Chinese Medical Journal®

Front-line therapy for brain metastases and non-brain metastases in advanced epidermal growth factor receptor-mutated non-small cell lung cancer: a network meta-analysis

Yixiang Zhu[1], Chengcheng Liu[2], Ziyi Xu[1], Zihua Zou[1], Tongji Xie[1], Puyuan Xing[1], Le Wang[3], Junling Li[1]

[1]Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China;

[2]Department of Colorectal Surgery and Oncology, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310009, China;

[3]Department of Cancer Prevention, Zhejiang Cancer Hospital, Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences, Hangzhou, Zhejiang 310022, China.

Abstract

Background: The brain is a common metastatic site in patients with non-small cell lung cancer (NSCLC), resulting in a relatively poor prognosis. Systemic therapy with epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) is recommended as the first-line treatment for *EGFR*-mutated, advanced NSCLC patients. However, intracranial activity varies in different drugs. Thus, brain metastasis (BM) should be considered when choosing the treatment regimens. We conducted this network meta-analysis to explore the optimal first-line therapeutic schedule for advanced *EGFR*-mutated NSCLC patients with different BM statuses.

Methods: Randomized controlled trials focusing on EGFR-TKIs (alone or in combination) in advanced and *EGFR*-mutant NSCLC patients, who have not received systematic treatment, were systematically searched up to December 2021. We extracted and analyzed progression-free survival (PFS) and overall survival (OS). A network meta-analysis was performed with the Bayesian statistical model to determine the survival outcomes of all included therapy regimens using the R software. Hazard ratios (HRs) and 95% confidence intervals (CIs) were used to compare intervention measures, and overall rankings of therapies were estimated under the Bayesian framework.

Results: This analysis included 17 RCTs with 5077 patients and 12 therapies, including osimertinib + bevacizumab, aumolertinib, osimertinib, afatinib, dacomitinib, standards of care (SoC, including gefitinib, erlotinib, or icotinib), SoC + apatinib, SoC + bevacizumab, SoC + ramucirumab, SoC + pemetrexed based chemotherapy (PbCT), PbCT, and pemetrexed free chemotherapy (PfCT). For patients with BM, SoC + PbCT improved PFS compared with SoC (HR = 0.40, 95% CI: 0.17–0.95), and osimertinib + bevacizumab was most likely to rank first in PFS, with a cumulative probability of 34.5%, followed by aumolertinib, with a cumulative probability of 28.3%. For patients without BM, osimertinib + bevacizumab, osimertinib, aumolertinib, SoC + PbCT, dacomitinib, SoC + ramucirumab, SoC + bevacizumab, and afatinib showed superior efficacy compared with SoC (HR = 0.43, 95% CI: 0.20–0.90; HR = 0.46, 95% CI: 0.31–0.68; HR = 0.51, 95% CI: 0.34–0.77; HR = 0.50, 95% CI: 0.38–0.66; HR = 0.62, 95% CI: 0.43–0.89; HR = 0.64, 95% CI: 0.44–0.94; HR = 0.61, 95% CI: 0.48–0.76; HR = 0.71, 95% CI: 0.50–1.00), PbCT (HR = 0.29, 95% CI: 0.11–0.74; HR = 0.31, 95% CI: 0.15–0.62; HR = 0.34, 95% CI: 0.17–0.69; HR = 0.34, 95% CI: 0.18–0.64; HR = 0.42, 95% CI: 0.21–0.82; HR = 0.43, 95% CI: 0.22–0.87; HR = 0.41, 95% CI: 0.22–0.74; HR = 0.48, 95% CI: 0.31–0.75), and PfCT (HR = 0.14, 95% CI: 0.06–0.32; HR = 0.15, 95% CI: 0.09–0.26; HR = 0.17, 95% CI: 0.09–0.29; HR = 0.16, 95% CI: 0.10–0.26; HR = 0.20, 95% CI: 0.12–0.35; HR = 0.21, 95% CI: 0.12–0.39; HR = 0.20, 95% CI: 0.12–0.31; HR = 0.23, 95% CI: 0.16–0.34) in terms of PFS. And, SoC + apatinib showed relatively superior PFS when compared with PbCT (HR = 0.44, 95% CI: 0.22–0.92) and PfCT (HR = 0.21, 95% CI: 0.12–0.39), but similar PFS to SoC (HR = 0.65, 95% CI: 0.42–1.03). No statistical differences were observed for PFS in patients without BM between PbCT and SoC (HR = 1.49, 95% CI: 0.84–2.64), but both showed favorable PFS when compared with PfCT (PfCT *vs.* SoC, HR = 3.09, 95% CI: 2.06–4.55; PbCT *vs.* PfCT, HR = 0.14, 95% CI: 0.06–0.32). For patients without BM, osimertinib + bevacizumab was most likely to rank the first, with cumulative probabilities of 47.1%. For OS, SoC + PbCT was most likely to rank first in patients with and without BM, with cumulative probabilities of 46.8%, and 37.3%, respectively.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000002468

Yixiang Zhu and Chengcheng Liu contributed equally to this work.

Correspondence to: Le Wang, Department of Cancer Prevention, Zhejiang Cancer Hospital, Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences, Hangzhou, Zhejiang 310022, China
E-Mail: wangle@zjcc.org.cn;
Junling Li, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China
E-Mail: lijunling@cicams.ac.cn

Chinese Medical Journal 2023;136(21)

Received: 28-04-2023; **Online:** 09-05-2023 **Edited by:** Xiangxiang Pan and Peifang Wei

Conclusion: Osimertinib + bevacizumab is most likely to rank first in PFS in advanced *EGFR*-mutated NSCLC patients with or without BM, and SoC + PbCT is most likely to rank first in OS.

Keywords: Non-small cell lung carcinoma; Epidermal growth factor receptor; Brain metastases; Survival analysis; Network meta-analysis; First-line treatment

Introduction

Brain metastasis (BM) is one of the most common types of metastases in patients with non-small cell lung cancer (NSCLC) and poses a great threat to survival and quality of life for patients.[1,2] Approximately 20% of NSCLC patients are initially diagnosed with BM, and BM may occur in 20% to 50% of NSCLC patients.[3,4] Epidermal growth factor receptor (*EGFR*) gene mutations are common among NSCLC patients, with the frequency of approximately 50% in Asian patients and 10% to 20% in Caucasian patients;[5-7] and patients with *EGFR*-sensitive mutations have a higher propensity to develop BM than those who are negative.[8,9] Compared with chemotherapy, EGFR tyrosine kinase inhibitor (TKI) therapy significantly prolongs overall survival (OS) in metastatic *EGFR*-mutated NSCLC patients.[9] For symptomatic and uncontrolled BM, local therapy is recommended as the first-line treatment.[10] For stable BM, which refers to clinically asymptomatic and controlled BM, systemic therapy is recommended.

Several EGFR-TKIs are recommended for the first-line therapy in metastatic *EGFR*-mutated NSCLC, such as first-generation EGFR-TKIs (gefitinib, erlotinib, and icotinib),[10] second-generation EGFR-TKIs (dacomitinib and afatinib), and third-generation EGFR-TKIs (osimertinib). Combined therapy of EGFR-TKIs and other drugs (antiangiogenic drugs and chemotherapy) has also been established as a first-line treatment to enhance efficacy and overcome drug resistance.[11] Because of the blood–brain barrier, patients with BM have a poor intracranial response to chemotherapy and first-/second-generation EGFR-TKIs.[12] The penetration (cerebral spinal fluid [CSF]/plasma or CSF/blood) of first-generation and second-generation EGFR-TKIs was only 1.1% to 3.3% and 1.7%, respectively.[13] The BRAIN study indicated that icotinib might be better for patients with *EGFR*-mutated NSCLC accompanied by multiple BM, with a significantly longer intracranial progression-free survival (PFS) than whole-brain radiation therapy plus chemotherapy.[14] However, no difference in OS was observed in this study. A preclinical study indicated that compared with other EGFR-TKIs, osimertinib provided markedly greater central nervous system activity in *EGFR*-mutated NSCLC BM models.[15] The penetration (CSF/plasma or CSF/blood) of osimertinib was 2.5–16.0%,[13] and the objective response rate (ORR) was 76%.[16] However, in the subgroup analysis of FLAURA, osimertinib only showed a favorable trend in OS.[16,17] The combination of first-generation TKIs with antiangiogenic agents and chemotherapy improved PFS in advanced, *EGFR*-mutated NSCLC patients, even in those with BM.[18,19] However, the existing data on treatments for BM are mostly derived from subgroup analyses, lacking phase III studies and direct comparisons. Therefore, the optimal first-line therapy in NSCLC patients carrying *EGFR*-sensitive mutations with stable BM remains controversial. In addition, the prognosis of patients with BM is poorer than that of patients without BM. Hence, regimens should be selected according to the BM status. To address these questions, we conducted a network meta-analysis (NMA) of randomized controlled trials (RCTs) by comparing a number of interventions with diverse contrasts simultaneously, which is widely used in the absence of head-to-head trial data,[20] to gain insight into the relative efficacy of first-line regimens in advanced *EGFR*-mutated NSCLC patients with and without BM.

Methods

Database and search strategy

RCTs focusing on EGFR-TKIs (alone or in combination) in advanced and *EGFR*-mutant NSCLC patients, who have not received systematic treatment, were systematically searched from the PubMed, Cochrane Library, and EMBASE with the terms NSCLC, EGFR, TKI, first-line, PFS, OS, and RCT up to December 31, 2021. Detailed search strategies are available in Supplementary Table 1, http://links.lww.com/CM9/B524. To acquire data from unpublished trials, abstracts presented at the conferences of the American Society of Clinical Oncology and the European Society for Medical Oncology in 2021 were further searched. This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on October 06, 2020, and it was last updated on October 06, 2020 (registration number INPLASY2020100018).

Outcome definition

The primary and secondary outcomes in this study were PFS and OS, respectively.

Screening studies

To guarantee transitivity, trials with strict criteria for patient grouping were identified and included. Studies that met all of the following inclusion criteria were included in the final analysis: (1) study patients: advanced or metastatic NSCLC with *EGFR*-sensitive mutations; (2) interventions: EGFR-TKIs with or without anti-vascular endothelial growth factor receptor or chemotherapy; (3) contrasts: chemotherapy or EGFR-TKIs; (4) outcomes: PFS and/or OS; and (5) study design: RCT.

We excluded studies according to the exclusion criteria: (1) without *EGFR*-mutant patients; (2) without the intervention of EGFR-TKIs; (3) without survival outcome; (4) non-first-line therapy; (5) comment, review, protocol, or editor opinion; and (6) duplicated studies.

Data extraction and risk assessment for bias

Based on eligibility criteria initially predefined by our research working group, the titles and abstracts of identified records were screened, and then the full texts of potentially eligible studies were further assessed. For the final included studies, our research group extracted the data and conducted a risk assessment. A form was pre-designed by a review working group for data extraction, including the following information: (1) basic information: first author, year of publication, and country; (2) trial design: design types, population characteristics, sample size, and treatments in the control and intervention groups, and (3) outcomes: data on PFS and OS.

We used the Cochrane risk-of-bias tool[21] to evaluate allocation concealment (selection bias), random sequence generation (selection bias), blinding of outcome assessment (detection bias), blinding of participants and personnel (performance bias), selective reporting (reporting bias), incomplete outcome data (attrition bias), and other biases.

Statistical analysis

The random-effect model was adopted for the analysis. The hazard ratios (HRs) and the associated standard errors of OS and PFS were used for NMA. The network plots were produced using Stata software (version 15.0, StataCorp LLC, College Station, TX, USA) to suggest interactions among the evaluated regimens from the included trials.[21] Heterogeneity across the included studies was assessed by the Q test and I^2 statistics. I^2 values <25%, 25% to 50%, and >50% indicated low, moderate, or high heterogeneity, respectively.[22]

The Bayesian framework was used with a Markov chain Monte Carlo simulation technique with R software (version 3.6.3, https://www.r-project.org/). In addition, we applied the HRs and 95% CI to compare the intervention measures.[23] Owing to the limited number of included studies and the lack of direct comparisons for most evaluated interventions, a random-effect model was used using the "gemtc" and "rjags" packages. To fit the model, we set four different series of initial values for five kinds of parameters, including the number of chains, tuning iterations, simulation iterations, and thinning intervals. For both PFS and OS, our analysis generated 10,000 sample iterations with 5000 burn-ins and a thinning interval of five. Using visual inspection of the four chains, we estimated the convergence of iterations to establish homogenous parameter estimation through the density plot.[24] Under the Bayesian framework, overall rankings of therapies were estimated. For the ranking, higher cumulative probability means better regimen. Transitivity and consistency are two key assumptions that had to be met to conduct the NMA. To guarantee transitivity, trials with strict criteria for patient allocation were identified and included, and the same condition for evaluated treatments was optimized. Model fit was assessed by examining the posterior deviance information criterion (DIC). We performed a weighted integration of the evidence through fitting random- effects NMA models. Inconsistency was assessed by comparing the DICs of our primary analyses (based on NMA models that assume consistency between direct and indirect evidence) and the DICs yielded by inconsistency models (which provide effect estimates based on direct evidence only) by using the node-splitting procedure for all loops.

Results

Characteristics

We identified 4841 unique records from the dataset, 4534 articles were excluded by initial title and abstract screening, and 307 articles were retrieved and reviewed. Finally, a total of 17 RCTs with 5077 patients were included in this study [Figure 1], among which 12 studies included 825 patients with BM, while 17 studies included 4252 patients without BM [Table 1].[16-19,25-40] A total of 12 intervention treatments, including osimertinib + bevacizumab, aumolertinib, osimertinib, afatinib, dacomitinib, standards of care (SoC, including gefitinib, erlotinib, or icotinib), SoC + apatinib, SoC + bevacizumab, SoC + ramucirumab, SoC + pemetrexed based chemotherapy (PbCT), PbCT, and pemetrexed free chemotherapy (PfCT), were finally included.

Risk of bias

The risk of bias assessment for included studies was mainly performed according to the Cochrane handbook. There is a low to medium risk of bias [Figure 2]. All included studies described the method used to generate the allocation sequence, concealed the allocation sequence, and reported the related outcomes based on the trial protocol and other potential biases [Figure 2]. No significant bias was found in most studies, except trial NCT01466660 (Lung 7), which had a high risk of bias in terms of completeness because of the inconsistent number of patients. In this study, there were 50 patients with BM in the baseline demographics, but there were 51 patients in the subgroup analyses.[31] Furthermore, most studies did not clearly state the method for blinding in terms of the intervention.

Network meta-analysis of the efficacy of different treatments

This NMA identified 16 studies for PFS and 12 studies for OS. In patients with BM, there were 11 and eight studies with PFS [Figure 3A] and OS [Figure 3B] outcomes, respectively. For patients without BM, 16 studies reported PFS [Figure 3C], while 12 studies included OS outcomes [Figure 3D].

PFS for all advanced, *EGFR*-mutant NSCLC patients

Compared with afatinib, SoC, PbCT, and PfCT, osimertinib was associated with better PFS for all patients with advanced and *EGFR*-mutant NSCLC (HR = 0.62, 95% CI: 0.43–0.89; HR = 0.47, 95% CI: 0.36–0.59; HR = 0.31, 95% CI: 0.17–0.51; HR = 0.16, 95% CI: 0.10–0.24; Figure 4A). Compared with SoC + apatinib, afatinib, SoC,

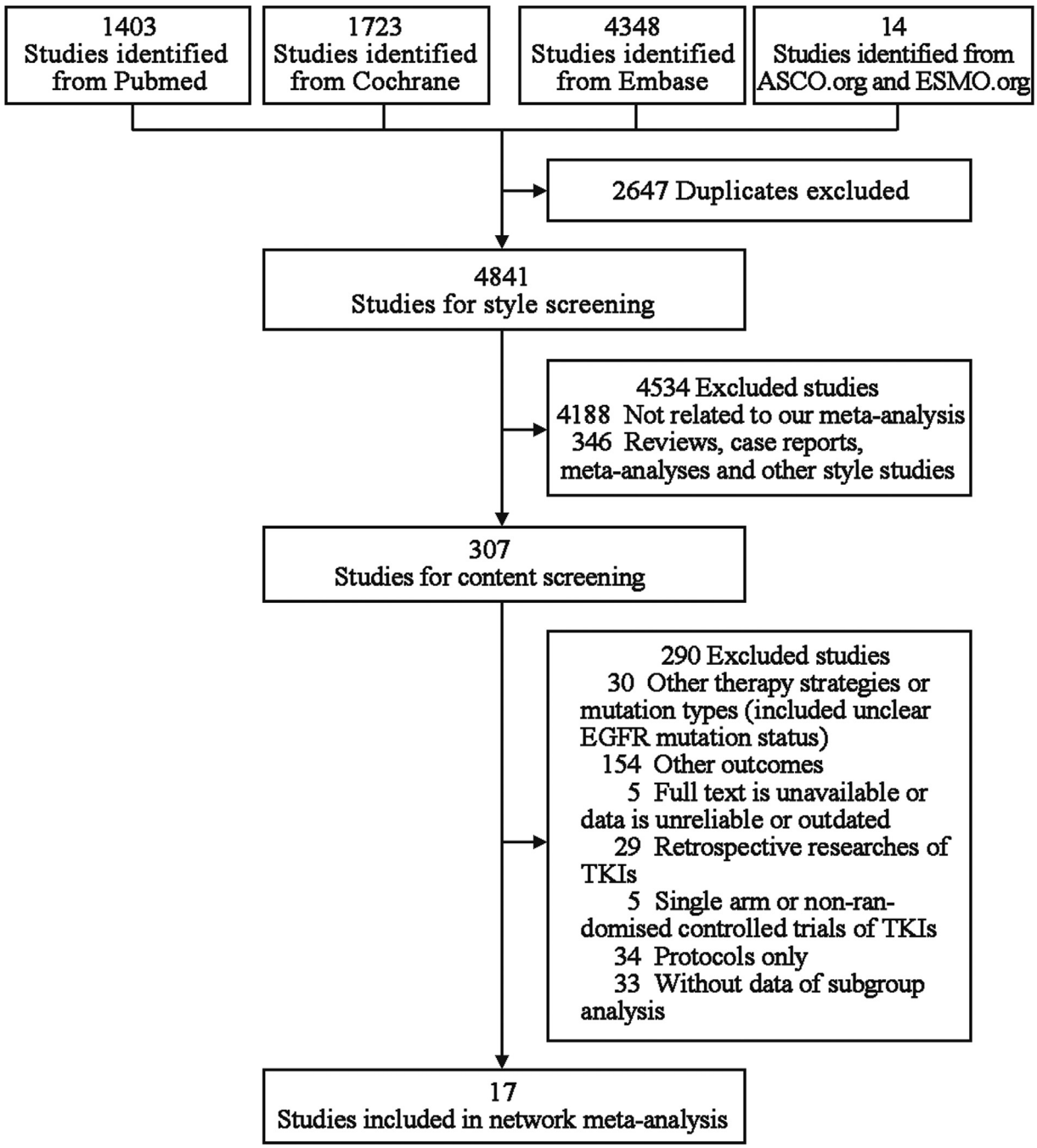

Figure 1: Flow chart of the screening, exclusion and inclusion of this study. ASCO: American Society of Clinical Oncology; ESMO: European Society for Medical Oncology; TKIs: Tyrosine kinase inhibitors.

PbCT, and PfCT, SoC + PbCT improved the PFS of all patients with advanced and *EGFR*-mutant NSCLC (HR = 0.66, 95% CI: 0.46–0.99; HR = 0.63, 95% CI: 0.44–0.87; HR = 0.47, 95% CI: 0.38–0.57; HR = 0.31, 95% CI: 0.18–0.49; HR = 0.16, 95% CI: 0.10–0.23; Figure 4A). Osimertinib + bevacizumab, aumolertinib, SoC + PbCT, osimertinib, SoC + apatinib, dacomitinib, SoC + ramucirumab, SoC + bevacizumab, and afatinib all showed superior efficacy in PFS for all advanced, *EGFR*-mutant NSCLC patients compared with SoC (HR = 0.42, 95% CI: 0.23–0.77; HR = 0.47, 95% CI: 0.35–0.62; HR = 0.47, 95% CI: 0.38–0.57; HR = 0.47, 95% CI: 0.36–0.59; HR = 0.71, 95% CI: 0.50–0.98; HR = 0.62, 95% CI: 0.47–0.82; HR = 0.64, 95% CI: 0.48–0.85; HR = 0.60, 95% CI: 0.50–0.73; HR = 0.75, 95% CI: 0.58–0.99), PbCT (HR = 0.27, 95% CI: 0.12–0.60; HR = 0.31, 95% CI: 0.17–0.52; HR = 0.31, 95% CI: 0.18–0.49; HR = 0.31, 95% CI: 0.17–0.51; HR = 0.47, 95% CI: 0.26–0.80; HR = 0.42, 95% CI: 0.24–0.68; HR = 0.43, 95% CI: 0.25–0.71; HR = 0.40, 95% CI: 0.24–0.62; HR = 0.59, 95% CI: 0.35–0.70), and PfCT (HR = 0.14, 95% CI: 0.07–0.27; HR = 0.16, 95% CI: 0.10–0.24; HR = 0.16, 95% CI: 0.10–0.23; HR = 0.16, 95% CI: 0.10–0.24; HR = 0.24, 95% CI: 0.15–0.38; HR = 0.21, 95% CI: 0.14–0.35;

Table 1: Baseline characteristics of studies included in the NMA.

Study	Region	Year (patients registration)	Phase	Clinical trial number	Sample size (*n/n*)	Median age (years)	Female (%)	Adenocarcinoma (%)	Non-smoking (%)	BM status (*n/n*)		Intervention	Control	Outcomes	
										BM	Non-BM			PFS	OS
FLAURA[16,17]	Global (multi-center)	2014–2016	III (double-blind)	NCT02296125	279/277	64/64	63.8/62.1	99/98	65.2/63.2	53/63	226/214	Osimertinib	SoC	Yes	Yes
CTONG1509[18]	China (multi-center)	2016–2017	III (open-label)	NCT02759614	157/154	57/59	61.8/62.3	100/100	NA	44/47	113/107	SoC + bevacizumab	SoC	Yes	Yes
NEJ009[19]	Japan (multi-center)	2011	III (open-label)	UMIN000006340	170/172	64.8/64.0*	67.1/62.8	99/99	56.5/56.4	50/38	120/134	SoC + PbCT	SoC	Yes	Yes
ENSURE[25]	China (multi-center)	2011–2012	III (open-label)	NCT01342965	110/107	57.5/56.0	61.8/60.7	95/94	71.8/69.2	None	110/107	SoC	PfCT	Yes	Yes
Noronha *et al*[26]	India (mono-center)	2016–2018	II (open-label)	CTRI/2016/08/007149	174/176	54/56	49.4/47.2	98/97	83.3/85.2	30/34	144/142	SoC + PbCT	SoC	Yes	No
Han *et al*[27]	China (mono-center)	2011	II (open-label)	NCT02148380	40/41	NA	62.5/56.1	100/100	67.5/65.9	8/7	32/34	SoC + PbCT	SoC	No	Yes
ARCHER1050[28]	Global (multi-center)	2013	III (open-label)	NCT01774721	227/225	62/61	64.3/55.6	NA	64.8/64.0	None	227/225	Dacomitinib	SoC	Yes	Yes
LUX-LUNG-3[29]	Global (multi-center)	2009	III (open-label)	NCT00949650	186/97	62/61†	63.9/67.0†	100/100	67.4/70.4	20/15	166/82	Afatinib	PbCT	Yes	Yes
LUX-LUNG-6[29]	East-Asia (multi-center)	2010	III (open-label)	NCT01121393	213/104	58/58†[30]	64.0/68.0†	100/100	74.8/81.1	28/18	185/86	Afatinib	PfCT	Yes	Yes
LUX-LUNG-7[31]	Global (multi-center)	2011	IIb (open-label)	NCT01466660	160/159	63/63	56.9/66.7	99/99	66.3/66.7	26/24	134/135	Afatinib	SoC	Yes	Yes
JO25567[32,33]	Japan (multi-center)	2011–2012	II (open-label)	JapicCTI-111390	75/77	67/67	60.0/66.2	99/99	56.0/58.4	None	75/77	SoC + bevacizumab	SoC	Yes	Yes
NEJ026[34–35]	Japan (multi-center)	2015–2016	III (open-label)	UMIN000017069	112/112	67/68	63.4/65.2	98/100	58.0/57.1	36/36	76/76	SoC + bevacizumab	SoC	Yes	Yes
RELAY[36]	Global (multi-center)	2016–2018	III (double-blind)	NCT02411448	224/225	65/64	62.9/63.1	96/97	59.8/61.8	None	224/225	SoC + ramucirumab	SoC	Yes	No
ACTIVE[37]	China (multi-center)	NA	III (double-blind)	NCT02824458	157/156	57/60*	58.0/60.3	NA	73.2/77.6	51/41	106/115	SoC + apatinib	SoC	Yes	No
WJOG9717L[38]	Japan (multi-center)	2018	II (open-label)	UMIN000030206	61/61	67/66*	60.7/62.3	100.0/98.4	62.3/49.2	18/23	48/33	Osimertinib + bevacizumab	Osimertinib	Yes	No
AENEAS[39]	China (multi-center)	2018–2019	III (open-label)	NCT03849768	214/215	59/62*	62.6/62.8	98.1/98.1	72.9/67.0	56/59	158/156	Aumolertinib	SoC	Yes	No
BEVERLY[40]	Italy (multi-center)	2016-2019	III (open-label)	NCT02633189	80/80	65.9/67.7	65.0/62.5	NA	57.5/46.3	None	80/80	SoC + bevacizumab	SoC	Yes	Yes

Data are expressed as intervention/control unless indicated otherwise. *Mean age. †The Median of age and the proportion of sex of different treatments came from all patients. BM: Brain metastases; EGFR: Epidermal growth factor receptor; NA: Not available; NMA: Network meta-analysis; OS: Overall survival; PbCT: Pemetrexed based chemotherapy; PfCT: Pemetrexed free chemotherapy; PFS: Progression-free survival; SoC: Standards of care, including gefitinib, erlotinib, and icotinib.

HR = 0.21, 95% CI: 0.14–0.33; HR = 0.20, 95% CI: 0.14–0.29; HR = 0.25, 95% CI: 0.18–0.35). Aumolertinib, SoC + PbCT, osimertinib, and SoC + ramucirumab showed superior efficacy in PFS for all advanced, *EGFR*-mutant NSCLC patients compared with afatinib (HR = 0.62, 95% CI: 0.41–0.90; HR = 0.63, 95% CI: 0.44–0.87; HR = 0.62, 95% CI: 0.43–0.89; HR = 0.49, 95% CI: 0.35–0.70), and SoC + PbCT showed superior efficacy than SoC + apatinib (HR = 0.66, 95% CI: 0.46–0.99). No statistical difference was observed in PFS between PbCT and SoC (HR = 1.50, 95% CI: 0.99–2.46), but both regimens showed favorable PFS compared with PfCT (SoC *vs.* PfCT, HR = 0.33, 95% CI: 0.24–0.47; PbCT *vs.* PfCT, HR = 0.50, 95% CI: 0.32–0.85). Additionally, there were no significant differences in PFS in all advanced, *EGFR*-mutant NSCLC patients treated with osimertinib + bevacizumab, aumolertinib, SoC + PbCT, or osimertinib; there were also no significant differences in SoC + apatinib, dacomitinib, SoC + ramucirumab, and SoC + bevacizumab [Figure 4A].

PFS for advanced and *EGFR*-mutant NSCLC patients with or without BM

SoC + PbCT improved PFS in patients with brain metastases compared with SoC (HR = 0.40, 95% CI: 0.17–0.95; Figure 4B). No significant differences were found among osimertinib + bevacizumab, aumolertinib, and SoC + PbCT [Figure 4B]. For patients without BM, the results were similar to the findings in all patients [Figure 4C]. Osimertinib + bevacizumab, osimertinib, aumolertinib, SoC + PbCT, dacomitinib, SoC + ramucirumab, SoC + bevacizumab, and afatinib showed superior efficacy compared with SoC (HR = 0.43, 95% CI: 0.20–0.90; HR = 0.46, 95% CI: 0.31–0.68; HR = 0.51, 95% CI: 0.34–0.77; HR = 0.50, 95% CI: 0.38–0.66; HR = 0.62, 95% CI: 0.43–0.89; HR = 0.64, 95% CI: 0.44–0.94; HR = 0.61, 95% CI: 0.48–0.76; HR = 0.71, 95% CI: 0.50–1.00), PbCT (HR = 0.29, 95% CI: 0.11–0.74; HR = 0.31, 95% CI: 0.15–0.62; HR = 0.34, 95% CI: 0.17–0.69; HR = 0.34, 95% CI: 0.18–0.64; HR = 0.42, 95% CI: 0.21–0.82; HR = 0.43, 95% CI: 0.22–0.87; HR = 0.41, 95% CI: 0.22–0.74; HR = 0.48, 95% CI: 0.31–0.75), and PfCT (HR = 0.14, 95% CI: 0.06–0.32; HR = 0.15, 95% CI: 0.09–0.26; HR = 0.17, 95% CI: 0.09–0.29; HR = 0.16, 95% CI: 0.10–0.26; HR = 0.21, 95% CI: 0.12–0.35; HR = 0.21, 95% CI: 0.12–0.39; HR = 0.20, 95% CI: 0.12–0.31; HR = 0.23, 95% CI: 0.16–0.34) in terms of PFS in patients without BM. SoC + apatinib showed relatively superior PFS in patients without BM compared with PbCT (HR = 0.44, 95% CI: 0.22–0.92) and PfCT (HR = 0.21, 95% CI: 0.12–0.39), but presented a similar effect with SoC (HR = 0.65, 95% CI: 0.42–1.03). There was no observed statistical difference in PFS in patients without BM treated with PbCT or SoC (HR = 1.49, 95% CI: 0.84–2.64), but both showed favorable PFS compared with PfCT (PfCT *vs.* SoC, HR = 3.09, 95% CI: 2.06–4.55; PbCT *vs.* PfCT, HR = 0.14, 95% CI: 0.06–0.32). In addition, no significant differences were observed among patients without BM treated with osimertinib + bevacizumab, osimertinib, aumolertinib, SoC + PbCT, SoC + apatinib, dacomitinib, SoC + ramucirumab, SoC + bevacizumab, or afatinib [Figure 4C].

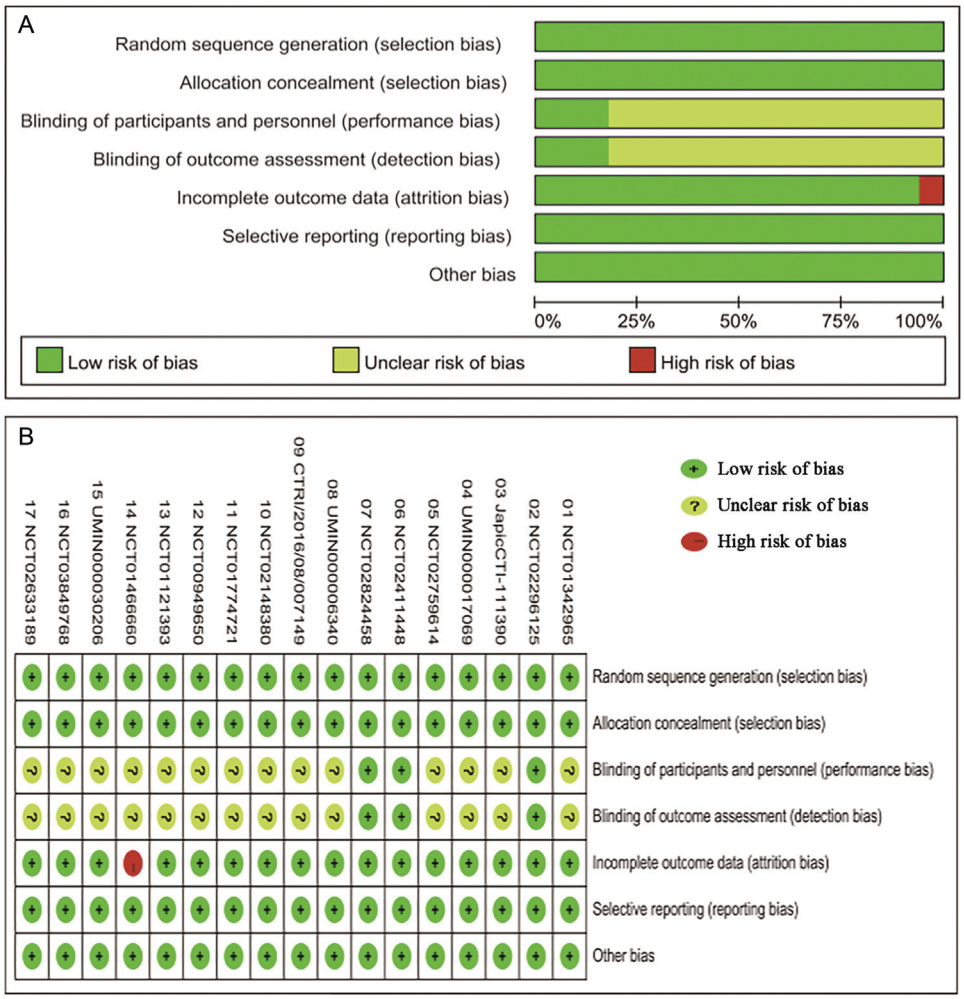

Figure 2: Risk of bias assessment for inclusion literatures by Cochrane handbook. (A) Global assessment for the risk of different kinds of bias for all trials. (B) Independent assessment of risk of bias for each trial.

OS for all advanced, *EGFR*-mutant NSCLC patients

SoC + PbCT had superior OS compared with SoC (HR = 0.61, 95% CI: 0.43–0.84) and PfCT (HR = 0.57, 95% CI: 0.33–0.91), and SoC + bevacizumab had superior OS compared with SoC (HR = 0.69, 95% CI: 0.55–0.89) [Figure 4D]. There were not significant differences in others treatments.

OS for advanced and *EGFR*-mutant NSCLC patients with or without BM

For patients with BM, no significant differences in OS were found among all treatments [Figure 4E]. For patients without BM, SoC + PbCT (HR = 0.64, 95% CI: 0.36–1.14) and SoC + bevacizumab (HR = 0.70, 95% CI: 0.47–1.09) seemed to have a trend of benefit for OS compared with SoC, but no significant differences were found for other treatments [Figure 4F].

Ranking of treatment regimens

Bayesian ranking profiles of all evaluated treatment regimens in different populations are shown in Figure 5. In terms of PFS, both in all patients and patients without BM, osimertinib + bevacizumab was most likely to rank the first, with cumulative probabilities of 51.2% and 47.1%, respectively. For those with BM, osimertinib + bevacizumab ranked the first for PFS, with a cumulative probability of 34.5%, followed by aumolertinib, with a cumulative probability of 28.3%. For OS, in all patients and patients with or without BM, SoC + PbCT was most likely to rank the first, with cumulative probabilities of 58.4%, 46.8%, and 37.3%, respectively.

Heterogeneity and inconsistency assessment

Most comparisons from one or two studies, minor heterogeneities could be found. However, high heterogeneities could be found from the comparisons between PfCT and afatinib (51.90%) for PFS in all patients, and SoC + bevacizumab and SoC for PFS in patients with brain metastases (60.60%). The fit of the consistency model was used in the analysis due to the superiority of lower DIC than that from the inconsistency model. Differences between the consistency model and the inconsistency model were accepted (less than 5 [Supplementary Table 2, http://links.lww.com/CM9/B524]). No significant differences

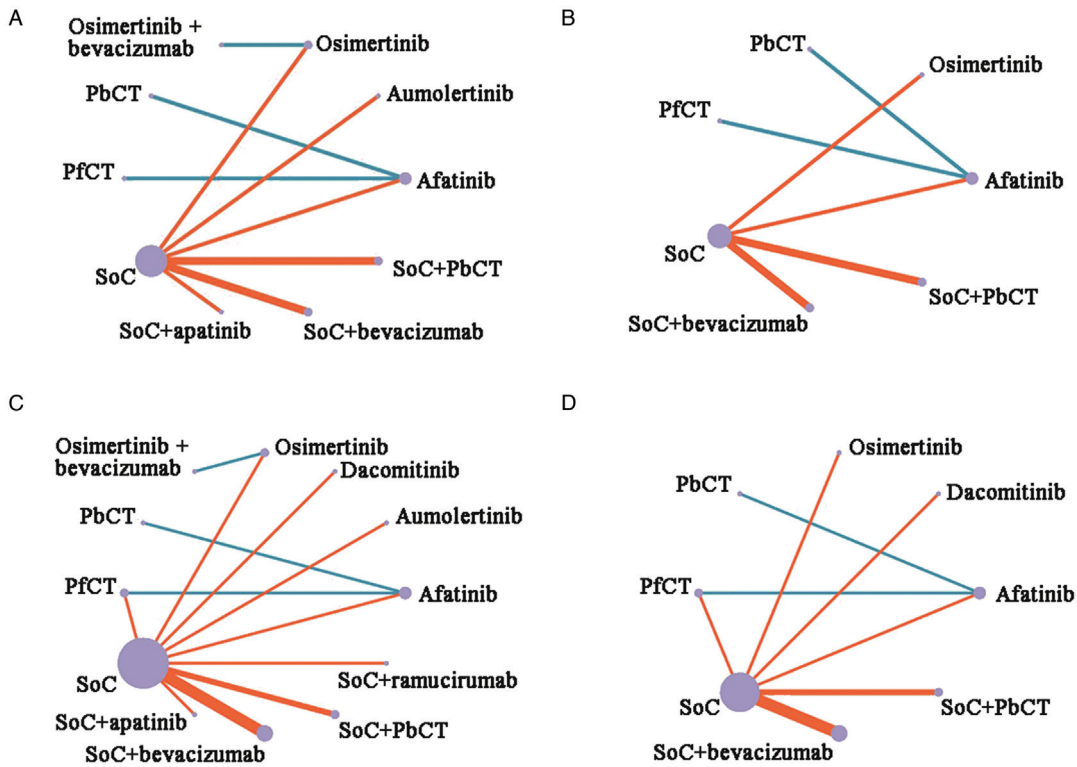

Figure 3: Network diagrams of comparisons on different outcomes of treatments in advanced, *EGFR*-mutant NSCLC patients according to the BM statuses. (A) Comparisons for PFS in patients with BM. (B) Comparisons for OS in patients with BM. (C) Comparisons for PFS in patients without BM. (D) Comparisons for OS in patients without BM. The size of the nodes relates to the number of participants in that intervention type, and the thickness of lines between the interventions relates to the number of studies for that comparison. Red lines indicate the original comparisons are available and blue lines indicate the original comparisons are not available. BM: Brain metastases; EGFR: Epidermal growth factor receptor; NSCLC: Non-small cell lung cancer; OS: Overall survival; PbCT: Pemetrexed based chemotherapy; PfCT: Pemetrexed free chemotherapy; PFS: Progression-free survival; SoC: Standards of care, including gefitinib, erlotinib, and icotinib.

were found between direct and indirect estimates for any outcome ($P > 0.05$) [Supplementary Table 3, http://links.lww.com/CM9/B524].

Discussion

The brain is a common metastatic site in patients with NSCLC, resulting in a relatively poor prognosis.[41] Despite the rapid development of treatment agents—EGFR-TKIs for NSCLC, their efficacy is poorer in advanced, *EGFR*-mutant, BM NSCLC patients than in those without BM.[42] Patients with *EGFR*-mutated NSCLC are prone to develop BM, and the medical demands for patients with BM are largely unmet. Therefore, the status of BM should be considered in clinical practice while selecting the optimal treatment. A few NMAs have drawn conclusions regarding the optimal therapy in *EGFR*-mutated NSCLC, but no data have indicated the preferable approach for BM patients.[43] Additionally, some combined regimens of osimertinib + bevacizumab, first-generation EGFR-TKIs with antiangiogenic drugs or chemotherapy were not included into analysis,[44] and OS data from the FLAURA, JO25567, and NEJ026 studies and updated results from the CTONG 1509, RELAY, ACTIVE, AENEAS, and WJOG9717L studies were not included in previously NMAs.[43,44] Thus, we performed a NMA to investigate the survival outcomes of advanced *EGFR*-mutated NSCLC patients with different BM statuses and therapeutic regimens to identify the optimal therapeutic strategy. To our knowledge, this meta-analysis included the largest sample size to date and involved mostly current regimens to evaluate the optimal therapy for *EGFR*-mutated NSCLC patients with BM. Furthermore, this NMA identified the optimal EGFR-TKI regimen for non-BM, NSCLC patients.

A previous study showed that osimertinib has superior efficacy and decreases the risk of intracranial progression compared with standard EGFR-TKIs in NSCLC patients with BM.[45] Our study suggests that osimertinib + bevacizumab ranked the first for PFS, and SoC + PbCT ranks the first for OS in them. Due to immaturity of OS data, the OS comparison among osimertinib + bevacizumab, aumolertinib, and osimertinib was lacking. Previous studies demonstrated that bevacizumab was beneficial for patients with BM,[46-48] our results suggested that osimertinib + bevacizumab was related to the most favorable PFS for those with BM compared with others treatments. However, previous studies observed a shorter PFS with osimertinib plus bevacizumab than osimertinib alone in patients with *EGFR* T790M-mutated NSCLC,[49] and failed to show the efficacy of osimertinib plus bevacizumab for improving PFS in untreated patiens with *EGFR*-mutated NSCLC. Further researches were needed to explore the potential population, who can benefit from the regiment of osimertinib plus bevacizumab. Our OS results were consistent with a previous study, in which

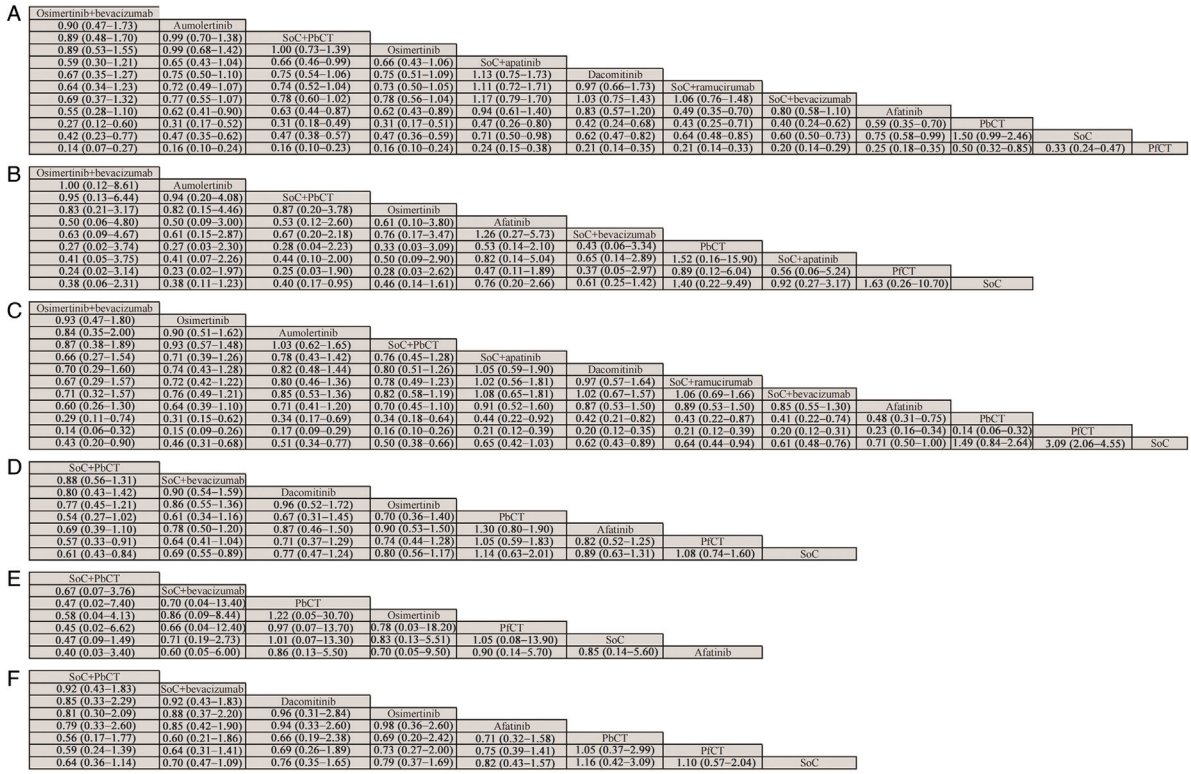

Figure 4: HRs and its 95% confidence intervals from network meta–analysis of different therapeutic regimens in advanced, *EGFR* mutation NSCLC patients. Data in each cell are HRs (95% confidence intervals) for the comparison of row-defining treatment *vs.* column-defining treatment. (A) Pooled HRs for PFS in all patients. (B) Pooled HRs for PFS in patients with BM. (C) Pooled HRs for PFS in patients without BM. (D) Pooled HRs for OS in all patients. (E) Pooled HRs for OS in patients with BM. (F) Pooled HRs for OS in patients without BM. Significant results are in bold. BM: Brain metastases; EGFR: Epidermal growth factor receptor; HR: Hazard ratio; NMA: Network meta–analysis; NSCLC: Non-small cell lung cancer; OS: Overall survival; PbCT: Pemetrexed based chemotherapy; PfCT: Pemetrexed free chemotherapy; PFS: Progression-free survival; SoC: Standards of care, including gefitinib, erlotinib, and icotinib.

gefitinib + PbCT was related to the most favorable PFS and OS compared with other therapies in *EGFR*-mutated NSCLC patients with BM.[21] The reason is not completely clear, and an explanation is possible that the combination of SoC and PbCT has a synergistic effect. A previous study indicated that gefitinib combined with pemetrexed enhanced cell growth inhibition, increased cell death, and prevented gefitinib resistance in *EGFR* exon 19 deletion NSCLC cell lines.[50] A previous study showed that pemetrexed-cisplatin regimen was also effective and well-tolerated as a first-line therapy for NSCLC patients with BM, with an intracranial ORR and PFS of 41.9% and 4.0 months, respectively.[51] Therefore, it was rational to deduce that EGFR-TKI plus pemetrexed-based chemotherapy showed more favorable efficacy for *EGFR*-mutated NSCLC patients with BM compared with EGFR-TKI therapy alone (especially first-generation EGFR-TKIs). As direct comparisons between EGFR-TKI plus chemotherapy and osimertinib were limited, our results need to be further validated.

Moreover, we explored different treatments in patients without BM. Osimertinib + bevacizumab was most likely ranked the best in terms of PFS, and SoC + PbCT might be ranked the first in OS. Since the OS data of osimertinib + bevacizumab and aumolertinib were immature, the OS results did not include them. In addition, several studies have confirmed that EGFR-TKIs are better than chemotherapy as a first-line therapy regimen in advanced *EGFR*-mutated NSCLC patients.[52-56] However, in this study, no significant difference was found between PbCT and SoC in NSCLC patients without BM.

Previous NMA[43] compared current first-line treatment regimens in advanced *EGFR*-mutated NSCLC patients and indicated that gefitinib combined with pemetrexed-based chemotherapy and osimertinib alone were associated with the most favorable PFS and OS. When including the regimens of osimertinib + bevacizumab and aumolertinib, data from our study suggested that osimertinib + bevacizumab is the optimal treatment regimen for PFS in advanced *EGFR*-mutated NSCLC patients, SoC + PbCT is still the optimal treatment regimen for OS, and no significant differences are found between SoC + PbCT and osimertinib.

Our study has some limitations. First, all available data in this study were extracted from subgroups of RCTs, which easily leads to a risk of bias. Second, adverse events were not available for analysis in this study because they are mostly available in general populations instead of subgroups. Third, there were some patients who accepted radiotherapy before systemic therapy, which may affect the results. Fourth, there was not further stratified analysis based on *EGFR* mutation types to explore the optimal first-line therapeutic schedule, limited by the number of studies included. The subgroup analysis in the BRAIN study suggested that patients with *EGFR* 19 deletion were more likely to benefit from EGFR-TKIs.[14] The median BM-related PFS in patients with *EGFR* 19 deletion

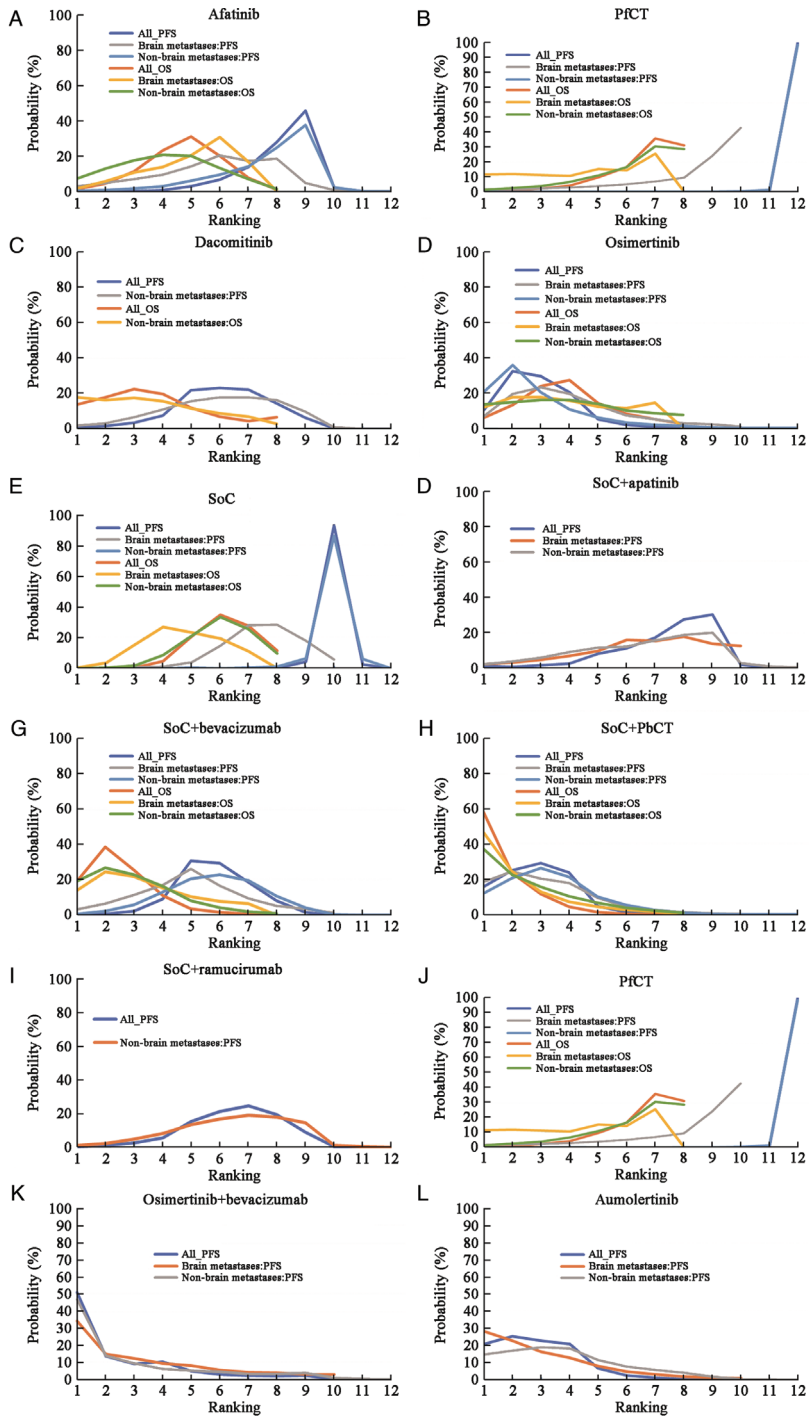

Figure 5: Bayesian ranking profiles of comparable treatments on efficacy for *EGFR*-mutated NSCLC patients with or without brain metastases. Profiles indicate the probability of each comparable treatment being ranked from first to last on PFS and OS in all, brain metastases and non-brain metastases patients. (A) The ranking of afatinib for PFS and OS in all, brain metastases and non-brain metastases patients. (B) The ranking of PbCT for PFS and OS in all, brain metastases and non-brain metastases patients. (C) The ranking for dacomitinib on PFS and OS in all and non-brain metastases patients. (D) The ranking of osimertinib for PFS and OS in all, brain metastases and non-brain metastases patients. (E) The ranking of SoC for PFS and OS in all, brain metastases and non-brain metastases patients. (F) The ranking of SoC+apatinib for PFS in all, brain metastases and non-brain metastases patients. (G) The ranking of SoC+bevacizumab for PFS and OS in all, brain metastases and non-brain metastases patients. (H) The ranking of SoC+PbCT for PFS and OS in all, brain metastases and non-brain metastases patients. (I) The ranking of SoC+ramucirumab for PFS in all and non-brain metastases patients. (J) The ranking of PfCT for PFS and OS in all, brain metastases and non-brain metastases patients. (K) The ranking of osimertinib+bevacizumab for PFS in all, brain metastases, and non-brain metastases patients. (L) The ranking of aumolertinib for PFS in all, brain metastases, and non-brain metastases patients. EGFR: Epidermal growth factor receptor; NSCLC: Non-small cell lung cancer; OS: Overall survival; PbCT: pemetrexed based chemotherapy; PfCT: pemetrexed free chemotherapy; PFS: Progression-free survival; SoC: Standards of care, including gefitinib, erlotinib, and icotinib.

mutation was significantly better than that in patients with L858R mutation (31.8 months *vs.* 8.3 months, $P = 0.03$) among NSCLC patients with *EGFR* mutation and BM, who were treated with osimertinib.[57] Therefore, it is necessary to distinguish different *EGFR* mutation types. In addition, there were heterogeneities in our analysis to some extent, which are caused by the differences in patient characteristics, the limited number of included RCTs,

healthcare systems, and research backgrounds. Thus, we applied a random-effects consistency model to guarantee robustness. Finally, the subsequent therapy of patients was not taken into account in analysis, which would considerably affect the OS.

To summarize, first-line treatments based on different BM statuses need to be considered in practice for advanced *EGFR*-mutated NSCLC patients. Osimertinib + bevacizumab is probably related to the most favorable PFS in advanced *EGFR*-mutated NSCLC patients with or without BM. For OS, SoC + PbCT is still most likely to be the preferable regimen regardless of BM status. The combination therapy may be more effective than monotherapy, and osimertinib combined with bevacizumab or chemotherapy is possible to be a new strategy in the future for some subgroups.

Conflicts of interest

None.

References

1. Nishino M, Soejima K, Mitsudomi T. Brain metastases in oncogene-driven non-small cell lung cancer. Transl Lung Cancer Res 2019;8:S298–S307. doi: 10.21037/tlcr.2019.05.15.
2. Venur VA, Karivedu V, Ahluwalia MS. Systemic therapy for brain metastases. Handb Clin Neurol 2018;149:137–153. doi: 10.1016/B978-0-12-811161-1.00011-6.
3. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, *et al*. International association for the study of lung cancer/American thoracic society/European respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6:244–285. doi: 10.1097/JTO.0b013e318206a221.
4. Ernani V, Stinchcombe TE. Management of brain metastases in non-small-cell lung cancer. J Oncol Pract 2019;15:563–570. doi: 10.1200/JOP.19.00357.
5. Shi Y, Au JS, Thongprasert S, Srinivasan S, Tsai CM, Khoa MT, *et al*. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). J Thorac Oncol 2014;9:154–162. doi: 10.1097/JTO.0000000000000033.
6. Barlesi F, Mazieres J, Merlio JP, Debieuvre D, Mosser J, Lena H, *et al*. Routine molecular profiling of patients with advanced non-small-cell lung cancer: Results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT). Lancet 2016;387:1415–1426. doi: 10.1016/S0140-6736(16)00004-0.
7. Rosell R, Moran T, Queralt C, Porta R, Cardenal F, Camps C, *et al*. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med 2009;361:958–967. doi: 10.1056/NEJMoa0904554.
8. Moravan MJ, Fecci PE, Anders CK, Clarke JM, Salama AKS, Adamson JD, *et al*. Current multidisciplinary management of brain metastases. Cancer 2020;126:1390–1406. doi: 10.1002/cncr.32714.
9. Greenhalgh J, Dwan K, Boland A, Bates V, Vecchio F, Dundar Y, *et al*. First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer. Cochrane Database Syst Rev 2016;5:CD010383. doi: 10.1002/14651858.CD010383.pub2.
10. Ettinger DS, Wood DE, Aggarwal C, Aisner DL, Akerley W, Bauman JR, *et al*. NCCN guidelines insights: non-small cell lung cancer, version 1.2020. J Natl Compr Canc Netw 2019;17:1464–1472. doi: 10.6004/jnccn.2019.0059.
11. Wu SG, Shih JY. Management of acquired resistance to EGFR TKI-targeted therapy in advanced non-small cell lung cancer. Mol Cancer 2018;17:38. doi: 10.1186/s12943-018-0777-1.
12. Zhang Z, Guo H, Lu Y, Hao W, Han L. Anaplastic lymphoma kinase inhibitors in non-small cell lung cancer patients with brain metastases: a meta-analysis. J Thorac Dis 2019;11:1397–1409. doi: 10.21037/jtd.2019.03.76.
13. Cheng H, Perez-Soler R. Leptomeningeal metastases in non-small-cell lung cancer. Lancet Oncol 2018;19:e43–e55. doi: 10.1016/S1470-2045(17)30689-7.
14. Yang JJ, Zhou C, Huang Y, Feng J, Lu S, Song Y, *et al*. Icotinib versus whole-brain irradiation in patients with EGFR-mutant non-small-cell lung cancer and multiple brain metastases (BRAIN): a multicentre, phase 3, open-label, parallel, randomised controlled trial. Lancet Respir Med 2017;5:707–716. doi: 10.1016/S2213-2600(17)30262-X.
15. Ballard P, Yates JW, Yang Z, Kim DW, Yang JC, Cantarini M, *et al*. Preclinical comparison of osimertinib with other EGFR-TKIs in EGFR-mutant NSCLC brain metastases models, and early evidence of clinical brain metastases activity. Clin Cancer Res 2016;22:5130–5140. doi: 10.1158/1078-0432.CCR-16-0399.
16. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, *et al*. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 2018;378:113–125. doi: 10.1056/NEJMoa1713137.
17. Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, *et al*. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. N Engl J Med 2020;382:41–50. doi: 10.1056/NEJMoa1913662.
18. Zhou Q, Xu CR, Cheng Y, Liu YP, Chen GY, Cui JW, *et al*. Bevacizumab plus erlotinib in Chinese patients with untreated, EGFR-mutated, advanced NSCLC (ARTEMIS-CTONG1509): a multicenter phase 3 study. Cancer Cell 2021;39:1279–1291.e3. doi: 10.1016/j.ccell.2021.07.005.
19. Hosomi Y, Morita S, Sugawara S, Kato T, Fukuhara T, Gemma A, *et al*. Gefitinib alone versus gefitinib plus chemotherapy for non-small-cell lung cancer with mutated epidermal growth factor receptor: NEJ009 study. J Clin Oncol 2020;38:115–123. doi: 10.1200/JCO.19.01488.
20. Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, *et al*. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 1. Value Health 2011;14:417–428. doi: 10.1016/j.jval.2011.04.002.
21. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. PLoS One 2013;8:e76654. doi: 10.1371/journal.pone.0076654.
22. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–560. doi: 10.1136/bmj.327.7414.557.
23. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med 2004;23:3105–3124. doi: 10.1002/sim.1875.
24. Brooks SP, Gelman A. General methods for monitoring convergence of iterative simulations. J Comput Graph Stat 1998;7:434–455. doi: 10.2307/1390675.
25. Wu YL, Zhou C, Liam CK, Wu G, Liu X, Zhong Z, *et al*. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. Ann Oncol 2015;26:1883–1889. doi: 10.1093/annonc/mdv270.
26. Noronha V, Patil VM, Joshi A, Menon N, Chougule A, Mahajan A, *et al*. Gefitinib versus gefitinib plus pemetrexed and carboplatin chemotherapy in EGFR-mutated lung cancer. J Clin Oncol 2020;38:124–136. doi: 10.1200/JCO.19.01154.
27. Han B, Jin B, Chu T, Niu Y, Dong Y, Xu J, *et al*. Combination of chemotherapy and gefitinib as first-line treatment for patients with advanced lung adenocarcinoma and sensitive EGFR mutations: a randomized controlled trial. Int J Cancer 2017;141:1249–1256. doi: 10.1002/ijc.30806.
28. Mok TS, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, *et al*. Improvement in overall survival in a randomized study that compared dacomitinib with gefitinib in patients with advanced non-small-cell lung cancer and EGFR-activating mutations. J Clin Oncol 2018;36:2244–2250. doi: 10.1200/JCO.2018.78.7994.
29. Schuler M, Wu YL, Hirsh V, O'Byrne K, Yamamoto N, Mok T, *et al*. First-line afatinib versus chemotherapy in patients with non-small cell lung cancer and common epidermal growth factor receptor gene mutations and brain metastases. J Thorac Oncol 2016;11:380–390. doi: 10.1016/j.jtho.2015.11.014.
30. Yang JC, Wu YL, Schuler M, Sebastian M, Popat S, Yamamoto N, *et al*. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and

LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol 2015;16:141–151. doi: 10.1016/S1470-2045(14)71173-8.
31. Park K, Tan EH, O'Byrne K, Zhang L, Boyer M, Mok T, *et al*. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol 2016;17:577–589. doi: 10.1016/S1470-2045(16)30033-X.
32. Seto T, Kato T, Nishio M, Goto K, Atagi S, Hosomi Y, *et al*. Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study. Lancet Oncol 2014;15:1236–1244. doi: 10.1016/S1470-2045(14)70381-X.
33. Yamamoto N, Seto T, Nishio M, Goto K, Okamoto I, Yamanaka T, *et al*. Erlotinib plus bevacizumab (EB) versus erlotinib alone (E) as first-line treatment for advanced EGFR mutation–positive non-squamous non–small-cell lung cancer (NSCLC): survival follow-up results of JO25567. J Clin Oncol 2018;36 (15_suppl):9007. doi: 10.1200/JCO.2018.36.15_suppl.9007.
34. Saito H, Fukuhara T, Furuya N, Watanabe K, Sugawara S, Iwasawa S, *et al*. Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-positive advanced non-squamous non-small-cell lung cancer (NEJ026): interim analysis of an open-label, randomised, multicentre, phase 3 trial. Lancet Oncol 2019;20:625–635. doi: 10.1016/S1470-2045(19)30035-X.
35. Maemondo M, Fukuhara T, Saito H, Furuya N, Kobayashi K. NEJ026: final overall survival analysis of bevacizumab plus erlotinib treatment for NSCLC patients harboring activating EGFR-mutations. J Clin Oncol 2020;38 (15_suppl):9506. doi: 10.1200/JCO.2020.38.15_suppl.9506.
36. Nakagawa K, Garon EB, Seto T, Nishio M, Ponce Aix S, Paz-Ares L, *et al*. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20:1655–1669. doi: 10.1016/S1470-2045(19)30634-5.
37. Zhang L, Zhao H, Zhang Z, Yao W, Min X, Gu K, *et al*. LBA50 ACTIVE: Apatinib plus gefitinib versus placebo plus gefitinib as first-line treatment for advanced epidermal growth factor receptor-mutant (EGFRm) non-small-cell lung cancer (NSCLC): a multicentered, randomized, double-blind, placebo-controlled phase III trial (CTONG1706). Ann Oncol 2020;31 (Suppl 4):S1181. doi: 10.1016/j.annonc.2020.08.2283.
38. Kenmotsu H, Wakuda K, Mori K, Kato T, Sugawara S, Kirita K, *et al*. LBA44 - primary results of a randomized phase II study of osimertinib plus bevacizumab versus osimertinib monotherapy for untreated patients with non-squamous non-small cell lung cancer harboring EGFR mutations: WJOG9717L study. Ann Oncol 2021;32 (Suppl 5):S1283–S1346. doi:10.1016/annonc/annonc741.
39. Lu S, Dong XR, Jian H, Chen JH, Chen GY, Sun YP, *et al*. Randomized phase III trial of aumolertinib (HS-10296, Au) versus gefitinib (G) as first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) and EGFR exon 19 del or L858R mutations (EGFRm). Ann Oncol 2021;39 (Supplement 5):9013. doi: 10.1200/JCO.2021.39.15_suppl.9013.
40. Piccirillo MC, Bonanno L, Garassino MCC, Dazzi C, Cavanna L, Esposito G, *et al*. 1207O Bevacizumab + erlotinib vs erlotinib alone as first-line treatment of pts with EGFR mutated advanced non squamous NSCLC: final analysis of the multicenter, randomized, phase III BEVERLY trial. Ann Oncol 2021;32 (Supplement 5): S950. doi:10.1016/annonc/annonc729.
41. Adamo V, Franchina T, Adamo B, Scandurra G, Scimone A. Brain metastases in patients with non-small cell lung cancer: focus on the role of chemotherapy. Ann Oncol 2006;17 (Suppl 2):ii73–ii75. doi: 10.1093/annonc/mdj930.
42. Li C, Nie W, Guo J, Xiong A, Zhong H, Chu T, *et al*. Osimertinib alone as second-line treatment for brain metastases (BM) control may be more limited than for non-BM in advanced NSCLC patients with an acquired EGFR T790 M mutation. Respir Res 2021;22:145. doi: 10.1186/s12931-021-01741-9.
43. Zhao Y, Liu J, Cai X, Pan Z, Liu J, Yin W, *et al*. Efficacy and safety of first line treatments for patients with advanced epidermal growth factor receptor mutated, non-small cell lung cancer: systematic review and network meta-analysis. BMJ 2019;367:l5460. doi: 10.1136/bmj.l5460.
44. Dai L, Luo CY, Hu GX, Chen G, Wu CX, Yin J, *et al*. Comparative analysis of first-line treatment regimens for advanced EGFR-mutant non-small cell lung cancer patients with stable brain metastases. Ann Palliat Med 2020;9:2062–2071. doi: 10.21037/apm-20-1136.
45. Reungwetwattana T, Nakagawa K, Cho BC, Cobo M, Cho EK, Bertolini A, *et al*. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. J Clin Oncol 2018;36:3290–3297. doi: 10.1200/JCO.2018.78.3118.
46. Jiang T, Zhang Y, Li X, Zhao C, Chen X, Su C, *et al*. EGFR-TKIs plus bevacizumab demonstrated survival benefit than EGFR-TKIs alone in patients with EGFR-mutant NSCLC and multiple brain metastases. Eur J Cancer 2019;121:98–108. doi: 10.1016/j.ejca.2019.08.021.
47. Feng PH, Chen KY, Huang YC, Luo CS, Wu SM, Chen TT, *et al*. Bevacizumab reduces S100A9-positive MDSCs linked to intracranial control in patients with EGFR-mutant lung adenocarcinoma. J Thorac Oncol 2018;13:958–967. doi: 10.1016/j.jtho.2018.03.032.
48. Chikaishi Y, Kanayama M, Taira A, Nabe Y, Shinohara S, Kuwata T, *et al*. Effect of erlotinib plus bevacizumab on brain metastases in patients with non-small cell lung cancer. Ann Transl Med 2018;6:401. doi: 10.21037/atm.2018.09.33.
49. Toi Y, Hayashi H, Fujimoto D, Tachihara M, Furuyu N, Otani S, *et al*. A randomized phase II study of osimertinib with or without bevacizumab in advanced lung adenocarcinoma patients with EGFR T790 M mutation (West Japan Oncology Group 8715L). Ann Oncol 2020;31:S813–S814. doi: 10.1016/j.annonc.2020.08.1573.
50. La Monica S, Madeddu D, Tiseo M, Vivo V, Galetti M, Cretella D, *et al*. Combination of gefitinib and pemetrexed prevents the acquisition of TKI resistance in NSCLC cell lines carrying EGFR-activating mutation. J Thorac Oncol 2016;11:1051–1063. doi: 10.1016/j.jtho.2016.03.006.
51. Barlesi F, Gervais R, Lena H, Hureaux J, Berard H, Paillotin D, *et al*. Pemetrexed and cisplatin as first-line chemotherapy for advanced non-small-cell lung cancer (NSCLC) with asymptomatic inoperable brain metastases: a multicenter phase II trial (GFPC 07-01). Ann Oncol 2011;22:2466–2470. doi: 10.1093/annonc/mdr003.
52. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, *et al*. 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 2010;11:121–128. doi: 10.1016/S1470-2045(09)70364-X.
53. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, *et al*. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380–2388. doi: 10.1056/NEJMoa0909530.
54. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, *et al*. 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 2011;12:735–742. doi: 10.1016/S1470-2045(11)70184-X.
55. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, *et al*. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327–3334. doi: 10.1200/JCO.2012.44.2806.
56. Shi YK, Wang L, Han BH, Li W, Yu P, Liu YP, *et al*. First-line icotinib versus cisplatin/pemetrexed plus pemetrexed maintenance therapy for patients with advanced EGFR mutation-positive lung adenocarcinoma (CONVINCE): a phase 3, open-label, randomized study. Ann Oncol 2017;28:2443–2450. doi: 10.1093/annonc/mdx359.
57. Yamaguchi H, Wakuda K, Fukuda M, Kenmotsu H, Mukae H, Ito K, *et al*. A phase II study of osimertinib for radiotherapy-naive central nervous system metastasis from NSCLC: results for the T790 M cohort of the OCEAN study (LOGIK1603/WJOG9116L). J Thorac Oncol 2021;16:2121–2132. doi: 10.1016/j.jtho.2021.07.026.

How to cite this article: Zhu Y, Liu C, Xu Z, Zou Z, Xie T, Xing P, Wang L, Li J. Front-line therapy for brain metastases and non-brain metastases in advanced epidermal growth factor receptor-mutated non-small cell lung cancer: a network meta-analysis. Chin Med J 2023;136:2551–2561. doi: 10.1097/CM9.0000000000002468