



Comparative analysis of first-line treatment regimens for advanced EGFR-mutant non-small cell lung cancer patients with stable brain metastases

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Background: To compare the survival outcomes of first-line treatment regimens for advanced epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) patients with stable brain metastases.

Methods: We conducted a systematic review of available data from randomized controlled trials (RCTs) of first-line treatment regimens of NSCLC patients with stable brain metastases. Progression free survival (PFS) and overall survival (OS) were extracted and analysed from the RCT subgroups. A network meta-analysis was constructed using the Bayesian statistical model to synthesize the survival outcomes of all the treatments.

Results: The analysis included 6 eligible RCT subgroups with 417 patients and 7 treatment regimens: osimertinib, afatinib, first-generation EGFR-TKI (gefitinib or erlotinib), erlotinib + bevacizumab, gefitinib + pemetrexed + carboplatin, gemcitabine + cisplatin, and pemetrexed + cisplatin. Of these seven treatment regimens, gefitinib + pemetrexed + carboplatin had the highest potential for favorable PFS and OS, followed by osimertinib, in the treatment of advanced EGFR-mutant NSCLC patients with stable brain metastases. None of the results met the predetermined statistical significance of $P < 0.05$.

Conclusions: The regimens of "Gefitinib + pemetrexed + carboplatin" and "Osimertinib" were associated with the most favorable PFS and OS compared to the other therapies in advanced EGFR-mutant NSCLC patients with stable brain metastases, although the difference between these regimens and the others was not statistically significantly different.

Keywords: Epidermal growth factor receptor (EGFR); brain metastases; combination treatments; network meta-analysis; progression free survival; overall survival (OS)

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Introduction

Lung cancer has the highest incidence and mortality rate of any cancer worldwide (1). Non-small cell lung cancer (NSCLC) comprises approximately 85% of all lung cancer cases (2). Epidermal growth factor receptor (EGFR) gene mutations are carried by around 50% of NSCLC patients in East Asian countries (3) and about 10–15% of the Caucasian NSCLC patients (4). EGFR mutations are more commonly found in women, East Asians, adenocarcinoma patients, and people who have never smoked (5). Interestingly, for advanced EGFR-mutant NSCLC patients, EGFR tyrosine kinase inhibitor (TKIs) therapy, rather than chemotherapy, is preferred (6). There are a number of different generations of EGFR-TKIs. First-generation EGFR-TKIs include erlotinib, gefitinib, and icotinib (which was made in China) (7), while dacomitinib and afatinib are second-generation EGFR-TKIs. Meanwhile, third-generation EGFR-TKIs include osimertinib, which has been used as a first-line anti-NSCLC therapy. Furthermore, EGFR-TKIs have been used in combination with other treatments (chemotherapy, monoclonal antibodies, and immunotherapy) as first-line treatment to improve efficacy and curb drug resistance (8).

Brain metastasis is one of the leading causes of lung cancer mortality (9). Of NSCLC patients, 20% have brain metastases at diagnosis, and approximately 25–50% of patients develop metastasis during the course of their disease (10). The blood-brain barrier protects the central nervous system and restricts drug access, which makes NSCLC patients with brain metastases a special group (11). The main treatments for NSCLC with brain metastases are local therapy (WBRT (whole brain radiation therapy), SRS (stereotactic radiotherapy), surgery), and systemic therapy (chemotherapy, gene target therapy, immunotherapy and combination therapy). For symptomatic/uncontrolled and stable brain metastases, local and systemic therapy are the recommended first-line treatments, respectively (7,12). Stable brain metastases refers to clinically asymptomatic and controlled brain metastases [defined in (randomized controlled trials) RCTs as metastases that are asymptomatic and/or do not require treatment with anticonvulsants or steroids and/or no leptomeningeal disease, and/or symptomatic/uncontrolled metastases that remained stable for at least four weeks after local brain radiotherapy or surgery prior to randomization]. For EGFR-mutant NSCLC patients with stable brain metastases, first-line options include osimertinib, gefitinib, erlotinib, afatinib, or a combination regimen (erlotinib + bevacizumab or

gefitinib + pemetrexed + carboplatin). Previous study has performed preclinical comparison of osimertinib with other EGFR-TKIs in EGFR-mutant NSCLC brain metastases models, and early evidence of clinical brain metastases activity (13); previous network meta-analysis has compared all first-line treatments for patients with advanced EGFR-mutant NSCLC (14); however, data comparing the survival outcomes of the current first-line treatments in EGFR-mutant NSCLC patients with stable brain metastases is limited.

We conducted a network meta-analysis of RCTs to provide insight into the relative survival outcomes of first-line treatments for EGFR-mutant NSCLC patients with stable brain metastases. We present the following article in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/apm-20-1136>).

Methods

Data sources and search strategy

We conducted our study based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension (15). In brief, we performed a systematic search of the PubMed, EMBASE, Cochrane Library, and ClinicalTrials.gov databases for relevant articles up to 25 November, 2019. There were no language restrictions. In addition, supplementary searches of conference proceedings of the American Society of Clinical Oncology, European Society of Medical Oncology, European Cancer Conference, and World Conference on Lung Cancer from between 2014 and 2019 were also carried out. The search took into account both Medical Subject Headings (MeSH) and text words, using the main search terms “NSCLC” and “EGFR”, and was limited to “RCT”. The full search strategy is provided in the *Table S1*.

Study selection

The titles and abstracts of all the studies that were initially returned were screened, and the full papers of studies were assessed for final selection.

We included phase II/III randomised controlled trials that met the following criteria: (I) studies that enrolled patients with histologically or cytologically confirmed advanced (stage III/IV/recurrent) NSCLC harboring activating EGFR mutations, including Leu858Arg, exon 19 deletions, and others, were included for analysis. (II)

We also included studies that compared two or more first-line treatments in patients with advanced EGFR-mutant NSCLC. (III) Studies that enrolled and performed subgroup analysis of patients with brain metastases. (IV) Studies that reported either progression-free survival (PFS) or overall survival (OS).

We excluded studies not adhering to the inclusion criteria. Other exclusion criteria were: (I) studies that enrolled patients with symptomatic/uncontrolled brain metastases were excluded. (II) Patients who received treatments other than those approved by any food and drug administration were excluded. (III) Studies that did not report hazard ratio (HR) were also excluded.

Data extraction and quality assessment

We evaluated RCTs involving advanced EGFR-mutant NSCLC patients with stable brain metastases and the treatment recommendations in the China expert consensus (12), which were based on expert interpretations of the RCT subgroup data. The data of the brain metastases subgroup from the RCTs of patients with advanced EGFR-mutant NSCLC were extracted for statistical analysis and systematic review. For unreported data, we contacted the authors or the pharmaceutical companies.

The quality and risk of bias of the individual RCTs were assessed using the Cochrane Collaboration's risk-of-bias tool (16). The tool is based on random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. The RCTs were judged as having low, high, or unclear risk of bias.

Study selection and data extraction were managed by all authors independently. Two authors (LD and CL) independently assessed risk of bias in the individual studies. Any disagreement between the two authors were resolved by consensus and arbitration by a panel of adjudicators (LD, CL, GH, GC, CW, JY, ZJ, GH, JZ and WF).

Statistical analyses

The risk of bias in the RCTs was assessed by Review Manager (RevMan, 5.3, The cochrane collaboration, London, UK). The data on HRs with 95% credible interval were extracted from the included studies. The network plots were drawn using GeMTC package in R software

(version 3.6.3, R Foundation, Vienna, Austria) to show the interaction of the different treatment regimens in the included studies. The direct and indirect treatments in our network meta-analysis and their effects were analyzed using the Bayesian statistical model. Statistical significance was set at a $P=0.05$. Statistical heterogeneity was estimated by means of the I^2 statistic, which indicates heterogeneity caused by total variation across trials rather than by chance. Values $<25\%$ indicate a small amount of inconsistency while values $>50\%$ indicate a huge amount of inconsistency (17).

Results

Study selection and study quality

We electronically and manually searched a total of 2,025 records. After the titles and abstracts were screened, 1,793 records were excluded. Of the 151 abstracts and manuscripts that qualified for full-text reading, only six unique RCTs finally included for analysis are shown in *Figure 1*.

According to the Cochrane Collaboration's risk-of-bias tool, all six RCTs in our study were considered to be of acceptable quality and have low risk of bias. The main risk was that all the data came from subgroups. *Figure S1* and *Table S2* show the risk of bias assessments in detail.

Systematic review and characteristics

None of the RCTs specifically focused on advanced EGFR-mutant NSCLC patients with stable brain metastases. We therefore collected data from subgroups of patients with advanced EGFR-mutant NSCLC. The six RCTs included were: (FLAURA (18,19), NEJ026 (20), NEJ009 (21), LUX-lung7 (22,23), LUX-lung6 (24), and LUX-lung3 (24). These studies involved 417 patients, who received 7 different first-line regimens: osimertinib, first-generation EGFR-TKI (We defined "erlotinib or gefitinib" as first-generation EGFR-TKI), afatinib, gemcitabine + cisplatin, pemetrexed + cisplatin, erlotinib + bevacizumab and gefitinib + pemetrexed + carboplatin. The overall study and the brain metastases subgroup characteristics are shown in *Table 1* and *Table 2*, respectively.

In the FLAURA study, patients with central nervous system metastases whose condition was neurologically stable were eligible; most of these patients had brain metastases, but we could not exclude the small number of patients without brain metastases.

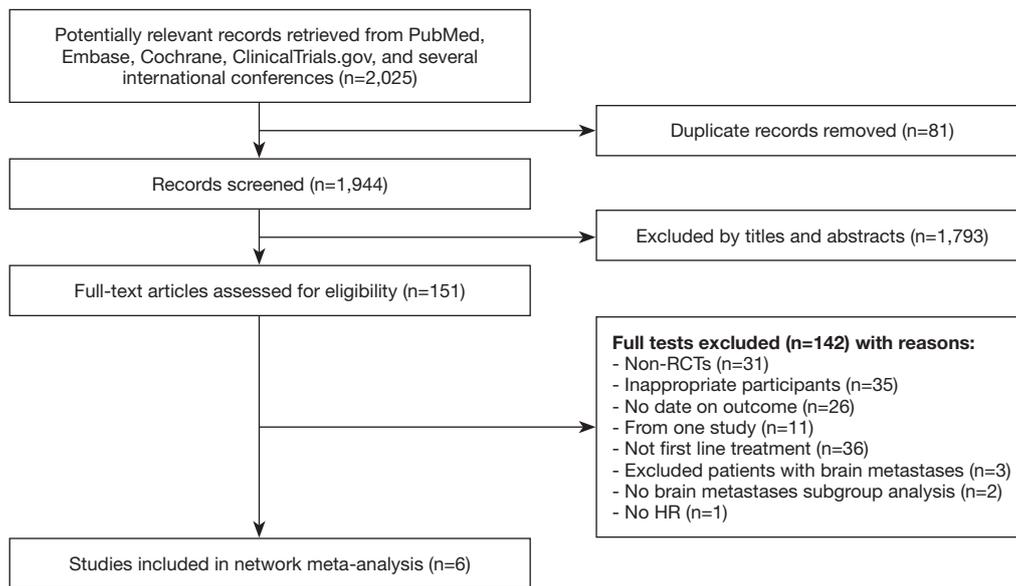


Figure 1 Flow chart of the study selection. RCT, randomized controlled trial; HR, hazard ratio.

Table 1 Overall characteristics of the included studies

Study (phase)	Ethnicity	Sample size	Female (%)	Median age	EGFR mutation types	Intervention arm	Control arm	Reported outcomes
FLAURA, 2019 (III)	Multiple	279/277	64.0/62.0	64.0/64.0	19 deletion, L858R	Osimertinib	Gefitinib or Erlotinib	PFS; OS; ORR; Grade ≥ 3 Aes
NEJ026, 2019 (III)	Asian	114/114	63.4/65.2	67.0/68.0	19 deletion, L858R	Erlotinib + bevacizumab	Erlotinib	PFS; ORR; Grade ≥ 3 Aes
NEJ009, 2019 (III)	Asian	170/172	62.8/67.1	64.1/64.8	19 deletion, L858R, G719A, G719C, G719S, and L861Q	Gefitinib + PC	Gefitinib	PFS; OS; ORR; Grade ≥ 3 Aes
LUX-lung7, 2017 (IIB)	Asian	160/159	57.0/67.6	63.0/63.0	19 deletion, L858R	Afatinib	Gefitinib	PFS; OS; ORR; Grade ≥ 3 Aes
LUX-lung6, 2016 (III)	Asian	242/122	64.0/68.0	58.0/58.0	19 deletion, L858R and other mutations	Afatinib	Gemcitabine + cisplatin	PFS; OS; ORR; Grade ≥ 3 Aes
LUX-lung3, 2016 (III)	Multiple	230/115	63.9/67.0	61.5/61.0	19 deletion, L858R and other mutations	Afatinib	Pemetrexed + cisplatin	PFS; OS; ORR; Grade ≥ 3 Aes

Data are expressed as intervention/control unless indicated otherwise. PFS, progression free survival; OS, overall survival; ORR, objective response rate; Aes, adverse events; PC, pemetrexed + carboplatin; NR, not reported; HR, hazard ratio.

Network meta-analysis

We constructed a complete network meta-analysis that included 6 RCTs, comprising of 7 treatments: osimertinib, first-generation EGFR-TKI, Erlotinib + bevacizumab, gefitinib + pemetrexed + carboplatin, afatinib, gemcitabine + cisplatin, or pemetrexed + cisplatin for PFS, and 6 treatments: osimertinib, first-generation EGFR-TKI, gefitinib + pemetrexed + carboplatin, afatinib, gemcitabine

+ cisplatin, or pemetrexed + cisplatin for OS (*Figure 2*).

The combination of gefitinib + pemetrexed + carboplatin yielded a better PFS rate than osimertinib (HR: 0.84; 95% CI: 0.34 to 2.11), first-generation EGFR-TKIs (erlotinib or gefitinib) (HR: 0.61; 95% CI: 0.32 to 1.17), erlotinib + bevacizumab (HR: 0.68; 95% CI: 0.28 to 1.67), afatinib (HR: 0.69; 95% CI: 0.28 to 1.71), gemcitabine + cisplatin (HR: 0.50, 95% CI: 0.15 to 1.67), and pemetrexed + cisplatin

Table 2 Brain metastases subgroup characteristics of the included studies

Study	Sample size	Intervention arm	Control arm	PFS (HR; 95% CI)	OS (HR; 95% CI)
FLAURA, 2019	53/63	Osimertinib	Gefitinib or Erlotinib	0.47 (0.30–0.74)	0.830.53–1.30
NEJ026, 2019	36/36	Erlotinib + bevacizumab	Erlotinib	0.78 (0.42–1.43)	NR
NEJ009, 2019	38/50	Gefitinib + PC	Gefitinib	0.32 (0.19–0.53)	0.66 (0.40–1.07)
LUX-lung7, 2017	26/24	Afatinib	Gefitinib	0.76 (0.41–1.44)	1.16 (0.61–2.21)
LUX-lung6, 2016	30/19	Afatinib	Gemcitabine + cisplatin	0.47 (0.18–1.21)	1.13 (0.56–2.26)
LUX-lung3, 2016	27/15	Afatinib	Pemetrexed + cisplatin	0.54 (0.23–1.25)	1.15 (0.49–2.67)

PFS, progression free survival; HR, hazard ratio.

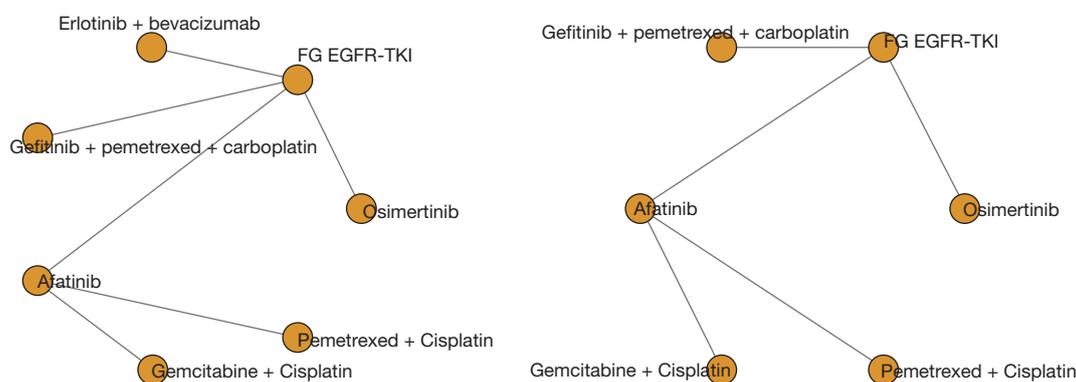


Figure 2 Complete network based on six RCTs. (A) Comparisons of progression-free survival in advanced EGFR-mutant NSCLC patients with stable brain metastases. (B) Comparisons of overall survival in advanced EGFR-mutant NSCLC patients with stable brain metastases. EGFR epidermal growth factor receptor; RCT, randomized controlled trial; NSCLC, non-small cell lung cancer.

(HR: 0.52; 95% CI: 0.17 to 1.66) (Figure 3). Compared to the other EGFR-TKI monotherapies, osimertinib yielded the greatest benefit. Furthermore, gefitinib + pemetrexed + carboplatin and osimertinib had the first (57%) and second (37%) highest performance probability, respectively (Figure 4 and Table S3). Two chemotherapy regimens (gemcitabine + cisplatin and pemetrexed + cisplatin) had the worst PFS rate. Notably, none of the results achieved the predetermined statistical significance of $P < 0.05$.

Our data showed that gefitinib + pemetrexed + carboplatin yielded a better OS rate than osimertinib (HR: 0.91; 95% CI: 0.60 to 1.37), first-generation EGFR-TKIs (erlotinib or gefitinib) (HR: 0.84; 95% CI: 0.62 to 1.13), afatinib (HR: 0.78; 95% CI: 0.49 to 1.25), gemcitabine + cisplatin (HR: 0.82; 95% CI: 0.46 to 1.49), and pemetrexed + cisplatin (HR: 0.84; 95% CI: 0.45 to 1.56) (Figure 3). Gefitinib + pemetrexed + carboplatin had a 47% chance of being the best; Compared to the other EGFR-TKIs monotherapies, osimertinib yielded the greatest benefit,

with a performance probability of 29% (Figure 5 and Table S3). As with PFS rate, gemcitabine + cisplatin and pemetrexed + cisplatin had the worst OS rate. Notably, none of the results achieved the predetermined statistical significance of $P < 0.05$.

Further analysis showed low global heterogeneity for both the PFS ($I^2 = 16%$) and OS ($I^2 = 18%$) rates.

Discussion

In this study, we investigated the relative survival outcomes (PFS and OS rates) of each of the first-line regimens currently used to treat advanced EGFR-mutant NSCLC patients with stable brain metastases. The results suggested that gefitinib + pemetrexed + carboplatin provided the best PFS and OS rates for such patients. Compared to the other EGFR-TKIs monotherapies, Osimertinib achieved the best PFS and OS rates in patients with advanced EGFR-mutant NSCLC with stable brain metastases. Meanwhile,

PFS							
Osimertinib	0.72 (0.38, 1.35)	0.81 (0.33, 1.97)	1.19 (0.47, 2.92)	0.82 (0.33, 2.03)	0.59 (0.16, 1.97)	0.62 (0.20, 1.94)	
1.38 (0.74, 2.60)	FG EGFR-TKI	1.11 (0.58, 2.13)	1.64 (0.86, 3.10)	1.13 (0.59, 2.18)	0.82 (0.29, 2.28)	0.86 (0.34, 2.22)	
1.24 (0.51, 3.06)	0.90 (0.47, 1.72)	Erlotinib + bevacizumab	1.48 (0.60, 3.60)	1.02 (0.40, 2.56)	0.74 (0.22, 2.45)	0.77 (0.24, 2.45)	
0.84 (0.34, 2.11)	0.01 (0.32, 1.17)	0.08(0.28, 1.67)	Gefitinib+ PC	0.69 (0.28, 1.71)	0.50 (0.15, 1.67)	0.52 (0.17, 1.60)	
1.22 (0.49, 3.07)	0.89 (0.46, 1.70)	0.98 (0.39, 2.51)	1.45 (0.58, 3.63)	Afatinib	0.73 (0.33, 1.59)	0.76 (0.38, 1.52)	
1.69 (0.51, 5.69)	1.22 (0.44, 3.42)	1.35 (0.41, 4.61)	2.00 (0.60, 6.72)	1.38 (0.63, 3.03)	Gemcitabine + cis	1.06 (0.37, 3.03)	
1.61 (0.51, 4.99)	1.16 (0.45, 2.96)	1.29 (0.41, 4.09)	1.91 (0.60, 5.95)	1.31 (0.66, 2.61)	0.94 (0.33, 2.71)	Pemetrexed + cis	
OS							
Osimertinib	0.92 (0.69, 1.23)	–	1.1 (0.73, 1.68)	0.87 (0.55, 1.37)	0.91 (0.51, 1.66)	0.93 (0.50, 1.73)	
1.08 (0.81, 1.44)	FG EGFR-TKI	–	1.19 (0.89, 1.61)	0.94 (0.66, 1.33)	0.98 (0.59, 1.64)	1.01 (0.58, 1.75)	
0.91 (0.60, 1.37)	0.84 (0.62, 1.13)	–	Gefitinib+ PC	0.78 (0.49, 1.25)	0.82 (0.46, 1.49)	0.84 (0.45, 1.50)	
1.16 (0.73, 1.83)	1.07 (0.75, 1.52)	–	1.28 (0.80, 2.03)	Afatinib	1.05 (0.73, 1.52)	1.07 (0.71, 1.02)	
1.10 (0.60, 1.97)	1.02 (0.61, 1.68)	–	1.21 (0.67, 2.19)	0.95 (0.66, 1.37)	Gemcitabine + cis	1.02 (0.59, 1.76)	
1.08 (0.58, 2.01)	0.99 (0.57, 1.72)	–	1.19 (0.64, 2.23)	0.93 (0.62, 1.41)	0.98 (0.57, 1.69)	Pemetrexed + cis	

Figure 3 Treatment comparisons for PFS, OS [HRs (95% CI)]. PFS, progression free survival; OS, overall survival; NG, not given; HR, hazard ratio; FG, first-generation; PC, pemetrexed + carboplatin; EGFR epidermal growth factor receptor; cis, cisplatin.

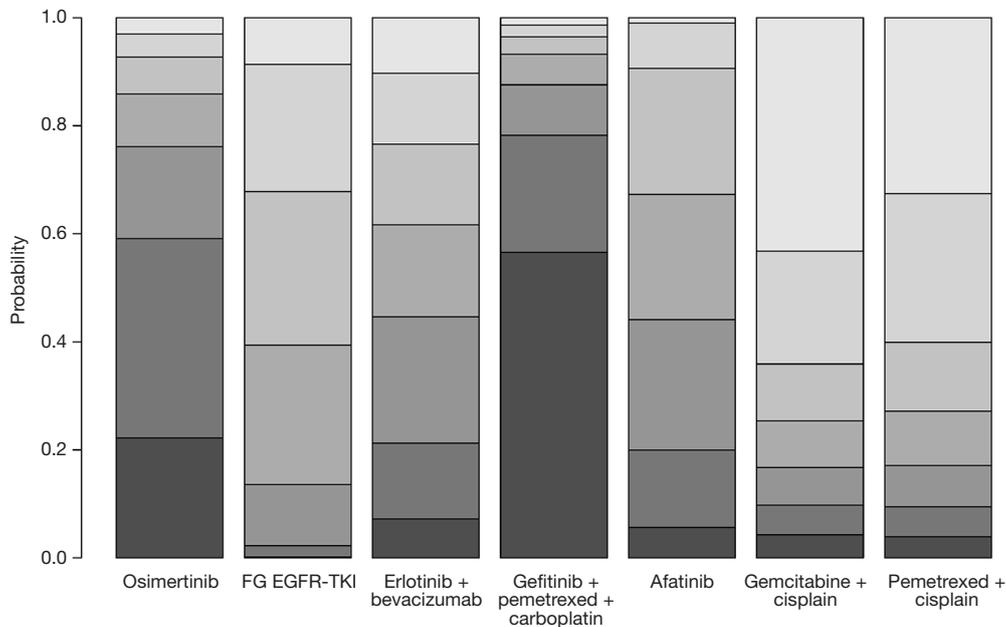


Figure 4 Bayesian ranking profiles of treatments based on PFS. FG, first-generation; PFS, progression free survival.

the chemotherapy regimens (gemcitabine + cisplatin and pemetrexed + cisplatin) had the poorest PFS and OS rates.

Previous network meta-analyses (14) that compared all first-line treatments for advanced EGFR-mutant NSCLC patients found that gefitinib + pemetrexed-based

chemotherapy and osimertinib were associated with the greatest benefits for PFS and OS. Gefitinib + pemetrexed based chemotherapy was also associated with the best objective response rate. The combinations of erlotinib + bevacizumab and gefitinib + pemetrexed were associated

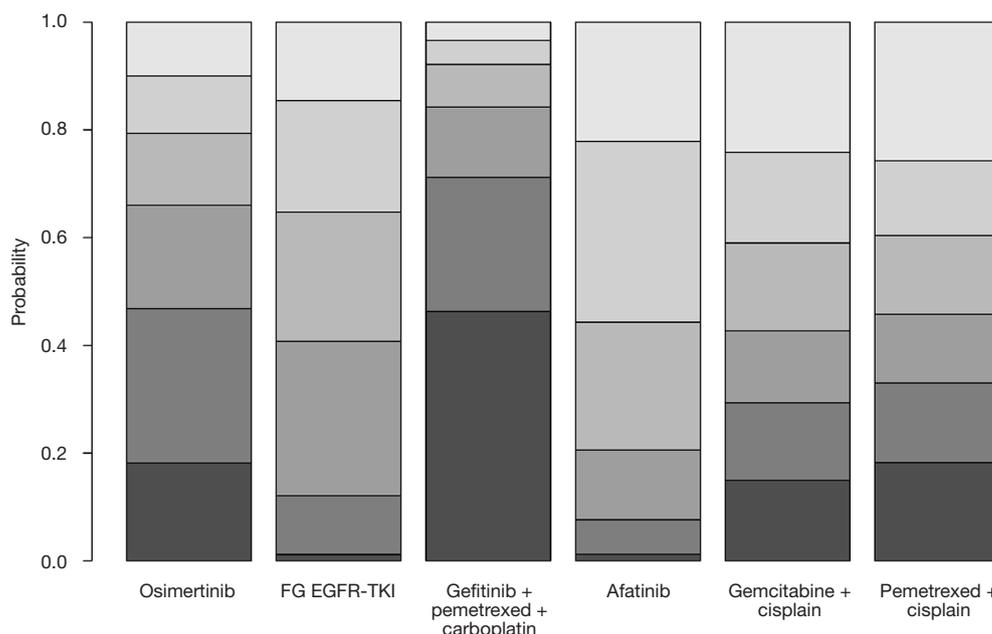


Figure 5 Bayesian ranking profiles of treatments based on OS. FG, first-generation; OS, overall survival.

with increased risk of grade 3 adverse events, compared to the other EGFR-TKI monotherapies. Data from our study suggested that a combination of gefitinib, pemetrexed, and carboplatin was the most favorable regimen in terms of PFS (with 57% probability of being the best; *Figure 3* and *Table S3*) and OS (with 47% probability of being the best; *Figure 4* and *Table S3*), although this was not statistically significant. In vitro and in vivo studies have demonstrated that a combination of EGFR-TKIs and chemotherapy produces a synergistic effect (25-29).

The FLAURA study showed that, compared with standard EGFR-TKIs, osimertinib improved both the median PFS (18.9 vs. 10.2 months) and the overall OS (38.6 vs. 31.8 months) for advanced EGFR-mutant NSCLC patients (18,19). Based on the results of the FLAURA study, the NCCN clinical practice guidelines recommended osimertinib as a first-line therapy for patients with advanced EGFR-mutant NSCLC (7). In addition, a network meta-analysis showed that, compared to the other TKIs, osimertinib had a potentially better efficacy (in relation to both PFS and OS) as a first-line treatment for advanced EGFR-mutant NSCLC patients (30). Furthermore, subgroup analysis of CNS metastases reported that osimertinib had better efficacy than and reduced the risk of CNS progression compared to standard EGFR-TKI (31). Consequently, Shanghai expert consensus recommended

osimertinib as a first-line treatment for advanced EGFR-mutant NSCLC with stable brain metastases (12).

Our study performed network meta-analysis to compare all of the first-line treatments in subgroup data. Our data showed that while osimertinib was associated with better survival outcomes compared to the other EGFR-TKI monotherapies, a combination of gefitinib + pemetrexed + carboplatin was potentially better than osimertinib (PFS, HR: 0.84, 95% CI: 0.34 to 2.11; OS, HR: 0.91, 95% CI: 0.60 to 1.37), as shown in *Figure 3*. These results suggest that a combination therapy with osimertinib may be more effective than the current standard regimens. Preliminary data from ongoing studies have shown that a combination of osimertinib plus ramucirumab has therapeutic potential when used as a second-line treatment for EGFR-mutant, T790M-positive NSCLC patients with brain metastases (32). A phase 1/2 study of osimertinib plus bevacizumab as a first-line treatment regimen for patients with EGFR-mutant NSCLC observed a PFS of 18.4 months (33). A retrospective analysis of osimertinib combined with chemotherapy showed an improvement in the CNS metastasis (34). However, osimertinib had a much improved toxicity profile compared to gefitinib plus pemetrexed-based chemotherapy. Compared to the gefitinib plus pemetrexed regimen, osimertinib had fewer adverse events of grade 3 or higher in patients with advanced EGFR mutated NSCLC (14). In addition, a recent meta-

analysis involving 15 studies supported the potential role of osimertinib in the treatment of advanced EGFR-mutant NSCLC patients with intracranial metastases (35). Based on the current evidence, we put forward the use of osimertinib as a first-line treatment for advanced EGFR-mutant NSCLC patients with stable brain metastases.

Several studies (36-42) have shown that EGFR-TKIs are superior to chemotherapy as first-line treatment for patients with advanced EGFR-mutant NSCLC. In our analysis, the chemotherapy regimens (gemcitabine + cisplatin and pemetrexed + cisplatin) were associated with less favorable outcomes in advanced EGFR-mutant NSCLC patients with stable brain metastases.

By analyzing evidence from all RCTs, our review provides clinicians with a reference by which to consider the survival outcomes of the current treatment options. The use of gefitinib + pemetrexed + carboplatin was associated with the most favorable survival outcomes and, as osimertinib had a better toxicity profile than gefitinib and pemetrexed-based chemotherapy (14), gefitinib + pemetrexed + carboplatin and osimertinib were both considered as optimal treatments for advanced EGFR-mutant NSCLC patients with stable brain metastases. Future RCTs should be designed to focus on potentially more effective combinations, such as osimertinib + chemotherapy or bevacizumab.

However, our study has some limitations. First, it was based on a small sample size and was retrospective in nature, which made it difficult to compare local heterogeneity between any two identical samples. Second, all of the data in our study was collected from subgroups; thus, the risk of bias cannot be ruled out. Third, analysis of adverse events and objective response rate proved challenging as this data was not available for the subgroups. Fourth, the demographic data of patients with brain metastases would have been helpful for evaluating differences between treatment groups but were not available. Fifth, the FLAURA study enrolled patients with CNS metastases whose condition was neurologically stable. While most of these patients had brain metastases, it was not possible to exclude the few patients without brain metastases from this analysis. Finally, our network meta-analysis assumed that the patient populations from different trials were similar, and that any differences would not substantially influence the results.

Conclusions

In summary, a regimen of gefitinib + pemetrexed + carboplatin was associated with the best PFS and OS in

advanced EGFR-mutant NSCLC patients with stable brain metastases, followed by osimertinib. Gefitinib + pemetrexed + carboplatin and osimertinib could be optimal first-line treatments for patients with advanced EGFR-mutant NSCLC with stable brain metastases. This review of the literature available for current treatment regimens may provide insights for the design of future clinical trials.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/apm-20-1136>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table S1 Literature search criteria

((("Carcinoma, Non-Small-Cell Lung"[Mesh]) OR (((((((non-small-cell lung cancer[Title]) OR (non-small cell lung cancer[Title]) OR (non small-cell lung cancer[Title]) OR (non small cell lung cancer[Title]) OR (non-small-cell lung carcinoma[Title]) OR (non-small cell lung carcinoma[Title])) OR (non small-cell lung carcinoma[Title]) OR (non small cell lung carcinoma[Title]) OR (nsccl[Title])) AND ((epidermal growth factor receptor[title/abstract]) OR (EGFR[Title/Abstract])) AND (((((((((((treatment[Title/Abstract]) OR (therapy[Title/Abstract]) OR (tyrosine kinase inhibitor) OR (TKI[Title/Abstract]) OR (osimertinib[Title/Abstract]) OR (dacomitinib[Title/Abstract]) OR (afatinib [Title/Abstract]) OR (erlotinib[Title/Abstract]) OR (gefitinib[Title/Abstract]) OR (icotinib[Title/Abstract]) OR (chemotherapy[Title/Abstract]) OR (first-line[Title/Abstract]) OR (first line[Title/Abstract]) OR (treatment-naive[Title/Abstract]) OR (treatment-naïve[Title/Abstract]) OR (untreated[Title/Abstract])) AND (((((compare[Title/Abstract]) OR (comparison[Title/Abstract]) OR (comparative[Title/Abstract]) OR (comparing[Title/Abstract]) OR (versus[Title/Abstract]) OR (vs[Title/Abstract])) AND (((((((Randomized Controlled Trial[Publication Type]) OR (controlled clinical trial[Publication Type]) OR (randomized[Title/Abstract]) OR (randomised[Title/Abstract]) OR (randomly [Title/Abstract]) OR (trial[Title/Abstract]) OR (phase[Title/Abstract]) AND ("0001/01/01"[Date - Publication] : "2019/12/22"[Date - Publication]))

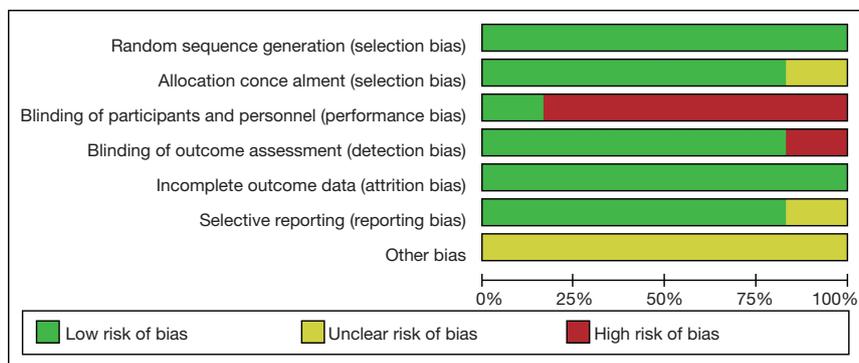


Figure S1 Cochrane risk of bias tool assessment.

Table S2 Quality and risk of bias assessment

Study	Sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome data	Incomplete outcome data	Selective reporting	Other sources of bias
FLAURA (2019)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk (data from subgroup analysis)
NEJ026 (2019)	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Unclear risk (data from subgroup analysis)
NEJ009 (2019)	Low risk	Unclear risk	High risk	Low risk	Low risk	Unclear risk	Unclear risk (data from subgroup analysis)
Lux-Lung 7 (2017)	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Unclear risk (data from subgroup analysis)
Lux-Lung 6 (2016)	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Unclear risk (data from subgroup analysis)
Lux-Lung 3 (2016)	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Unclear risk (data from subgroup analysis)

Table S3 Bayesian ranking results of network meta-analysis

Treatment	Rank of possibility (%)						
	1	2	3	4	5	6	7
Progression-free survival for stable brain metastases from advanced EGFR-mutated patients							
Osimertinib	22	37	17	10	7	4	3
S EGFR-TKI	0	2	11	26	28	24	9
Erlotinib + bev	7	14	23	17	15	13	10
Gefitinib + PC	57	22	9	6	3	2	1
Afatinib	6	14	24	23	23	8	1
Gemcitabine + cis	4	5	7	9	11	21	43
Pemetrexed + cis	4	6	8	10	13	27	33
Overall survival for stable brain metastases from advanced EGFR-mutated patients							
Osimertinib	19	29	19	13	10	10	–
S EGFR-TKI	1	11	29	24	20	14	–
Gefitinib + PC	47	25	13	7	5	3	–
Afatinib	1	6	13	23	34	22	–
Gemcitabine + cis	14	15	14	17	17	24	–
Pemetrexed + cis	18	14	12	15	14	27	–

S EGFR-TKI, standard EGFR-TKI; bev, bevacizumab; PC, pemetrexed + carboplatin; cis, cisplatin.