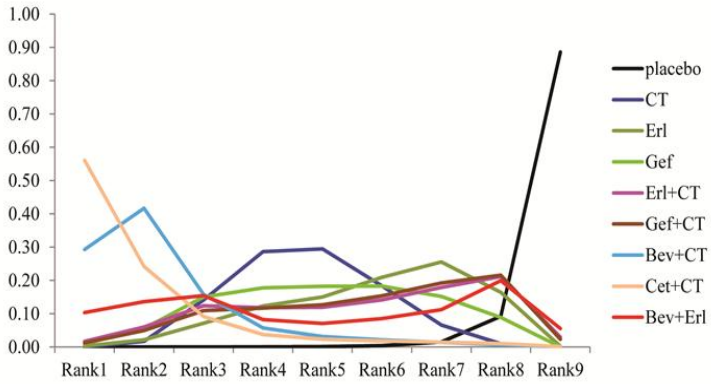
Treatment	placebo	CT	Erl	Gef	Erl+CT	Gef+CT	Bev+CT	Cet+CT	Bev+Erl
placebo		1.26 (1.08-1.48)	1.22 (1.05-1.41)	1.25 (1.08-1.44)	1.23 (0.98-1.54)	1.23 (0.99-1.52)	1.42 (1.14-1.76)	1.49 (1.14-1.93)	1.27 (0.94-1.67)
CT	0.80 (0.68-0.93)		0.97 (0.85-1.09)	0.99 (0.88-1.11)	0.97 (0.82-1.14)	0.97 (0.84-1.12)	1.12 (0.96-1.31)	1.18 (0.95-1.45)	1.00 (0.76-1.30)
Erl	0.83 (0.71-0.95)	1.04 (0.92-1.18)		1.03 (0.88-1.19)	1.01 (0.82-1.24)	1.01 (0.83-1.22)	1.17 (0.96-1.42)	1.22 (0.96-1.56)	1.04 (0.81-1.32)
Gef	0.80 (0.69-0.93)	1.01 (0.90-1.14)	0.98 (0.84-1.13)		0.99 (0.80-1.20)	0.98 (0.82-1.18)	1.14 (0.93-1.37)	1.19 (0.93-1.51)	1.02 (0.76-1.34)
Erl+CT	0.82 (0.65-1.02)	1.03 (0.88-1.21)	1.00 (0.81-1.22)	1.03 (0.84-1.24)		1.01 (0.81-1.25)	1.16 (0.92-1.45)	1.22 (0.93-1.58)	1.04 (0.75-1.41)
Gef+CT	0.83 (0.66-1.01)	1.04 (0.89-1.19)	1.00 (0.82-1.20)	1.03 (0.85-1.23)	1.01 (0.80-1.25)		1.16 (0.93-1.43)	1.22 (0.94-1.56)	1.04 (0.76-1.39)
Bev+CT	0.71 (0.57-0.88)	0.90 (0.77-1.04)	0.87 (0.71-1.05)	0.89 (0.73-1.07)	0.87 (0.69-1.09)	0.87 (0.70-1.07)		1.06 (0.81-1.36)	0.90 (0.66-1.20)
Cet+CT	0.68 (0.52-0.88)	0.86 (0.69-1.06)	0.83 (0.64-1.05)	0.85 (0.66-1.07)	0.84 (0.63-1.08)	0.83 (0.64-1.07)	0.97 (0.73-1.24)		0.80 (0.60-1.20)
Bev+Erl	0.81 (0.60-1.07)	1.02 (0.76-1.33)	0.98 (0.75-1.25)	1.01 (0.75-1.33)	0.99 (0.71-1.35)	0.99 (0.71-1.34)	1.14 (0.83-1.53)	1.20 (0.84-1.67)	

Fig. 6

A

Treatment	Rank1	Rank2	Rank3	Rank4	Rank5	Rank6	Rank7	Rank8	Rank9
placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.09	0.89
CT	0.00	0.02	0.14	0.29	0.29	0.18	0.07	0.01	0.00
Erl	0.00	0.02	0.07	0.12	0.15	0.21	0.26	0.16	0.00
Gef	0.01	0.06	0.15	0.18	0.18	0.18	0.15	0.09	0.00
Erl+CT	0.02	0.06	0.12	0.12	0.12	0.14	0.18	0.21	0.03
Gef+CT	0.01	0.05	0.11	0.12	0.13	0.15	0.19	0.22	0.02
Bev+CT	0.29	0.42	0.16	0.06	0.03	0.02	0.01	0.01	0.00
Cet+CT	0.56	0.24	0.09	0.04	0.02	0.02	0.01	0.01	0.00
Bev+Erl	0.10	0.14	0.15	0.08	0.07	0.09	0.11	0.20	0.06

B



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 tyrosine kinase inhibitors (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 genotpying in practice. Although ctDNA or CTC would be a reliable method to detect mutations, its specificity, sensitivity and costs still need to be assessed. 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 efficacy to other included regimens in treating patients with locally advanced or metastatic NSCLS 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[53, 54], direct head to head comparisons beteween these agents have not been well established, especially in unselected patients with advanced NSCLC. Unique to this analysis, multiple-treatments comparisons were used to complish a mixed-treatments analysis and obtained the information on the effectiveness of each agents. Our findings were similar to previous publications. 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' PFS and OS among chemotherapy-native patients compared with other targeted drugs, which was consistent with our direct and indirect comparisons.[53] However, it did not prove the difference among other targeted drugs. Using network meta-analysis, we assessed the substantial differences among these agents 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.[22] In this study, although no statistically significant differences betweeen combination treatments in terms of PFS and OS, Bev+CT and Bev+Erl were among the top ranked regarding PFS, Cet+CT had the greatest probability to rank the first respect to OS, followed by Bev+CT, Erl+CT was probable to be the rank 3 for PFS but rank 8 in terms of OS. The formation of new blood vessels palyed 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[55], 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.

The conclusion of this study will lead us to the argument about whether the targeted drugs should be used in clinical practice to have the best outcome as a whole. Several points needed to be considered. For example, 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.

Nevertheless, this network meta-analysis showed the different efficacy of these included regimens from the available evidence. At the same time, several limitations needed to be considered. First, the number of studies included were relatively small. The indirect estimates were often very similar to the direct comparisons due to only single comparison were available. For example, the informative value of the direct comparison Bev+Erl arms was limited by low number of events. This resulted in trials' heterogeneity. Second, different baselines of trial populations, such as age, gender, interventions, comorbidities, and differences in other possible prognostic factors, may introduce potential confounding and bias to the analysis. Third, the established networks lacked sufficient direct comparisons between combination therapies. Finally, this study only analyzed the PFS and OS, the objective response rate and the adverse events needed to be assessed in the future study.

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

ACKNOWLEDGMENTS

This work was supported by National Natural Science Foundation of China (grant number 81560451), Kunming University of Science and Technology Talent Introduction Fund (grant number KKSY201560001) and Science and technology project of Yunnan Province (grant number 2015IA003 and 2013FZ177).

REFERENCE

1. A. Jemal, R. Siegel, J. Xu and E. Ward, Cancer statistics, *CA Cancer J Clin.*, 2010; 60: 277-300.
2. S. Ramalingam and C. Belani, Systemic chemotherapy for advanced non-small cell lung cancer: recent advances and future directions, *Oncologist.*, 2008; 13(1): 5-13.
3. D.S. Ettinger, W. Akerley, H. Borghaei, A.C. Chang, R.T. Cheney, L.R. Chirieac, T.A. D'Amico, T.L. Demmy, A.K. Ganti, R. Govindan, F.W. Grannis, Jr., L. Horn, T.M. Jahan, M. Jahanzeb, A. Kessinger, R. Komaki, F.M. Kong, M.G. Kris, L.M. Krug, I.T. Lennes, B.W. Loo, Jr., R. Martins, J. O'Malley, R.U. Osarogiagbon, G.A. Otterson, J.D. Patel, M.C. Pinder-Schenck, K.M. Pisters, K. Reckamp, G.J. Riely, E. Rohren, S.J. Swanson, D.E. Wood, S.C. Yang, M. Hughes and K.M. Gregory, Non-small cell lung cancer, *J Natl Compr Canc Netw.*, 2012; 10: 1236-71.
4. B.A. Chan and B.G. Hughes, Targeted therapy for non-small cell lung cancer: current standards and the promise of the future, *Transl Lung Cancer Res.*, 2015; 4: 36-54.
5. V.D. Cataldo, D.L. Gibbons, R. Perez-Soler and A. Quintas-Cardama, Treatment of non-small-cell lung cancer with erlotinib or gefitinib, *N Engl J Med.*, 2011; 364: 947-55.
6. R. Pirker, J.R. Pereira, A. Szczesna, J. von Pawel, M. Krzakowski, R. Ramlau, I. Vynnychenko, K.

Park, C.T. Yu, V. Ganul, J.K. Roh, E. Bajetta, K. O'Byrne, F. de Marinis, W. Eberhardt, T. Goddemeier, M. Emig and U. Gatzemeier, Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial, *Lancet* 373 (2009), 1525-31.

7. T.J. Lynch, T. Patel, L. Dreisbach, M. McCleod, W.J. Heim, R.C. Hermann, E. Paschold, N.O. Iannotti, S. Dakhil, S. Gorton, V. Pautret, M.R. Weber and D. Woytowitz, Cetuximab and first-line taxane/carboplatin chemotherapy in advanced non-small-cell lung cancer: results of the randomized multicenter phase III trial BMS099, *J Clin Oncol* 28 (2010), 911-7.
8. A. Sandler, Bevacizumab in non small cell lung cancer, *Clin Cancer Res* 13 (2007), s4613-6.
9. M. Reck, J. von Pawel, P. Zatloukal, R. Ramlau, V. Gorbounova, V. Hirsh, N. Leighl, J. Mezger, V. Archer, N. Moore and C. Manegold, Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL), *Ann Oncol* 21 (2010), 1804-9.
10. A. Sandler, R. Gray, M.C. Perry, J. Brahmer, J.H. Schiller, A. Dowlati, R. Lilenbaum and D.H. Johnson, Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer, *N Engl J Med* 355 (2006), 2542-50.
11. P.A. Janne, A.T. Shaw, J.R. Pereira, G. Jeannin, J. Vansteenkiste, C. Barrios, F.A. Franke, L. Grinsted, V. Zazulina, P. Smith, I. Smith and L. Crino, Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: a randomised, multicentre, placebo-controlled, phase 2 study, *Oncol* 14 (2013), 38-47.
12. M. Maemondo, A. Inoue, K. Kobayashi, S. Sugawara, S. Oizumi, H. Isobe, A. Gemma, M. Harada, H. Yoshizawa, I. Kinoshita, Y. Fujita, S. Okinaga, H. Hirano, K. Yoshimori, T. Harada, T. Ogura, M. Ando, H. Miyazawa, T. Tanaka, Y. Saijo, K. Hagiwara, S. Morita, T. Nukiwa and G. North-East Japan Study, Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR, *N Engl J Med* 362 (2010), 2380-8.
13. T. Mitsudomi, S. Morita, Y. Yatabe, S. Negoro, I. Okamoto, J. Tsurutani, T. Seto, M. Satouchi, H. Tada, T. Hirashima, K. Asami, N. Katakami, M. Takada, H. Yoshioka, K. Shibata, S. Kudoh, E. Shimizu, H. Saito, S. Toyooka, K. Nakagawa and M. Fukuoka, Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial, *Lancet Oncol* 11 (2010), 121-8.
14. R. Rosell, E. Carcereny, R. Gervais, A. Vergnenegre, B. Massuti, E. Felip, R. Palmero, R. Garcia-Gomez, C. Pallares, J.M. Sanchez, R. Porta, M. Cobo, P. Garrido, F. Longo, T. Moran, A. Insa, F. De Marinis, R. Corre, I. Bover, A. Illiano, E. Dansin, J. de Castro, M. Milella, N. Reguart, G. Altavilla, U. Jimenez, M. Provencio, M.A. Moreno, J. Terrasa, J. Munoz-Langa, J. Valdivia, D. Isla, M. Domine, O. Molinier, J. Mazieres, N. Baize, R. Garcia-Campelo, G. Robinet, D. Rodriguez-Abreu, G. Lopez-Vivanco, V. Gebbia, L. Ferrera-Delgado, P. Bombaron, R. Bernabe, A. Bearz, A. Artal, E. Cortesi, C. Rolfo, M. Sanchez-Ronco, A. Drozdowskyj, C. Queralt, I. de Aguirre, J.L. Ramirez, J.J. Sanchez, M.A. Molina, M. Taron and L. Paz-Ares, Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial, *Lancet Oncol* 13 (2012), 239-46.
15. C. Zhou, Y.L. Wu, G. Chen, J. Feng, X.Q. Liu, C. Wang, S. Zhang, J. Wang, S. Zhou, S. Ren, S. Lu, L. Zhang, C. Hu, Y. Luo, L. Chen, M. Ye, J. Huang, X. Zhi, Y. Zhang, Q. Xiu, J. Ma and C. You, Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study, *Lancet Oncol* 12 (2011), 735-42.
16. G. Salanti, J.P. Higgins, A.E. Ades and J.P. Ioannidis, Evaluation of networks of randomized trials, *Stat Methods Med Res* 17 (2008), 279-301.
17. D.M. Caldwell, A.E. Ades and J.P. Higgins, Simultaneous comparison of multiple treatments: combining direct and indirect evidence, *BMJ* 331 (2005), 897-900.
18. F. McCormick, G.L. Cvetanovich, J.M. Kim, J.D. Harris, A.K. Gupta, G.D. Abrams, A.A. Romeo and M.T. Provencher, An assessment of the quality of rotator cuff randomized controlled trials: utilizing the Jadad score and CONSORT criteria, *J Shoulder Elbow Surg* 22 (2013), 1180-5.
19. J.P. Higgins, S.G. Thompson, J.J. Deeks and D.G. Altman, Measuring inconsistency in meta-analyses, *BMJ* 327 (2003), 557-60.
20. H.C. Bucher, G.H. Guyatt, L.E. Griffith and S.D. Walter, The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials, *J Clin Epidemiol* 50 (1997), 683-91.
21. B.S. Woods, N. Hawkins and D.A. Scott, Network meta-analysis on the log-hazard scale, combining count and hazard ratio statistics accounting for multi-arm trials: a tutorial, *BMC Med Res Methodol* 10 (2010), 54.
22. J.P. Jansen, B. Crawford, G. Bergman and W. Stam, Bayesian meta-analysis of multiple treatment comparisons: an introduction to mixed treatment comparisons, *Value Health* 11 (2008), 956-64.
23. A. Liberati, D.G. Altman, J. Tetzlaff, C. Mulrow, P.C. Gotzsche, J.P. Ioannidis, M. Clarke, P.J. Devereaux, J. Kleijnen and D. Moher, The PRISMA statement for reporting systematic reviews and meta-

analyses of studies that evaluate healthcare interventions: explanation and elaboration, *BMJ* 339 (2009), b2700.

24. M. Nishio, T. Horai, H. Kunitoh, Y. Ichinose, Y. Nishiwaki, T. Hida, N. Yamamoto, M. Kawahara, N. Saijo and M. Fukuoka, Randomized, open-label, multicenter phase II study of bevacizumab in combination with carboplatin and paclitaxel in chemotherapy-naive Japanese patients with advanced or recurrent nonsquamous non-small cell lung cancer (NSCLC): JO19907., *J Clin Oncol* 27 (2009), http://meeting.ascopubs.org/cgi/content/abstract/27/15S/8036.
25. D.H. Johnson, L. Fehrenbacher, W.F. Novotny, R.S. Herbst, J.J. Nemunaitis, D.M. Jablons, C.J. Langer, R.F. DeVore, 3rd, J. Gaudreault, L.A. Damico, E. Holmgren and F. Kabbinavar, Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer, *J Clin Oncol* 22 (2004), 2184-91.
26. R.S. Herbst, G. Giaccone, J.H. Schiller, R.B. Natale, V. Miller, C. Manegold, G. Scagliotti, R. Rosell, I. Oliff, J.A. Reeves, M.K. Wolf, A.D. Krebs, S.D. Averbuch, J.S. Ochs, J. Grous, A. Fandi and D.H. Johnson, Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial--INTACT 2, *J Clin Oncol* 22 (2004), 785-94.
27. R.S. Herbst, D. Prager, R. Hermann, L. Fehrenbacher, B.E. Johnson, A. Sandler, M.G. Kris, H.T. Tran, P. Klein, X. Li, D. Ramies, D.H. Johnson and V.A. Miller, 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* 23 (2005), 5892-9.
28. U. Gatzemeier, A. Pluzanska, A. Szczesna, E. Kaukel, J. Roubec, F. De Rosa, J. Milanowski, H. Karnicka-Mlodkowski, M. Pesek, P. Serwatowski, R. Ramlau, T. Janaskova, J. Vansteenkiste, J. Strausz, G.M. Manikhas and J. Von Pawel, 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* 25 (2007), 1545-52.
29. A. Karampeazis, A. Voutsina, J. Souglakos, N. Kentepozidis, S. Giassas, C. Christofillakis, A. Kotsakis, P. Papakotoulas, A. Rapti, M. Agelidou, S. Agelaki, L. Vamvakas, G. Samonis, D. Mavroudis and V. Georgoulias, Pemetrexed versus erlotinib in pretreated patients with advanced non-small cell lung cancer: a Hellenic Oncology Research Group (HORG) randomized phase 3 study, *CANCER.*, 2013; 119: 2754-64.
30. R.S. Herbst, V.J. O'Neill, L. Fehrenbacher, C.P. Belani, P.D. Bonomi, L. Hart, O. Melnyk, D. Ramies, M. Lin and A. Sandler, 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: 4743-50.
31. R.S. Herbst, R. Ansari, F. Bustin, P. Flynn, L. Hart, G.A. Otterson, G. Vlahovic, C.H. Soh, P. O'Connor and J. Hainsworth, Efficacy of bevacizumab plus erlotinib versus erlotinib alone in advanced non-small-cell lung cancer after failure of standard first-line chemotherapy (BeTa): a double-blind, placebo-controlled, phase 3 trial, *Lancet.*, 2011; 377: 1846-54.
32. S. Niho, H. Kunitoh, H. Nokihara, T. Horai, Y. Ichinose, T. Hida, N. Yamamoto, M. Kawahara, T. Shinkai, K. Nakagawa, K. Matsui, S. Negoro, A. Yokoyama, S. Kudoh, K. Kiura, K. Mori, H. Okamoto, H. Sakai, K. Takeda, S. Yokota, N. Saijo and M. Fukuoka, Randomized phase II study of first-line carboplatin-paclitaxel with or without bevacizumab in Japanese patients with advanced non-squamous non-small-cell lung cancer, *Lung Cancer.*, 2012; 76: 362-7.
33. E. Boutsikou, T. Kontakiotis, P. Zarogoulidis, K. Darwiche, E. Eleptheriadou, K. Porpodis, G. Galaktidou, L. Sakkas, W. Hohenforst-Schmidt, K. Tsakiridis, T. Karaiskos and K. Zarogoulidis, Docetaxel-carboplatin in combination with erlotinib and/or bevacizumab in patients with non-small cell lung cancer, *Onco Targets Ther.*, 2013; 6: 125-34.
34. G. Giaccone, R.S. Herbst, C. Manegold, G. Scagliotti, R. Rosell, V. Miller, R.B. Natale, J.H. Schiller, J. Von Pawel, A. Pluzanska, U. Gatzemeier, J. Grous, J.S. Ochs, S.D. Averbuch, M.K. Wolf, P. Rennie, A. Fandi and D.H. Johnson, Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial--INTACT 1, *J Clin Oncol.*, 2014; 22: 777-84.
35. N. Thatcher, A. Chang, P. Parikh, J. Rodrigues Pereira, T. Ciuleanu, J. von Pawel, S. Thongprasert, E.H. Tan, K. Pemberton, V. Archer and K. Carroll, Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer), *Lancet.*, 2005; 366: 1527-37.
36. T. Cufer, E. Vrdoljak, R. Gaafar, I. Erensoy and K. Pemberton, Phase II, open-label, randomized study (SIGN) of single-agent gefitinib (IRESSA) or docetaxel as second-line therapy in patients with advanced (stage IIIb or IV) non-small-cell lung cancer, *Anticancer Drugs.*, 2006; 17: 401-9.
37. R. Maruyama, Y. Nishiwaki, T. Tamura, N. Yamamoto, M. Tsuboi, K. Nakagawa, T. Shinkai, S. Negoro, F. Imamura, K. Eguchi, K. Takeda, A. Inoue, K. Tomii, M. Harada, N. Masuda, H. Jiang, Y. Itoh, Y. Ichinose, N. Saijo and M. Fukuoka, Phase III study, V-15-32, of gefitinib versus

docetaxel in previously treated Japanese patients with non-small-cell lung cancer, *J Clin Oncol.*, 2008; 26: 4244-52.
38. G. Goss, D. Ferry, R. Wierzbicki, S.A. Laurie, J. Thompson, B. Biesma, F.R. Hirsch, M. Varella-Garcia, E. Duffield, O.U. Ataman, M. Zarenda and A.A. Armour, Randomized phase II study of gefitinib compared with placebo in chemotherapy-naive patients with advanced non-small-cell lung cancer and poor performance status, *J Clin Oncol.*, 2009; 27: 2253-60.
39. D.H. Lee, K. Park, J.H. Kim, J.S. Lee, S.W. Shin, J.H. Kang, M.J. Ahn, J.S. Ahn, C. Suh and S.W. Kim, Randomized Phase III trial of gefitinib versus docetaxel in non-small cell lung cancer patients who have previously received platinum-based chemotherapy, *Clin Cancer Res.*, 2010; 16: 1307-14.
40. J.F. Morere, J.M. Brechot, V. Westeel, V. Gounant, B. Lebeau, F. Vaylet, F. Barlesi, T. Urban, P.J. Souquet, D. Debieuvre, L. Baudrin, G. Zalcman, F. Morin, B. Milleron and D. Moro-Sibilot, Randomized phase II trial of gefitinib or gemcitabine or docetaxel chemotherapy in patients with advanced non-small-cell lung cancer and a performance status of 2 or 3 (IFCT-0301 study), *Lung Cancer.*, 2010; 70: 301-7.
41. K. Takeda, T. Hida, T. Sato, M. Ando, T. Seto, M. Satouchi, Y. Ichinose, N. Katakami, N. Yamamoto, S. Kudoh, J. Sasaki, K. Matsui, K. Takayama, T. Kashii, Y. Iwamoto, T. Sawa, I. Okamoto, T. Kurata, K. Nakagawa and M. Fukuoka, Randomized phase III trial of platinum-doublet chemotherapy followed by gefitinib compared with continued platinum-doublet chemotherapy in Japanese patients with advanced non-small-cell lung cancer: results of a west Japan thoracic oncology group trial (WJTOG0203), *J Clin Oncol.*, 2010; 28: 753-60.
42. R.M. Gaafar, V.F. Surmont, G.V. Scagliotti, R.J. Van Klaveren, D. Papamichael, J.J. Welch, B. Hasan, V. Torri and J.P. van Meerbeeck, A double-blind, randomised, placebo-controlled phase III intergroup study of gefitinib in patients with advanced NSCLC, non-progressing after first line platinum-based chemotherapy (EORTC 08021/ILCP 01/03), *Eur J Cancer.*, 2011; 47: 2331-40.
43. M. Fukuoka, Y.L. Wu, S. Thongprasert, P. Sunpaweravong, S.S. Leong, V. Sriuranpong, T.Y. Chao, K. Nakagawa, D.T. Chu, N. Saijo, E.L. Duffield, Y. Rukazenkov, G. Speake, H. Jiang, A.A. Armour, K.F. To, J.C. Yang and T.S. Mok, Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS), *JOURNAL OF CLINICAL ONCOLOGY.*, 2011; 29: 2866-74.
44. J.Y. Douillard, F.A. Shepherd, V. Hirsh, T. Mok, M.A. Socinski, R. Gervais, M.L. Liao, H. Bischoff, M. Reck, M.V. Sellers, C.L. Watkins, G. Speake, A.A. Armour and E.S. Kim, Molecular predictors of outcome with gefitinib and docetaxel in previously treated non-small-cell lung cancer: data from the randomized phase III INTEREST trial, *JOURNAL OF CLINICAL ONCOLOGY.*, 2010; 28: 744-52.
45. F.A. Shepherd, J. Rodrigues Pereira, T. Ciuleanu, E.H. Tan, V. Hirsh, S. Thongprasert, D. Campos, S. Maoleekoonpiroj, M. Smylie, R. Martins, M. van Kooten, M. Dediu, B. Findlay, D. Tu, D. Johnston, A. Bezjak, G. Clark, P. Santabarbara and L. Seymour, Erlotinib in previously treated non-small-cell lung cancer, *N Engl J Med.*, 2005; 353: 123-32.
46. R. Lilenbaum, R. Axelrod, S. Thomas, A. Dowlati, L. Seigel, D. Albert, K. Witt and D. Botkin, 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: 863-9.
47. T.S. Mok, Y.L. Wu, C.J. Yu, C. Zhou, Y.M. Chen, L. Zhang, J. Ignacio, M. Liao, V. Srimuninnimit, M.J. Boyer, M. Chua-Tan, V. Sriuranpong, A.W. Sudoyo, K. Jin, M. Johnston, W. Chui and J.S. Lee, 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: 5080-7.
48. F. Cappuzzo, T. Ciuleanu, L. Stelmakh, S. Cicenas, A. Szczesna, E. Juhasz, E. Esteban, O. Molinier, W. Brugger, I. Melezinek, G. Klingelschmitt, B. Klughammer and G. Giaccone, Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study, *Lancet Oncol.*, 2010; 11: 521-9.
49. T. Ciuleanu, L. Stelmakh, S. Cicenas, S. Miliauskas, A.C. Grigorescu, C. Hillenbach, H.K. Johannsdottir, B. Klughammer and E.E. Gonzalez, Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study, *LANCET ONCOLOGY.*, 2012; 13: 300-8.
50. C. Gridelli, F. Ciardiello, C. Gallo, R. Feld, C. Butts, V. Gebbia, P. Maione, F. Morgillo, G. Genestreti, A. Favaretto, N. Leighl, R. Wierzbicki, S. Cinieri, Y. Alam, S. Siena, G. Tortora, R. Felletti, F. Riccardi, G. Mancuso, A. Rossi, F. Cantile, M.S. Tsao, M. Saieg, G. da Cunha Santos, M.C. Piccirillo, M. Di Maio, A. Morabito and F. Perrone, First-line erlotinib followed by second-line cisplatin-gemcitabine chemotherapy in advanced non-small-cell lung cancer: the TORCH randomized trial, *JOURNAL OF CLINICAL ONCOLOGY.*, 2012; 30: 3002-11.
51. T. Kawaguchi, M. Ando, K. Asami, Y. Okano, M. Fukuda, H. Nakagawa, H. Ibata, T. Kozuki, T. Endo, A. Tamura, M. Kamimura, K. Sakamoto, M. Yoshimi, Y. Soejima, Y. Tomizawa, S. Isa, M. Takada, H. Saka and A. Kubo, Randomized phase III trial of erlotinib versus docetaxel as second- or third-line therapy in patients with advanced non-

small-cell lung cancer: Docetaxel and Erlotinib Lung Cancer Trial (DELTA), *JOURNAL OF CLINICAL ONCOLOGY.*, 2014; 32: 1902-8.
52. C.A. Butts, D. Bodkin, E.L. Middleman, C.W. Englund, D. Ellison, Y. Alam, H. Kreisman, P. Graze, J. Maher, H.J. Ross, P.M. Ellis, W. McNulty, E. Kaplan, V. Pautret, M.R. Weber and F.A. Shepherd, Randomized phase II study of gemcitabine plus cisplatin or carboplatin, with or without cetuximab, as first-line therapy for patients with advanced or metastatic non small-cell lung cancer, *J Clin Oncol.*, 2007; 25: 5777-84.
53. J. Cui, X. Cai, M. Zhu, T. Liu and N. Zhao, The efficacy of bevacizumab compared with other targeted drugs for patients with advanced NSCLC: a meta-analysis from 30 randomized controlled clinical trials, *PLoS One.*, 2013; 8: e62038.
54. K. Yang, Y.J. Wang, X.R. Chen and H.N. Chen, Effectiveness and safety of bevacizumab for unresectable non-small-cell lung cancer: a meta-analysis, *Clin Drug Investig.*, 2010; 30: 229-41.
55. A. Onn, J. Bar and R.S. Herbst, Angiogenesis inhibition and lung-cancer therapy, *Lancet Oncol.*, 2014; 15: 124-5.