

Research Article

Comparison of the Efficacy of EGFR-TKIs Combined with Antiangiogenic Agents between Patients with Exon 19 Deletion and Patients with Exon 21 Leu858 Arg Mutation: A Systematic Review and Meta-Analysis

Xin-Bin Pan , Fa-Song Liang, Qin-Yu Tang, Huan-Wei Liang, and Xiao-Dong Zhu 

Department of Radiation Oncology, Guangxi Medical University Cancer Hospital, Nanning, Guangxi 530021, China

Correspondence should be addressed to Xiao-Dong Zhu; zhuxiaodonggx@163.com

Received 4 July 2022; Revised 22 September 2022; Accepted 13 October 2022; Published 20 October 2022

Academic Editor: Yuan Seng Wu

Copyright © 2022 Xin-Bin Pan et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Purpose. To compare the efficacy of EGFR-TKIs combined with antiangiogenic agents between non-small cell lung cancer patients with exon 19 deletion and patients with exon 21 Leu858 Arg mutation. **Methods.** Electronic databases (PubMed, Embase, and the Cochrane Central Register of Controlled Trials) were systematically searched for studies published until March 2022. Randomized control trials comparing the survival of EGFR-TKIs plus antiangiogenic agents with EGFR-TKI were extracted. The primary endpoint was progression-free survival (PFS). **Results.** Five randomized control trials involving 1533 patients were as follows: 818 patients had exon 19 deletion, and 715 patients with exon 21 Leu858 Arg mutation. The methodological quality of the 5 randomized control trials was high. EGFR-TKIs plus antiangiogenic agents improved PFS in patients with exon 19 deletion (hazard ratio [HR] = 0.62, 95% confidence interval [CI]: 0.51–0.75) and exon 21 Leu858 Arg mutation (HR = 0.61, 95% CI: 0.50–0.75). PFS did not differ between the exon 19 deletion and exon 21 Leu858 Arg mutation groups ($Z = 0.07$, $P = 0.94$). **Conclusions.** PFS was comparable between patients receiving EGFR-TKIs combined with antiangiogenic agents with exon 19 deletion and those with exon 21 Leu858 Arg mutation.

1. Introduction

Lung cancer is a leading cause of death worldwide, accounting for 18.0% of total cancer-related deaths [1]. Approximately 85% of cases of lung cancer are non-small cell lung cancer (NSCLC). Among NSCLC patients, 60% have metastatic disease at the time of diagnosis [2]. Epidermal growth factor receptor (EGFR) mutation-driven NSCLC occurs in 10–20% of white patients and 40–60% of Asian patients [3, 4].

Although several trials established EGFR tyrosine kinase inhibitor (TKI) therapy as standard treatment for EGFR-positive NSCLC patients [5–8], the median progression-free survival (PFS) was approximately 1 year as a result of acquired TKI therapeutic resistance [5–10]. To improve PFS, TKIs combined with antiangiogenic agents have been investigated. Several trials have suggested that the addition of

antiangiogenic agents to TKIs significantly reduces the risk of disease progression [11–21].

However, it is unclear whether the efficacy of TKIs combined with antiangiogenic agents is similar between patients with exon 19 deletion and patients with exon 21 Leu858 Arg mutation. Several trials have reported that patients with exon 21 Leu858 Arg mutation are more likely to benefit from TKI combined with antiangiogenic agents than patients with exon 19 deletion [17, 19, 21]. In contrast, other studies have suggested that patients with exon 19 deletion are more likely to benefit from TKI combined with antiangiogenic agents than patients with exon 21 Leu858 Arg mutation [16, 18, 20]. Thus, the current systematic review was conducted to compare the PFS between NSCLC patients treated with TKI combined with antiangiogenic agents who had exon 19 deletion and those with exon 21 Leu858 Arg mutation.

2. Materials and Methods

2.1. Data Sources and Searches. The PubMed, Embase, and Cochrane Central Register of Controlled Trials were systematically searched up to March 2022. The search was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines [22, 23]. The main search terms and their combinations included NSCLC, non-small cell lung cancer, EGFR, epidermal growth factor receptor, TKI, a tyrosine kinase inhibitor, antiangiogenic agents, VEGF, and VEGFR. Abstracts from the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), and International Association of Lung Cancer websites were also reviewed. Two researchers (PXB and LFS) independently carried out the literature retrieval. If multiple articles covered the same study population, the study with the most recent and complete survival data was utilized. Any disagreements between the two reviewers were resolved by consulting a third reviewer (ZXD).

2.2. Study Selection. Studies were included if they met the following criteria: (1) randomized clinical trials; (2) untreated patients with cytologically or histologically confirmed advanced EGFR-mutant NSCLC; (3) compared EGFR-TKIs plus antiangiogenic agents with EGFR-TKI monotherapy in the first-line setting; and (4) reported PFS of patients with exon 19 deletion and exon 21 Leu858 Arg mutation. Studies failing to meet these criteria were excluded.

2.3. Data Extraction and Quality Assessment. Data extraction was performed by 2 authors (LFS and TQY). Two authors (PXB and LHW) separately assessed the methodological quality of the included studies. The methodological quality of randomized clinical trials was evaluated by the Cochrane Risk of Bias tool [24], which assesses the following seven domains: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other bias. All disagreements were resolved by discussion and consensus.

2.4. Statistical Analysis. The pooled hazard ratios (HRs) for PFS and its 95% confidence intervals (CIs) were used to measure the treatment outcome. The I^2 -statistic was used to determine the level of statistical heterogeneity between studies. If there was no statistical heterogeneity ($I^2 < 50\%$, $P \geq 0.1$) among studies, a fixed effects model was used for HR analysis. If there was statistical heterogeneity ($I^2 \geq 50\%$, $P < 0.1$) among studies, a random effects model was used. Forest plots were generated to show the estimated HRs, representing the theoretical gain in absolute percentage on the basis of PFS. The upper limit and lower limit of 95% CIs were calculated. The stability of the results was estimated using a sensitivity analysis by the exclusion of a particular trial from the analysis. Publication bias was assessed by the funnel plot and Begg's and Egger's tests.

All statistical analyses were performed using SPSS Statistics Version 26.0 software (IBM Co., Armonk, NY, USA) and R software version 4.1.3 (<https://www.R-project.org>). P values were two-tailed. Values of $P < 0.05$ were considered statistically significant.

3. Results

3.1. Characteristics of the Included Trials. Figure 1 shows the process of study selection. This study screened 438 studies according to the primary search strategy. Six trials were included in this systematic review [16–21]. Five studies were included in the meta-analysis [16–19, 21].

A total of 1533 patients were included 818 patients had exon 19 deletion, and 715 patients had exon 21 Leu858 Arg mutation. Table 1 summarizes the characteristics of the 6 included studies. Table 2 lists the primary endpoint of the 6 trials. Two studies reported overall survival (OS) [18, 20]. Figure 2 shows the methodological quality of the 6 included studies. Among the 6 studies, 2 trials were phase 2 randomized clinical trials, and 4 studies were phase 3 randomized clinical trials.

3.2. PFS of Patients with Exon 19 Deletion. PFS data of patients with exon 19 deletion were available from 5 trials [16–19, 21]. There was no significant heterogeneity among the 5 trials ($P = 0.63$, $I^2 = 0.00\%$); therefore, the fixed effects model was used for meta-analysis. As shown in Figure 3, patients with exon 19 deletion receiving EGFR-TKIs plus antiangiogenic agents had longer PFS than patients receiving EGFR-TKI monotherapy (HR = 0.62, 95% CI: 0.51–0.75).

There was no evidence of apparent publication bias according to Egger's test ($P = 0.329$) (Figure 4). Furthermore, sensitivity analysis was conducted by removing one study at a time from the analysis, and the results indicated that the conclusions were robust (Figure 5).

3.3. PFS of Patients with Exon 21 Leu858 Arg Mutation. PFS data of patients with exon 21 Leu858 Arg mutation were available from 5 trials [16–19, 21]. No significant heterogeneity among the 5 trials was found ($P = 0.81$, $I^2 = 0.00\%$). Thus, the fixed effects model was used for meta-analysis. Figure 6 shows that patients with exon 21 Leu858 Arg mutation who received EGFR-TKIs plus antiangiogenic agents had longer PFS than patients who received EGFR-TKI monotherapy (HR = 0.61, 95% CI: 0.50–0.75).

There was no evidence of apparent publication bias according to Egger's test ($P = 0.872$) (Figure 7). Furthermore, sensitivity analysis was conducted by removing one study at a time from the analysis, and the results indicated that the conclusions were robust (Figure 8).

3.4. Comparison of PFS among Patients Receiving EGFR-TKIs plus Antiangiogenic Agents with the Exon 19 Deletion and Those with Exon 21 Leu858 Arg Mutation. The Z-test was used to compare the PFS between patients receiving EGFR-

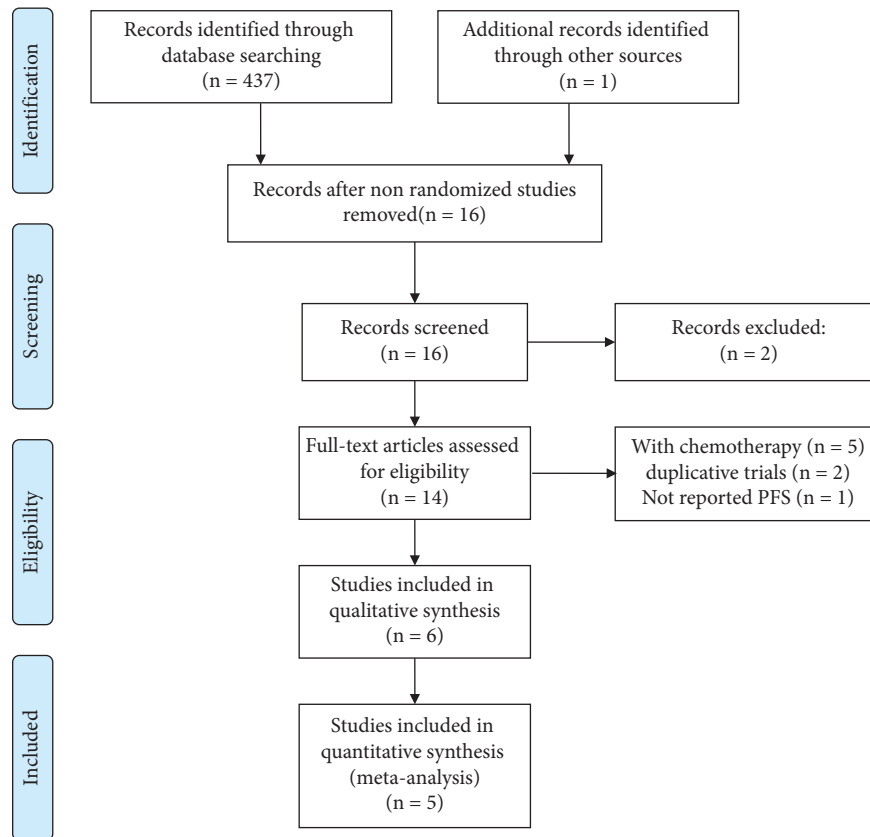


FIGURE 1: Flowchart depicting study selection.

TKIs plus antiangiogenic agents with exon 19 deletion and those with exon 21 Leu858 Arg mutation. The null hypothesis was that the PFS was comparable between patients with exon 19 deletion and those with exon 21 Leu858 Arg mutation receiving EGFR-TKIs plus antiangiogenic agents. A two-tailed P value less than 0.05 was considered to indicate statistical significance.

The Z value was 0.07 ($P = 0.94$). The results suggested that patients with exon 19 deletion and patients with exon 21 Leu858 Arg mutation receiving EGFR-TKIs plus antiangiogenic agents had a comparable PFS. Similarly, the NCT01532089 trial revealed the same result. [20] Although EGFR-TKIs plus antiangiogenic agents improved the PFS of patients with exon 19 deletion compared to patients with exon 21 Leu858 Arg mutation, the difference between the two groups was not statistically significant (HR = 0.83, 95% CI: 0.47–1.47; $P = 0.53$).

3.5. Comparison of OS between Exon 19 Deletion and Exon 21 Leu858 Arg Mutation. OS data of patients with exon 19 deletion were available from 2 trials [20, 25]. The NCT01532089 trial reported that the OS of patients with exon 19 deletion receiving EGFR-TKIs plus antiangiogenic agents was better than that of patients with exon 21 Leu858 Arg mutation (HR = 0.34, 95% CI: 0.16–0.72) [20]. In contrast, JO25567 suggested that no differences were observed between patients receiving EGFR-TKIs and those receiving EGFR-TKIs plus antiangiogenic agents [25]. The

HRs were 0.79 (95% CI: 0.44–1.44) and 0.83 (95% CI: 0.46–1.49) in the exon 19 deletion and exon 21 Leu858 Arg mutation groups, respectively.

4. Discussion

TKIs have been proven to be an effective first-line treatment for patients with EGFR mutation-driven NSCLC. However, the efficacy of TKIs varies among individual patients. Several randomized controlled phase 3 studies revealed that TKIs were more effective in patients harboring exon 19 deletion than in patients harboring exon 21 Leu858 Arg mutation [7, 9, 26–28]. These findings suggested that patients with exon 19 deletion were more sensitive to TKI treatment than those with exon 21 Leu858 Arg mutation. It was suggested that patients with exon 21 Leu858 Arg mutation needed more intense treatment to achieve a similar prognosis to patients with exon 19 deletion.

A possible explanation for the worse prognosis of the exon 21 Leu858 Arg mutation may be that this mutation exhibited a higher proportion of comutations than the exon 19 deletion [29]. The BENEFIT study reported that patients with EGFR co-mutations had a worse prognosis than those with EGFR mutations alone [30]. Another possible explanation may be that patients with exon 21 Leu858 Arg mutation were more likely to have T790M mutations than patients with exon 19 deletion [31]. NSCLC patients with T790M mutations before systemic treatment had worse PFS when treated with first-generation TKIs [32].

TABLE 1: Baseline characteristics of included studies.

Trials	Authors	Source (year)	Region	Study type	Study population	Treatments	Sample size		Primary endpoint
							Exon 19 deletion	Exon 21 Leu858 Arg mutation	
JO25567	Seto et al.	Lancet Oncol 2014	Japan	Phase 2 RCT	IIIB/IV or recurrent	Erlotinib 150 mg/d + bevacizumab 15 mg/kg Q3w	40	37	PFS
NEJ026	Saito et al.	Lancet Oncol 2019	Japan	Phase 3 RCT	IIIB/IV or recurrent	Erlotinib 150 mg/d + bevacizumab 15 mg/kg Q3w	55	57	PFS
RELAY	Nakagawa et al.	Lancet Oncol 2019	Worldwide	Phase 3 RCT	IV or recurrent	Erlotinib 150 mg/d + ramucirumab 10 mg/kg Q2w	120	105	PFS
NCT01532089	Stinchcombe et al.	JAMA Oncol 2019	USA	Phase 2 RCT	IV	Erlotinib 150 mg/d + bevacizumab 15 mg/kg Q3w	30	15	PFS
ARTEMIS	Zhou et al.	Cancer cell 2021	China	Phase 3 RCT	IIIB/IV or recurrent	Erlotinib 150 mg/d + bevacizumab 15 mg/kg Q3w	79	75	PFS
ACTIVE	Zhao et al.	J thorac Oncol 2021	China	Phase 3 RCT	IIIB/IV	Gefitinib 250 mg/d	83	73	PFS
						Gefitinib 250 mg/d + apatinib 500 mg/d	81	74	

RCT: randomized controlled trial. PFS: progression-free survival.

TABLE 2: Survivals of patients with exon 19 deletion and exon 21 Leu858 Arg mutation receiving EGFR-TKIs plus antiangiogenic agents and EGFR-TKIs.

Trials	EGFR mutation type	PFS		OS	
		HR	95% CI	HR	95% CI
JO25567	Exon 19 deletion	0.41	0.24–0.72	0.79	0.44–1.44
	Exon 21 Leu858 arg mutation	0.67	0.38–1.18	0.83	0.46–1.49
NEJ026	Exon 19 deletion	0.69	0.41–1.16		
	Exon 21 Leu858 arg mutation	0.57	0.33–0.97		
RELAY	Exon 19 deletion	0.65	0.47–0.90		
	Exon 21 Leu858 arg mutation	0.62	0.44–0.87		
NCT01532089	Exon 19 deletion	0.83	0.47–1.47	0.34	0.16–0.72
	Exon 21 Leu858 arg mutation	Reference		Reference	
ARTEMIS	Exon 19 deletion	0.62	0.42–0.93		
	Exon 21 Leu858 arg mutation	0.50	0.32–0.77		
ACTIVE	Exon 19 deletion	0.67	0.45–0.99		
	Exon 21 Leu858 arg mutation	0.72	0.48–1.09		

EGFR: epidermal growth factor receptor. HR: hazard ratio. CI: confidence interval. PFS: progression-free survival. OS: overall survival.

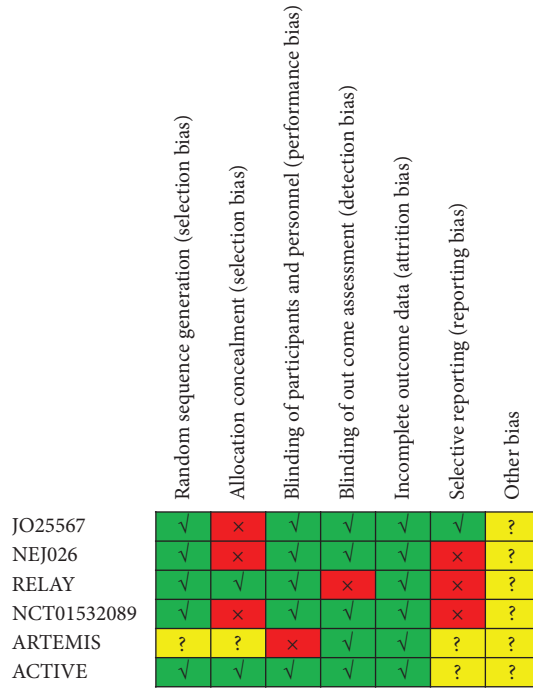


FIGURE 2: Risk of bias assessment of included studies.

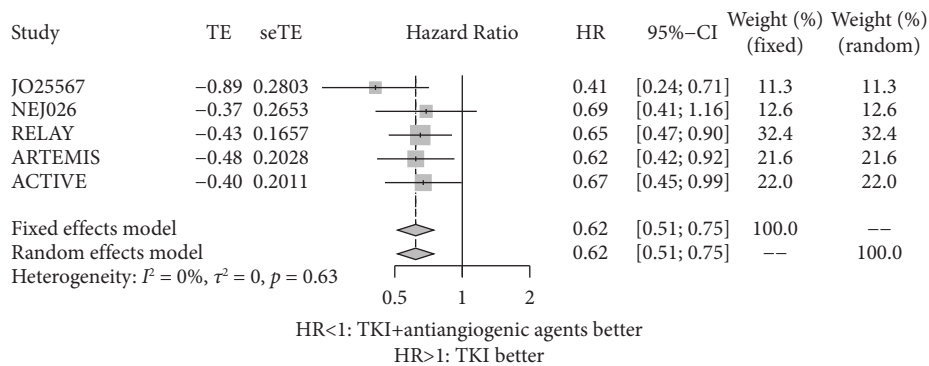


FIGURE 3: Forest plot of the hazard ratio of the progression-free survival of exon 19 deletion receiving EGFR-TKIs plus antiangiogenic agents and EGFR-TKIs. HR: hazard ratio; CI: confidence interval.

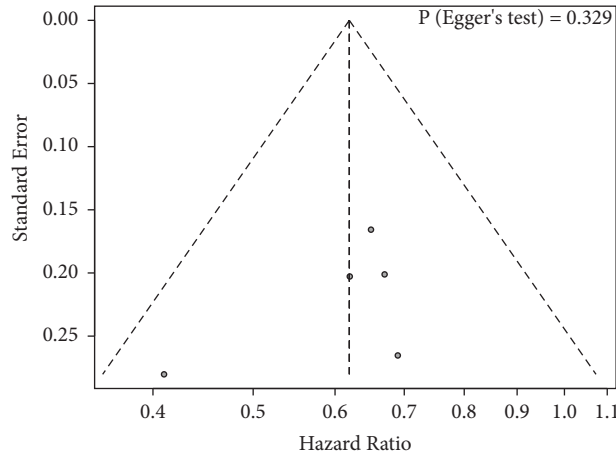


FIGURE 4: Publication bias assessment of exon 19 deletion receiving EGFR-TKIs plus antiangiogenic agents and EGFR-TKIs.

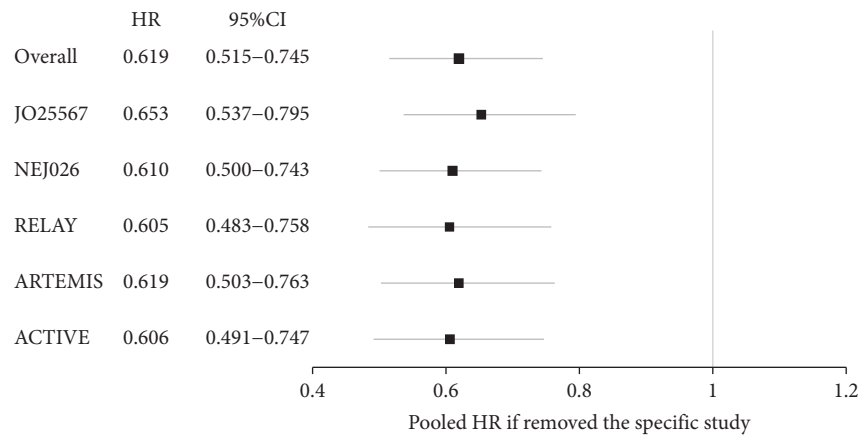


FIGURE 5: Sensitivity analysis of exon 19 deletion receiving EGFR-TKIs plus antiangiogenic agents and EGFR-TKIs.

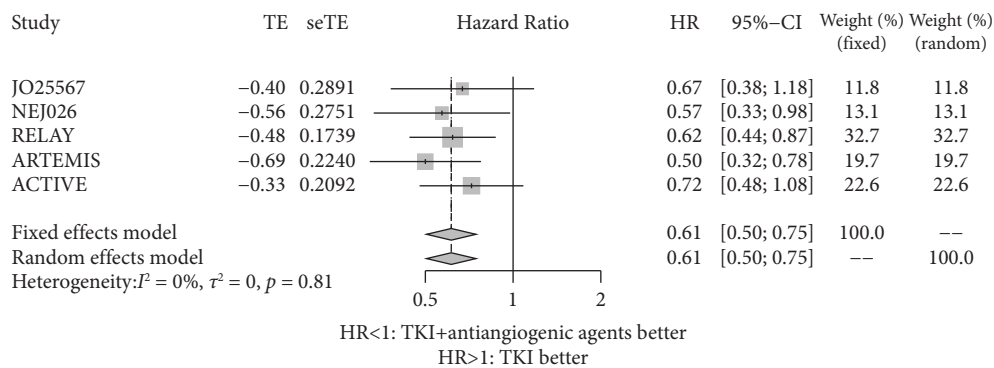


FIGURE 6: Forest plot of the hazard ratio of the progression-free survival of exon 21 Leu858 Arg mutation receiving EGFR-TKIs plus antiangiogenic agents and EGFR-TKIs. HR: hazard ratio; CI: confidence interval.

The FLAURA trial demonstrated that the third-generation TKI osimertinib shows superior efficacy compared to standard EGFR-TKIs in the first-line treatment of EGFR mutation-positive advanced NSCLC [28]. It was also reported that the HR of PFS was 0.43 (95% CI: 0.32–0.56) and 0.51 (95% CI: 0.36–0.71) in the exon 19 deletion and

exon 21 Leu858 Arg mutation groups, respectively. The results also suggested that patients with exon 21 Leu858 Arg mutation might have worse PFS than those with exon 19 deletion receiving third-generation TKIs.

Whether osimertinib plus antiangiogenic agents could further improve the PFS of patients with exon 21 Leu858 Arg

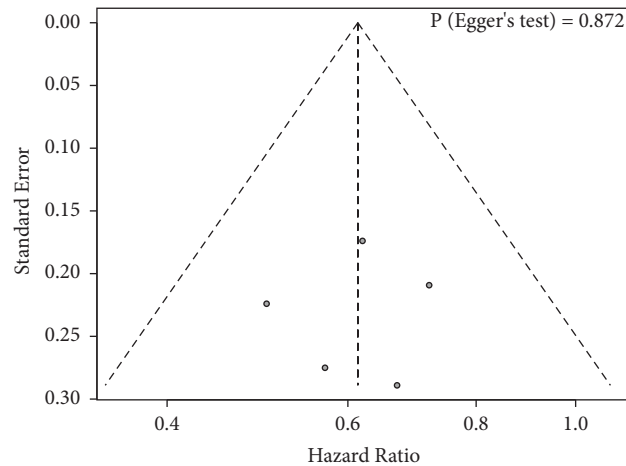


FIGURE 7: Publication bias assessment of exon 21 Leu858 Arg mutation receiving EGFR-TKIs plus antiangiogenic agents and EGFR-TKIs.

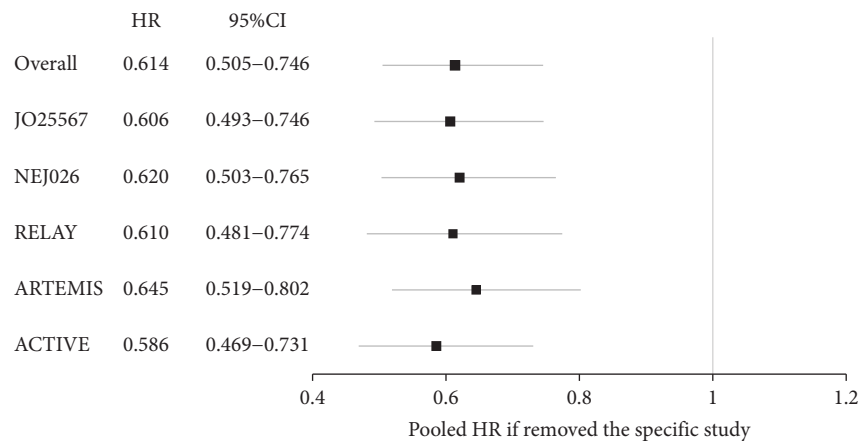


FIGURE 8: Sensitivity analysis of exon 21 Leu858 Arg mutation receiving EGFR-TKIs plus antiangiogenic agents and EGFR-TKIs.

mutation remains unclear. A phase 1 study comparing the efficacy of ramucirumab plus osimertinib reported that the objective response rate was 76%, and the median PFS was 11.0 months (90% CI: 5.5–19.3) [33]. However, the WJOG-8715 L trial compared osimertinib plus bevacizumab vs. osimertinib alone, and the combination treatment did not lead to prolonger PFS in patients with advanced lung adenocarcinoma with EGFR T790 M mutation (HR = 1.44, 95% CI: 0.83–2.52; $P = 0.20$). [34] Similarly, the BOOSTER trial also revealed that osimertinib plus bevacizumab did not improve the median PFS (HR = 0.96, 95% CI: 0.68–1.37) or OS (HR = 1.03, 95% CI: 0.67–1.56) compared to osimertinib alone [35]. These results suggested that the third-generation TKI plus antiangiogenic agents did not improve survival in patients with EGFR mutation-driven NSCLC.

However, the WJOG-8715 L and BOOSTER trials did not report the efficacy of osimertinib combined with antiangiogenic agents in patients with exon 19 deletion and exon 21 Leu858 Arg mutation [34, 35]. On the other hand, the two trials enrolled patients with EGFR mutation-driven NSCLC that acquired T790 M mutations after failure on previous EGFR-TKI therapy. Thus, our meta-analysis could not extract sufficient data to perform subgroup analysis.

Our meta-analysis suggested that combining antiangiogenic agents with TKIs improved PFS in NSCLC patients with exon 19 deletion and patients with exon 21 Leu858 Arg mutation. Moreover, PFS was not different between the two subgroups. The current meta-analysis revealed that both patients with exon 19 deletion and patients with exon 21 Leu858 Arg mutation could benefit from EGFR-TKIs plus antiangiogenic agents. Thus, NSCLC patients with exon 21 Leu858 Arg mutation were recommended to receive EGFR-TKIs plus antiangiogenic agents.

It was reported that patients with exon 19 deletion had a better OS than those with exon 21 Leu858 Arg mutation. [36] The NCT01532089 trial revealed a similar result: the OS of patients with exon 19 deletion receiving EGFR-TKIs plus antiangiogenic agents was better than that of patients with the 21 Leu858 Arg mutation (HR = 0.34, 95% CI: 0.16–0.72) [20]. In contrast, the HRs were comparable between the two subgroups (0.79 vs. 0.83). We did not have a sufficient amount of data to draw conclusions regarding OS; therefore, whether OS was comparable between the two subgroups receiving EGFR-TKIs plus antiangiogenic agents remains unclear. More trials are needed to verify the results.

The advantage of our meta-analysis was that the included studies were all randomized clinical trials with high quality. No evidence of apparent publication bias was observed. The sensitivity analysis indicated stable results by the exclusion of a particular trial from the analysis. However, limitations should be considered. Our meta-analysis was based on the PFS of patients with exon 19 deletion and exon 21 Leu858 Arg mutation reported from the subgroup analysis. The essence of subgroup analysis is exploratory. The results need to be verified in future randomized clinical trials.

In conclusion, PFS was comparable between patients with exon 19 deletion and exon 21 Leu858 Arg mutation receiving EGFR-TKIs combined with antiangiogenic agents.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

Xin-Bin Pan and Fa-Song Liang have contributed equally to this work.

References

- [1] H. Sung, J. Ferlay, R. L. Siegel et al., "Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," *CA: A Cancer Journal for Clinicians*, vol. 71, no. 3, pp. 209–249, 2021.
- [2] R. Govindan, N. Page, D. Morgensztern et al., "Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database," *Journal of Clinical Oncology*, vol. 24, no. 28, pp. 4539–4544, 2006.
- [3] W. H. Hsu, J. H. Yang, T. S. Mok, and H. H. Loong, "Overview of current systemic management of EGFR-mutant NSCLC," *Annals of Oncology*, vol. 29, no. suppl_1, pp. i3–i9, 2018.
- [4] C. N. Gann, N. Morsli, X. Chen, and J. Barrueco, "Response to 'Dai W et al. Am J Cancer Res 2015;5(10):3270-3275' from the makers of nintedanib," *Am J Cancer Res*, vol. 6, no. 7, pp. 1547–1548, 2016.
- [5] T. Mitsudomi, S. Morita, Y. Yatabe 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," *The Lancet Oncology*, vol. 11, no. 2, pp. 121–128, 2010.
- [6] R. Rosell, E. Carcereny, R. Gervais et al., "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," *The Lancet Oncology*, vol. 13, no. 3, pp. 239–246, 2012.
- [7] C. Zhou, Y. L. Wu, G. Chen 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," *The Lancet Oncology*, vol. 12, no. 8, pp. 735–742, 2011.
- [8] M. Maemondo, A. Inoue, K. Kobayashi et al., "Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR," *New England Journal of Medicine*, vol. 362, no. 25, pp. 2380–2388, 2010.
- [9] L. V. Sequist, J. C. H. Yang, N. Yamamoto et al., "Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations," *Journal of Clinical Oncology*, vol. 31, no. 27, pp. 3327–3334, 2013.
- [10] Y. L. Wu, C. Zhou, C. P. Hu et al., "Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial," *The Lancet Oncology*, vol. 15, no. 2, pp. 213–222, 2014.
- [11] Z. Deng, Y. Qin, Y. Liu, Y. Zhang, and Y. Lu, "Role of antiangiogenic agents combined with EGFR tyrosine kinase inhibitors in treatment-naïve lung cancer: a meta-analysis," *Clinical Lung Cancer*, vol. 22, no. 1, pp. e70–e83, 2021.
- [12] J. T. Ma, Y. J. Guo, J. Song et al., "Rational application of first-line EGFR-TKIs combined with antiangiogenic inhibitors in advanced EGFR-mutant non-small-cell lung cancer: a systematic review and meta-analysis," *BioMed Research International*, vol. 2021, Article ID 8850256, 15 pages, 2021.
- [13] F. Chen, N. Chen, Y. Yu, and J. Cui, "Efficacy and safety of epidermal growth factor receptor (EGFR) inhibitors plus antiangiogenic agents as first-line treatments for patients with advanced EGFR-mutated non-small cell lung cancer: a meta-analysis," *Frontiers Oncology*, vol. 10, p. 904, 2020.
- [14] S. Zhang, S. Li, J. Liu et al., "Comparative efficacy and safety of TKIs alone or in combination with antiangiogenic agents in advanced EGFR-mutated NSCLC as the first-line treatment: a systematic review and meta-analysis," *Clinical Lung Cancer*, vol. 23, no. 2, pp. 159–169, 2022.
- [15] Y. Chen, S. Wen, Y. Wu, L. Shi, X. Xu, and B. Shen, "Efficacy and safety of first-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) combined with chemotherapy or antiangiogenic therapy as first-line treatment in patients with EGFR-mutant non-small cell lung cancer: a systematic review and meta-analysis," *Critical Reviews in Oncology*, vol. 163, Article ID 103393, 2021.
- [16] H. Zhao, W. Yao, X. Min et al., "Apatinib plus gefitinib as first-line treatment in advanced EGFR-mutant NSCLC: the phase III ACTIVE study (CTONG1706)," *Journal of Thoracic Oncology*, vol. 16, no. 9, pp. 1533–1546, 2021.
- [17] Q. Zhou, C. R. Xu, Y. Cheng et al., "Bevacizumab plus erlotinib in Chinese patients with untreated, EGFR-mutated, advanced NSCLC (ARTEMIS-CTONG1509): a multicenter phase 3 study," *Cancer Cell*, vol. 39, no. 9, pp. 1279–1291.e3, 2021.
- [18] T. Seto, T. Kato, M. Nishio 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," *The Lancet Oncology*, vol. 15, no. 11, pp. 1236–1244, 2014.
- [19] H. Saito, T. Fukuhara, N. Furuya 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," *The Lancet Oncology*, vol. 20, no. 5, pp. 625–635, 2019.

- [20] T. E. Stinchcombe, P. A. Jänne, X. Wang et al., "Effect of erlotinib plus bevacizumab vs. erlotinib alone on progression-free survival in patients with advanced EGFR-mutant non-small cell lung cancer: a phase 2 randomized clinical trial," *JAMA Oncology*, vol. 5, no. 10, pp. 1448–1455, 2019.
- [21] K. Nakagawa, E. B. Garon, T. Seto 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," *The Lancet Oncology*, vol. 20, no. 12, pp. 1655–1669, 2019.
- [22] K. Phan, D. H. Tian, C. Cao, D. Black, and T. D. Yan, "Systematic review and meta-analysis: techniques and a guide for the academic surgeon," *Annals of Cardiothoracic Surgery*, vol. 4, no. 2, pp. 112–122, 2015.
- [23] D. Moher, A. Liberati, J. Tetzlaff, D. G. Altman, and P. Group, "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement," *BMJ*, vol. 339, no. jul21 1, p. b2535, 2009.
- [24] J. P. T. Higgins, D. G. Altman, P. C. Gotzsche et al., "The Cochrane Collaboration's tool for assessing risk of bias in randomised trials," *BMJ*, vol. 343, no. oct18 2, p. d5928, 2011.
- [25] N. Yamamoto, T. Seto, M. Nishio et al., "Erlotinib plus bevacizumab vs. erlotinib monotherapy as first-line treatment for advanced EGFR mutation-positive non-squamous non-small-cell lung cancer: survival follow-up results of the randomized JO25567 study," *Lung Cancer*, vol. 151, pp. 20–24, 2021.
- [26] D. M. Jackman, B. Y. Yeap, L. V. Sequist et al., "Exon 19 deletion mutations of epidermal growth factor receptor are associated with prolonged survival in non-small cell lung cancer patients treated with gefitinib or erlotinib," *Clinical Cancer Research*, vol. 12, no. 13, pp. 3908–3914, 2006.
- [27] Y. L. Wu, Y. Cheng, X. Zhou et al., "Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial," *The Lancet Oncology*, vol. 18, no. 11, pp. 1454–1466, 2017.
- [28] J. C. Soria, Y. Ohe, J. Vansteenkiste et al., "Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer," *New England Journal of Medicine*, vol. 378, no. 2, pp. 113–125, 2018.
- [29] S. Hong, F. Gao, S. Fu et al., "Concomitant genetic alterations with response to treatment and epidermal growth factor receptor tyrosine kinase inhibitors in patients with EGFR-mutant advanced non-small cell lung cancer," *JAMA Oncology*, vol. 4, no. 5, pp. 739–742, 2018.
- [30] Z. Wang, Y. Cheng, T. An et al., "Detection of EGFR mutations in plasma circulating tumour DNA as a selection criterion for first-line gefitinib treatment in patients with advanced lung adenocarcinoma (BENEFIT): a phase 2, single-arm, multicentre clinical trial," *The Lancet Respiratory Medicine*, vol. 6, no. 9, pp. 681–690, 2018.
- [31] H. Liang, written on behalf of Ame Lung Cancer Cooperative Group, Z. Pan et al., "The alteration of T790M between 19 del and L858R in NSCLC in the course of EGFR-TKIs therapy: a literature-based pooled analysis," *Journal of Thoracic Disease*, vol. 10, no. 4, pp. 2311–2320, 2018.
- [32] K. Y. Su, H. Y. Chen, K. C. Li et al., "Pretreatment epidermal growth factor receptor (EGFR) T790M mutation predicts shorter EGFR tyrosine kinase inhibitor response duration in patients with non-small-cell lung cancer," *Journal of Clinical Oncology*, vol. 30, no. 4, pp. 433–440, 2012.
- [33] H. A. Yu, L. G. Paz-Ares, J. C. H. Yang et al., "Phase I study of the efficacy and safety of ramucirumab in combination with osimertinib in advanced t790m-positive EGFR-mutant non-small cell lung cancer," *Clinical Cancer Research*, vol. 27, no. 4, pp. 992–1002, 2021.
- [34] H. Akamatsu, Y. Toi, H. Hayashi et al., "Efficacy of osimertinib plus bevacizumab vs. osimertinib in patients with EGFR t790m-mutated non-small cell lung cancer previously treated with epidermal growth factor receptor-tyrosine kinase inhibitor: west Japan Oncology group 8715L phase 2 randomized clinical trial," *JAMA Oncology*, vol. 7, no. 3, pp. 386–394, 2021.
- [35] R. A. Soo, J. Y. Han, U. Dafni et al., "A randomised phase II study of osimertinib and bevacizumab versus osimertinib alone as second-line targeted treatment in advanced NSCLC with confirmed EGFR and acquired T790M mutations: the European Thoracic Oncology Platform (ETOP 10-16) BOOSTER trial," *Annals of Oncology*, vol. 33, no. 2, pp. 181–192, 2022.
- [36] M. Sheng, F. Wang, Y. Zhao et al., "Comparison of clinical outcomes of patients with non-small-cell lung cancer harbouring epidermal growth factor receptor exon 19 or exon 21 mutations after tyrosine kinase inhibitors treatment: a meta-analysis," *European Journal of Clinical Pharmacology*, vol. 72, no. 1, pp. 1–11, 2016.