Original Article

Efficacy and safety of anlotinib in combination with immune checkpoint inhibitors or not as advanced non-small cell lung cancer treatment: a systematic review and network meta-analysis

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Background: Non-small cell lung cancer (NSCLC) remains a leading cause of cancer mortality. Combined anlotinib and immune checkpoint inhibitors (ICIs) therapy may have synergistic antitumor effects in NSCLC. This study aimed to comparing the efficacy and safety of anlotinib and ICIs treatment, monotherapy and combination in NSCLC.

Methods: We performed a systematic review and network meta-analysis of 14 studies involving 4,308 NSCLC patients across four regimens: anlotinib, ICIs, anlotinib plus ICIs, and placebo. Efficacy outcomes were progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and disease control rate (DCR). Safety outcomes included treatment-related adverse events (TRAEs), TRAE grade three or higher (TRAE ≥3). Analyses were performed in RevMan 5.3 and R 3.5.1 (gemtc package). P<0.05 or effect estimate with 95% confidence interval (CI) that did not include 1 indicated statistical significance.

Results: Fourteen publications involving 4,308 patients across four treatment regimens (anlotinib, ICIs, anlotinib plus ICIs, placebo) were included. For PFS, network meta-analysis showed all three interventions significantly improved PFS versus placebo. Anlotinib plus ICIs demonstrated the greatest PFS improvement [hazard ratio (HR) =0.24; 95% CI: 0.14, 0.36], followed by anlotinib (HR =0.37; 95% CI: 0.23, 0.58), and ICIs (HR =0.43; 95% CI: 0.27, 0.67). For OS, compared to placebo, anlotinib plus ICIs showed the greatest OS improvement (HR =0.52; 95% CI: 0.33, 0.74), followed by anlotinib (HR =0.66; 95% CI: 0.47, 0.95), and ICIs (HR =0.72; 95% CI: 0.54, 0.97). For ORR, anlotinib plus ICIs demonstrated the greatest improvement versus placebo [odds ratio (OR) =5.29; 95% CI: 3.32, 8.58], followed by anlotinib (OR =4.38; 95% CI: 2.42, 8.19), and ICIs (OR =2.17; 95% CI: 1.65, 2.89). For DCR, anlotinib plus ICIs showed the greatest improvement versus placebo (OR =13.32; 95% CI: 4.99, 45.09), followed by anlotinib (OR =5.56; 95% CI: 2.17, 14.38), and ICIs (OR =3.46; 95% CI: 1.29, 10.85). Compared to placebo, anlotinib was associated with the highest risk of TRAEs (OR =3.67, 95% CI: 1.12, 15.77), followed by ICIs (OR =1.83; 95% CI: 1.26, 2.69). Due to lack of data on anlotinib plus ICIs, no comparison was conducted. For grade ≥3 TRAEs, compared to placebo, anlotinib increased the risk (OR =3.67; 95% CI: 1.12, 15.77), while anlotinib plus ICIs (OR =2.45; 95% CI: 0.51, 11.6) and ICIs (OR =1.29; 95% CI: 0.33, 4.38) did not increase the risk.

Conclusions: Anlotinib combined with ICIs demonstrates improved efficacy over monotherapy for NSCLC treatment, without increased adverse events.

Keywords: Anlotinib; immune checkpoint inhibitors (ICIs); non-small cell lung cancer (NSCLC); meta-analysis

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Introduction

Background

Lung cancer remains the leading cause of cancer mortality worldwide, with approximately 350 deaths daily attributed to lung cancer (1). Non-small cell lung cancer (NSCLC) is the predominant histological subtype, representing over 85% of lung cancer cases (2).

Current therapeutic options for NSCLC include surgery, radiotherapy, chemotherapy, immunotherapy, and molecularly targeted agents, either as monotherapy or combination regimens (3). Platinum-doublet chemotherapy with immunotherapy is now the standard first-line treatment for NSCLC lacking targetable driver mutations (4). Following disease progression, standard second-line treatments encompass immune checkpoint inhibitors (ICIs) monotherapy, chemotherapy (docetaxel, pemetrexed, gemcitabine), or docetaxel plus antiangiogenics (5). For ICIs, particularly antibodies targeting programmed cell death protein 1 (anti-PD-1) and programmed death ligand 1 (anti-PD-L1), can reinvigorate cytotoxic $CD8^+$ T cells by blocking PD-1 on activated T cells and PD-L1 on tumor cells, thus harnessing adaptive immunity against NSCLC. In unresectable NSCLC, ICIs have been shown to improve overall survival (OS) and progression-free survival (PFS) following chemoradiation, becoming standard of care (6-8). Interestingly, recent studies demonstrate ICIs also confer improved survival in resectable NSCLC (8). Multitarget tyrosine kinase inhibitors (TKIs) may be considered for third-line NSCLC treatment (9).

Highlight box

Key findings

- The results of this network meta-analysis showed that anlotinib combined with immune checkpoint inhibitors (ICIs) demonstrates improved efficacy over monotherapy for non-small cell lung cancer (NSCLC) treatment, without increased adverse events.

What is known and what is new?

- Anlotinib plus ICIs showed superior progression-free survival and overall survival over anlotinib or ICIs monotherapy, improved objective response rate and disease control rate versus monotherapy, and had no significant differences in adverse events.
- This study aims to investigate the efficacy of anlotinib in combination with immune checkpoint inhibitors in the treatment of NSCLC, in order to provide a rational, informed basis for decision-making.

What is the implication, and what should change now?

- The study evaluated the efficacy and safety of anlotinib plus ICIs in NSCLC patients. Anlotinib plus ICIs can significantly improve efficacy in NSCLC patients.

Rationale and knowledge gap

Anlotinib is a novel multitarget TKI against vascular endothelial growth factor receptor 1 (VEGFR1), vascular endothelial growth factor receptor 2/kinase insert domain receptor (VEGFR2/KDR), and vascular endothelial growth factor receptor 3 (VEGFR3). A phase III trial showed anlotinib prolongs survival in third-line treated NSCLC (10). Several real-world studies demonstrated anlotinib efficacy in NSCLC (11,12). ICIs have exhibited benefit in NSCLC, with nivolumab showing superior OS over docetaxel (13), and atezolizumab improving OS versus docetaxel (14). Pembrolizumab also confers sustained benefit over docetaxel for previously treated PD-L1 positive advanced NSCLC (15). However, ICIs have limited durable response rates, curing only 10–30% of solid tumors (16).

Some studies have evaluated combined anlotinib and ICIs for NSCLC. Preclinical data indicate anlotinib plus ICIs may enhance immune cell infiltration, improve tumor immune microenvironment, and have synergistic antitumor effects (17,18). Clinically, anlotinib plus ICIs shows higher response than ICIs monotherapy in NSCLC, but with more adverse events (19). A phase II study reported efficacy, durability, and safety for sintilimab plus anlotinib (20), while a real-world study found no PFS difference between anlotinib plus ICIs versus anlotinib monotherapy (21). Collectively, current evidence suggests anlotinib plus ICIs may be more effective than monotherapy in NSCLC. However, there is controversy regarding whether the conclusions are statistically significant and whether there is an increased risk of adverse events.

Objective

This study aimed to compare anlotinib plus ICIs, anlotinib

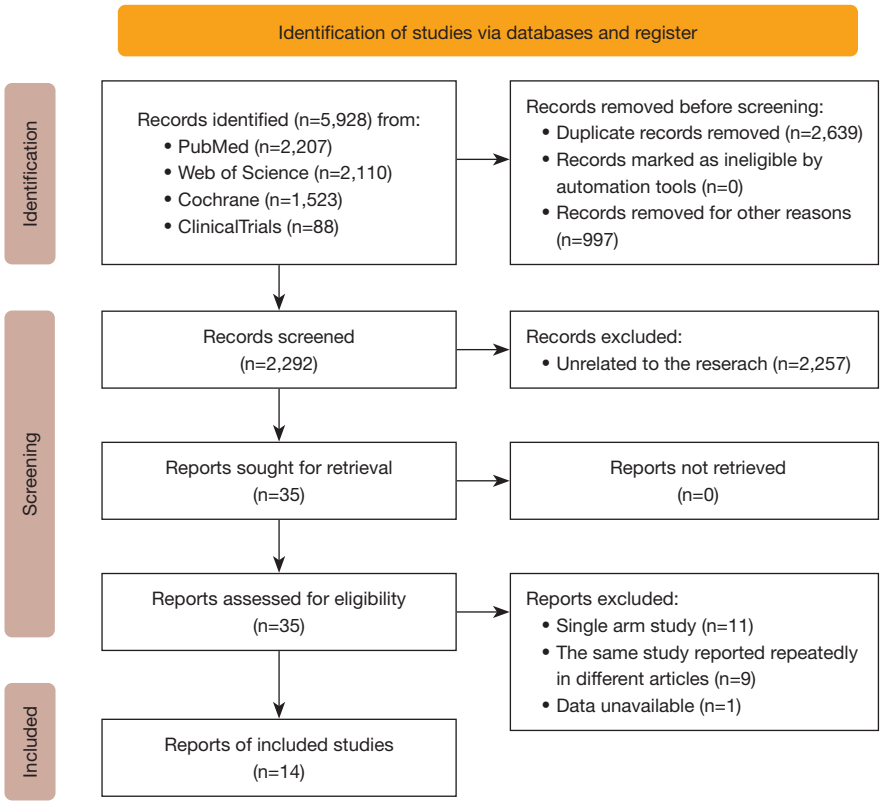

Figure 1 Flowchart of study selection and design.

monotherapy, and ICIs monotherapy using network meta-analysis to determine if combination therapy improves NSCLC efficacy over monotherapy, and to evaluate whether it increases adverse events, providing valuable insights to guide clinical practice. We present this article in accordance with the PRISMA reporting checklist (22) (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1483/rc).

Methods

Literature inclusion and exclusion criteria

A systematic literature search was conducted using PubMed, Web of Science, ClinicalTrials.gov, and the Cochrane Central Register of Controlled Trials (Cochrane) (23) from inception to July 1, 2023, to identify studies of anlotinib plus ICIs, anlotinib monotherapy, and ICIs monotherapy. Randomized controlled trials, real-world studies, and retrospective analyses were eligible for inclusion. The detailed search strategy is presented in Table S1. The electronic database search yielded 5,928 publications (*Figure 1*), of which 14 publications were included. Studies were included if they met the following criteria: (I) anlotinib versus placebo for NSCLC treatment; (II) anlotinib plus ICIs versus anlotinib, ICIs, or placebo for NSCLC; (III) ICIs versus placebo for NSCLC, including ICIs with prior anlotinib combination; (IV) reported at least one of PFS, OS, objective response rate (ORR), disease control rate (DCR), treatment-related adverse events (TRAEs), TRAE grade 3 or higher (TRAE ≥3). PFS, OS, ORR, and DCR are commonly used endpoints to evaluate the efficacy of cancer therapeutics. PFS is the time from treatment start/randomization to either progression or death from any cause (24). OS is defined as the time from treatment start/randomization to death from any cause (24). ORR was defined as the proportion of confirmed complete response (CR) or partial response (PR) at the best response (25). DCR was defined as the percentage of confirmed CR, PR or stable disease at the best response (25). Exclusion criteria were: (I) duplicate publications (retaining the study with longest follow-up); (II) single-arm studies; (III) reviews or meta-analyses. Title/abstract and full-text screening were performed independently by two reviewers, with a third

reviewer available for arbitration.

Data extraction and quality assessment

The following data were extracted from included studies: (I) baseline details including authors, publication year, study design, patient characteristics, pathology, treatment regimens, EGFR mutation rate, and sample size; (II) including of the outcome measures of the hazard ratios (HRs) and their 95% confidence intervals (CIs) for PFS and OS, sample size of ORR, DCR, TRAE, and TRAE ≥3. Commonly reported TRAE encompassed hypertension, fatigue, diarrhea, thyroid dysfunction, anorexia, hand-foot syndrome, nausea, and vomiting. Two independent investigators performed data extraction, with a third investigator reviewing any inconsistencies before selecting the final data.

Risk of bias was assessed per the Cochrane Handbook for Systematic Reviews of Interventions, evaluating random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Overall study quality was rated as "low", "high", or "unclear" risk of bias. Quality assessment was discussed collectively among all study investigators.

Statistical analysis

For survival outcomes (OS, PFS), HR compared treatments. For binary outcomes (ORR, DCR, TRAE, TRAE ≥3), odds ratios (ORs) were estimated. The surface under the cumulative ranking (SUCRA) curve determined optimal treatment (26). Missing values that were not filled were not included in the analysis. A random effects model was used for outcomes with heterogeneity (I^2>50%); otherwise, a fixed effect model was applied. Consistency and inconsistency models were fitted separately. The inconsistency model was fitted using the unrelated mean effects (UME) model (27,28). The consistency model was used if the deviance information criterion (DIC) differed by ≤5 from the inconsistency model; otherwise, the inconsistency model was used (29). Trace plots, density plots, and diagnostic plots were used to assess model robustness. For models with loops, node-splitting analysis assessed inconsistency between comparisons. Analyses were performed in RevMan 5.3 and R 3.5.1 (gemtc package) (30). P<0.05 or effect estimate with 95% CI that did not include 1 indicated statistical significance.

Results

Characteristics of the included studies

Fourteen publications involving 4,308 patients across four treatment regimens (anlotinib, ICIs, anlotinib plus ICIs, placebo) were included (10,11,19,21,31-40). The ten ICIs with reported anlotinib combination were pembrolizumab, nivolumab, sintilimab, toripalimab, atezolizumab, tislelizumab, camrelizumab and durvalumab. Main study characteristics are presented in *Table 1*.

Risk of bias in included studies

Of the 14 included studies, five randomized controlled trials had low risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, and blinded outcome assessment. The remaining nine retrospective studies had high risk of bias for allocation concealment and blinding of participants and personnel. Overall, studies showed good data integrity with low risk of selective reporting. Risk of bias details are presented in *Figure 2*.

Network meta-analysis

Network meta-analysis was conducted for efficacy (PFS, OS, ORR, DCR) and safety (TRAE, TRAE ≥3, common TRAE) outcomes. *Table 2* summarizes included studies per outcome measure, heterogeneity test (I^2 values), DIC values for consistency and inconsistency models, and the final model selected. Network plots for each outcome are displayed in *Figure 3*. Network plot of common TRAE network meta-analysis is shown in Figure S1. As evidenced by the model trace plots, density plots, and diagnostic plots (Figures S2-S5), the models demonstrated adequate convergence. Overall, the models exhibited satisfactory node consistency, as shown by the node-splitting analysis (Table S2).

Network meta-analyses for efficacy outcomes

For PFS, network meta-analysis showed that all the three interventions significantly improved PFS versus placebo. Anlotinib plus ICIs demonstrated the greatest PFS improvement (HR =0.24; 95% CI: 0.14, 0.36), followed by anlotinib (HR =0.37; 95% CI: 0.23, 0.58), and ICIs (HR =0.43; 95% CI: 0.27, 0.67). PFS improvement with anlotinib plus ICIs was superior to other treatments, with statistically significant differences. SUCRA rankings

Table 1 The characteristics of included studies

Study ID	Study design	Patients	Pathology	Treatment	Size (n)	EGFR positive (n)	Objective response (n)	Disease control (n)	PFS		OS		TRAE (n)	TRAE ≥3 (n)
									Median (months)	HR (95% CI)	Median (months)	HR (95% CI)		
Han 2018, (10)	Phase III clinical trials	Failed at least 1 lines of treatment	Adenocarcinoma/ squamous/others	Anlotinib	294	93	27	238	5.4	0.25 (0.19, 0.31)	9.6	0.68 (0.54, 0.87)	286	182
				Placebo	143	45	1	53	1.4	Control	6.3	Control	126	53
Zhang 2021, (11)	Case-control study	Advanced NSCLC	Adenocarcinoma/ squamous/others	Anlotinib plus ICIs	73	4	15	67	5.8	0.68 (0.68, 0.97)	10.5	0.83 (0.7, 0.99)	NR	13
				Anlotinib	66	14	12	47	4.2	Control	8.7	Control	NR	10
Shi 2022, (19)	A cohort study	NSCLC patients	Adenocarcinoma/ squamous/others	Anlotinib plus ICIs	240	66	36	279	5.9	0.727 (0.59, 0.9)	NR	NR	NR	47
				ICIs	191	18	21	201	4.1	Control	NR	NR	NR	21
Xiong 2021, (21)	Retrospective	Advanced NSCLC	Adenocarcinoma/ squamous/others	Anlotinib plus ICIs	30	4	3	21	4.2	0.627 (0.31, 1.26)	NR	NR	NR	14
		Relapsed NSCLC in the 2 or later-line		Anlotinib	24	5	3	17	3.1	Control	NR	NR	NR	8
Han 2018, (31)	Phase 2 clinical trials	Failed at least 2 lines of treatment	Adenocarcinoma/ squamous/others	Anlotinib	60	12	6	50	4.8	0.32 (0.2, 0.51)	9.3	0.78 (0.51, 1.18)	55	13
				Placebo	57	9	0	18	1.2	Control	6.3	Control	40	3
Wang 2022, (32)	Retrospective	NSCLC patients with EGFR negative	Adenocarcinoma/ squamous/others	Anlotinib	38	0	5	29	3.2	1.56 (1.1, 2.21)	9.5	1.94 (1.17, 3.21)	NR	NR
				Anlotinib plus ICIs	22	0	4	20	5	Control	18.4	Control	NR	NR
		NSCLC patients with EGFR positive	Adenocarcinoma/ squamous/others	Anlotinib	18	18	0	14	1.83	3.84 (1.72, 8.56)	28.34	1.07 (0.96, 1.19)	NR	NR
				Anlotinib plus ICIs	13	13	4	13	7.03	Control	31.37	Control	NR	NR
Zhang 2022, (33)	Retrospective	Failed at least 1 line of treatment	Non-squamous NSCLC patients	ICIs	20	NR	6	11	5.85	1.15 (1.01, 1.31)	NR	NR	NR	4
				Anlotinib	17	NR	5	10	4.36	1.35 (1.08, 1.68)	NR	NR	NR	13
				Anlotinib plus ICIs	23	NR	10	21	6.76	Control	NR	NR	NR	4
Chen 2021, (34)	Retrospective	Failed at least 1 line of treatment	NR	Anlotinib plus ICIs	28	NR	6	18	3.24	0.41 (0.23, 0.73)	15.97	0.41 (0.19, 0.87)	NR	NR
				ICIs	32	NR	1	13	1.5	Control	7.41	Control	NR	NR
He 2022, (35)	Retrospective	NSCLC patients	NR	Anlotinib plus ICIs	32	NR	20	26	9.8	0.73 (0.53, 1)	NR	NR	NR	NR
				ICIs	36	NR	13	20	7.2	Control	NR	NR	NR	NR
Yu 2023, (36)	Retrospective	Relapsed NSCLC in the 2 or later-line	NR	Anlotinib plus ICIs	71	NR	5	58	6	0.62 (0.47, 0.82)	16.13	0.74 (0.55, 0.99)	NR	NR
				ICIs	63	NR	2	36	3.41	Control	11.88	Control	NR	NR
Zhang 2021, (37)	Retrospective	Untreated NSCLC in the first-line	Adenocarcinoma/ squamous/others	Anlotinib plus ICIs	6	0	1	5	8	0.32 (0.08, 1.22)	NR	NR	NR	NR
				ICIs	6	0	0	2	3	Control	NR	NR	NR	NR
		Relapsed NSCLC in the 2 or later-line		Anlotinib plus ICIs	62	10	12	53	8	0.25 (0.21, 0.67)	NR	NR	NR	NR
				ICIs	41	0	1	24	2	Control	NR	NR	NR	NR
Antonia 2017, (38)	Phase 3 clinical trials	Failed at least 2 lines of treatment	Adenocarcinoma/ squamous/others	ICIs	476	29	126	359	16.8	0.52 (0.42, 0.65)	23.2	0.52 (0.39, 0.69)	460	142
				Placebo	237	14	34	153	5.6	Control	14.6	Control	222	61
Spigel 2022, (39)	Phase 3 clinical trials	Failed at least 2 lines of treatment	Adenocarcinoma/ squamous/others	ICIs	476	17	142		16.9	0.55 (0.45, 0.68)	47.5	0.72 (0.59, 0.89)	NR	NR
				Placebo	237	8	43		5.6	Control	29.1	Control	NR	NR
O'Brien 2022, (40)	Phase 3 clinical trials	NSCLC patients completely resected	Adenocarcinoma/ squamous/others	ICIs	590	39	NR	NR	NR	NR	NR	NR	556	198
				Placebo	587	34	NR	NR	NR	NR	NR	NR	529	150

NSCLC, non-small cell lung cancer; NR, no report; ICIs, immune checkpoint inhibitors; n, number; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; TRAE, treatment-related adverse event; TRAE ≥3, TRAE grade 3 or higher.

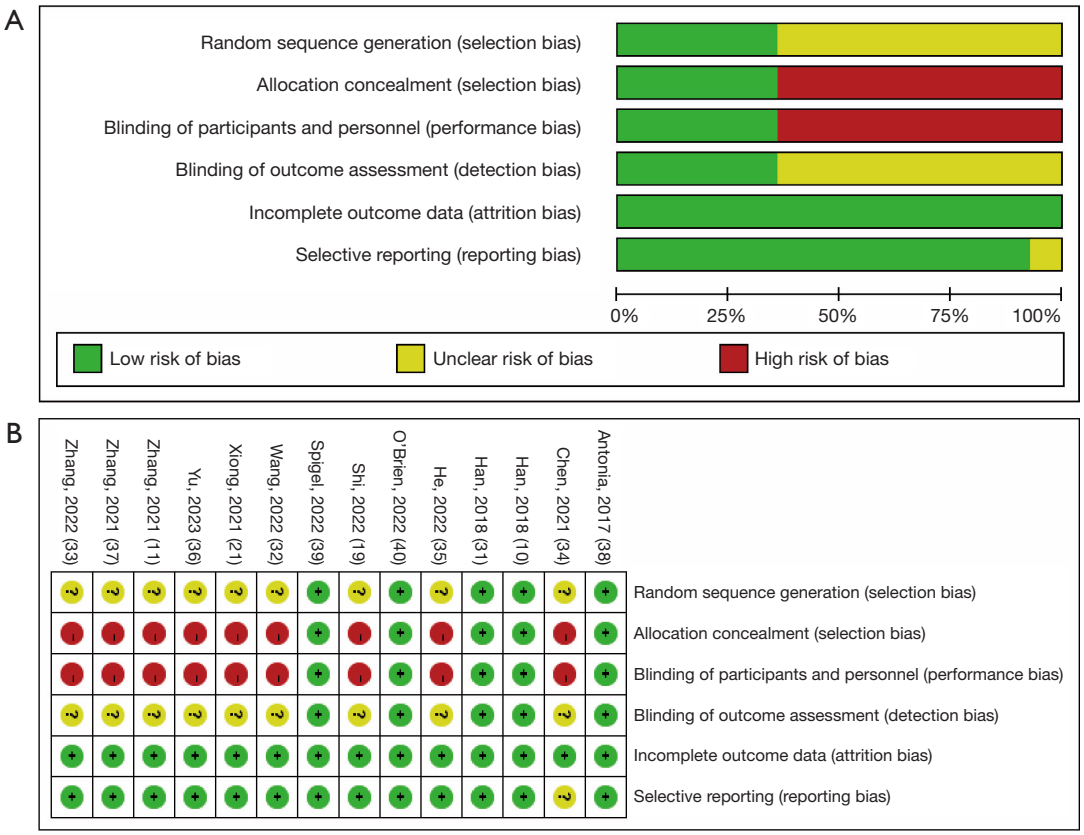

Figure 2 Quality assessment of included studies (10,11,19,21,31-40). + indicates low risk of bias; – indicates high risk of bias; ? indicates unknown risk of bias.

Table 2 Table of model parameter summary and model selection

Outcomes	I^2	DIC consistency	DIC inconsistency	Model selection
PFS	95.84	29.22	30.44	Random consistency
OS	67.42	19.46	19.78	Random consistency
ORR	20.94	58.75	57.73	Fixed consistency
DCR	67.70	52.11	52.18	Random consistency
TRAE	0.00	12.11	12.17	Fixed consistency
TRAE ≥3	59.94	35.43	34.91	Fixed consistency
Hypertension	0.00	21.82	21.79	Fixed consistency
Fatigue	6.89	27.39	27.39	Fixed consistency
Diarrhea	0.00	23.83	25.73	Fixed consistency
Thyroid abnormalities	0.00	20.21	21.63	Fixed consistency
Anorexia	0.00	19.73	19.65	Fixed consistency
Hand-foot syndrome	0.00	19.82	19.87	Fixed consistency
Nausea	0.00	17.69	18.55	Fixed consistency

PFS, progression-free survival; OS, overall survival; ORR, objective response rate; DCR, disease control rate; TRAE, treatment-related adverse event; TRAE ≥3, TRAE grade 3 or higher; I^2, statistical measure of heterogeneity; DIC, deviance information criterion.

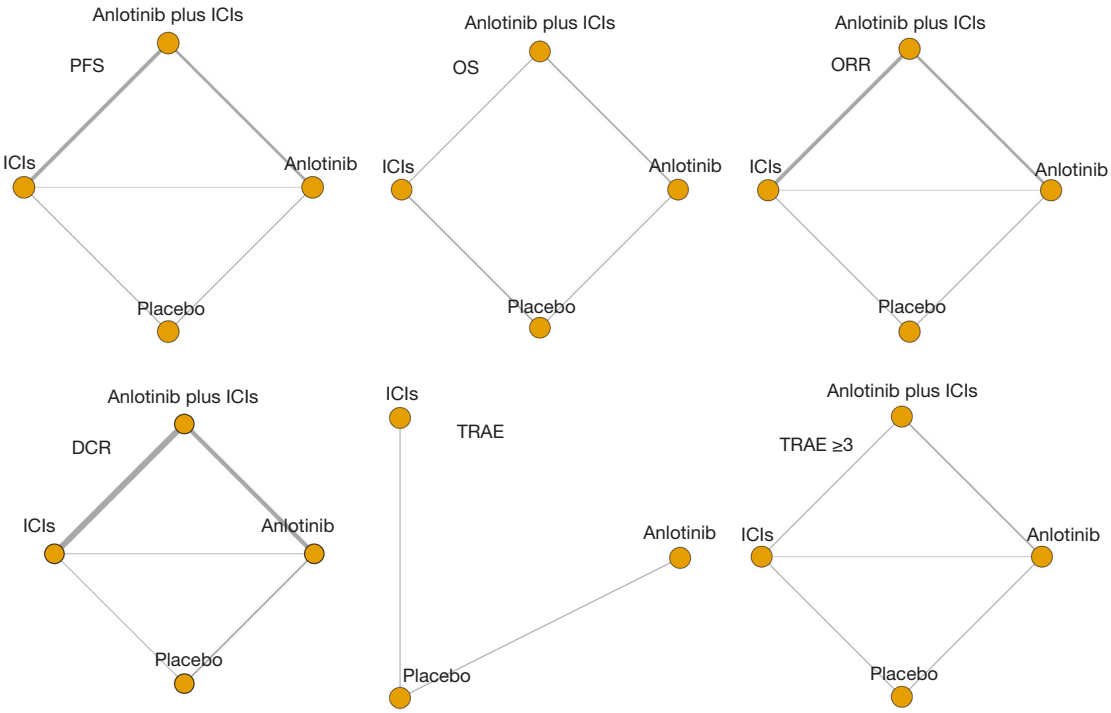

Figure 3 Network plot of network meta-analysis. PFS, progression-free survival; ICIs, immune checkpoint inhibitors; OS, overall survival; ORR, objective response rate; DCR, disease control rate; TRAE, treatment-related adverse event; TRAE ≥3, TRAE grade 3 or higher.

suggested anlotinib plus ICIs (0.99) as the optimal PFS intervention.

Similarly for OS, compared to placebo, anlotinib plus ICIs showed the greatest OS improvement (HR =0.52; 95% CI: 0.33, 0.74), followed by anlotinib (HR =0.66; 95% CI: 0.47, 0.95), and ICIs (HR =0.72; 95% CI: 0.54, 0.97). No significant difference existed between anlotinib and ICIs. Anlotinib plus ICIs showed slight statistical differences versus anlotinib and ICIs. SUCRA rankings favored anlotinib plus ICIs (0.98) for OS.

For ORR, anlotinib plus ICIs demonstrated the greatest improvement versus placebo (OR =5.29; 95% CI: 3.32, 8.58), followed by anlotinib (OR =4.38; 95% CI: 2.42, 8.19), and ICIs (OR =2.17; 95% CI: 1.65, 2.89). No significant difference was seen between anlotinib and anlotinib plus ICIs. SUCRA rankings suggested anlotinib plus ICIs (0.92) as optimal for ORR.

For DCR, anlotinib plus ICIs showed the greatest improvement versus placebo (OR =13.32; 95% CI: 4.99, 45.09), followed by anlotinib (OR =5.56; 95% CI: 2.17, 14.38), and ICIs (OR =3.46; 95% CI: 1.29, 10.85). DCR improvement with anlotinib plus ICIs was superior to other treatments, with statistically significant differences. SUCRA rankings favored anlotinib plus ICIs (0.99) for DCR.

Network meta-analyses for safety outcomes

For TRAE and TRAE ≥3, anlotinib, ICIs, and placebo were compared in the TRAE network due to unavailable Anlotinib Plus ICIs data. Versus placebo, anlotinib, anlotinib plus ICIs, and ICIs showed increased adverse event risk, with anlotinib monotherapy conferring the highest risk. Network meta-analysis of common TRAE found anlotinib plus ICIs had the greatest risk of hypertension, fatigue, anorexia, and hand-foot syndrome. However, except for a slightly increased fatigue risk (statistically significant), differences in hypertension, diarrhea, thyroid dysfunction, anorexia, hand-foot syndrome, and nausea risks for anlotinib plus ICIs versus anlotinib were not statistically significant.

Network meta-analysis results of effect estimate with 95% CI are presented in *Table 3*. *Table 4* shows SUCRA values per intervention for each outcome.

Discussion

In this meta-analysis of 14 studies and 4,308 NSCLC

Table 3 Multiple treatment comparison result based on network consistency model

Outcome	Treatment	Anlotinib	Anlotinib plus ICIs	ICIs	Placebo
PFS, HR (95% CI)	Anlotinib	–	1.56 (1.13, 2.32)	0.86 (0.58, 1.28)	0.37 (0.23, 0.58)
	Anlotinib plus ICIs	0.64 (0.43, 0.89)	–	0.55 (0.39, 0.73)	0.24 (0.14, 0.36)
	ICIs	1.16 (0.78, 1.72)	1.8 (1.37, 2.58)	–	0.43 (0.27, 0.67)
	Placebo	2.71 (1.74, 4.39)	4.22 (2.74, 7.09)	2.34 (1.5, 3.65)	–
OS, HR (95% CI)	Anlotinib	–	1.26 (0.99, 1.84)	0.91 (0.62, 1.36)	0.66 (0.46, 0.95)
	Anlotinib plus ICIs	0.79 (0.54, 1.01)	–	0.72 (0.47, 1.01)	0.52 (0.33, 0.74)
	ICIs	1.1 (0.74, 1.6)	1.39 (0.99, 2.15)	–	0.72 (0.54, 0.97)
	Placebo	1.51 (1.05, 2.15)	1.91 (1.35, 3.02)	1.38 (1.03, 1.86)	–
ORR, OR (95% CI)	Anlotinib	–	0.83 (0.49, 1.39)	2.01 (1.13, 3.63)	4.38 (2.42, 8.19)
	Anlotinib plus ICIs	1.21 (0.72, 2.03)	–	2.43 (1.63, 3.68)	5.29 (3.32, 8.58)
	ICIs	0.5 (0.28, 0.88)	0.41 (0.27, 0.61)	–	2.17 (1.65, 2.89)
	Placebo	0.23 (0.12, 0.41)	0.19 (0.12, 0.3)	0.46 (0.35, 0.61)	–
DCR, OR (95% CI)	Anlotinib	–	0.42 (0.16, 0.88)	1.61 (0.6, 3.75)	5.56 (2.17, 14.38)
	Anlotinib plus ICIs	2.4 (1.13, 6.11)	–	3.84 (2.09, 7.63)	13.32 (4.99, 45.09)
	ICIs	0.62 (0.27, 1.66)	0.26 (0.13, 0.48)	–	3.46 (1.29, 10.85)
	Placebo	0.18 (0.07, 0.46)	0.08 (0.02, 0.2)	0.29 (0.09, 0.78)	–
TRAE, OR (95% CI)	Anlotinib	–	–	2.65 (1.24, 5.95)	4.87 (2.51, 9.94)
	ICIs	0.38 (0.17, 0.81)	–	–	1.83 (1.26, 2.69)
	Placebo	0.21 (0.1, 0.4)	–	0.55 (0.37, 0.8)	–
TRAE ≥3, OR (95% CI)	Anlotinib	–	1.52 (0.49, 5.9)	2.89 (0.86, 14.48)	3.67 (1.12, 15.77)
	Anlotinib plus ICIs	0.66 (0.17, 2.02)	–	1.91 (0.5, 8.07)	2.45 (0.51, 11.6)
	ICIs	0.35 (0.07, 1.16)	0.52 (0.12, 2)	–	1.29 (0.33, 4.38)
	Placebo	0.27 (0.06, 0.89)	0.41 (0.09, 1.97)	0.78 (0.23, 3)	–
Hypertension, OR (95% CI)	Anlotinib	–	0.75 (0.45, 1.23)	13.5 (7.61, 24.43)	11.97 (7.63, 19.32)
	Anlotinib plus ICIs	1.34 (0.81, 2.21)	–	18.08 (8.42, 39.29)	16.03 (8.14, 32.05)
	ICIs	0.07 (0.04, 0.13)	0.06 (0.03, 0.12)	–	0.89 (0.62, 1.26)
	Placebo	0.08 (0.05, 0.13)	0.06 (0.03, 0.12)	1.13 (0.79, 1.61)	–
Fatigue, OR (95% CI)	Anlotinib	–	0.58 (0.34, 0.96)	1.95 (1.25, 3.05)	2.22 (1.53, 3.25)
	Anlotinib plus ICIs	1.72 (1.04, 2.91)	–	3.36 (1.7, 6.69)	3.84 (2.04, 7.29)
	ICIs	0.51 (0.33, 0.8)	0.3 (0.15, 0.59)	–	1.14 (0.9, 1.46)
	Placebo	0.45 (0.31, 0.65)	0.26 (0.14, 0.49)	0.88 (0.69, 1.11)	–
Diarrhea, OR (95% CI)	Anlotinib	–	1.10 (0.64, 1.91)	2.76 (1.62, 4.82)	3.62 (2.30, 5.89)
	Anlotinib plus ICIs	0.91 (0.52, 1.57)	–	2.51 (1.26, 5.12)	3.30 (1.70, 6.47)
	ICIs	0.36 (0.21, 0.62)	0.40 (0.20, 0.79)	–	1.31 (0.96, 1.79)
	Placebo	0.28 (0.17, 0.43)	0.30 (0.15, 0.59)	0.76 (0.56, 1.04)	–

Table 3 *(continued)*

Table 3 *(continued)*

Outcome	Treatment	Anlotinib	Anlotinib plus ICIs	ICIs	Placebo
Thyroid abnormalities, OR (95% CI)	Anlotinib	–	1.48 (0.58, 3.88)	1.72 (0.38, 8.05)	11.56 (6.58, 22.28)
	Anlotinib plus ICIs	0.68 (0.26, 1.71)	–	1.16 (0.34, 3.95)	7.9 (2.53, 24.07)
	ICIs	0.58 (0.12, 2.66)	0.86 (0.25, 2.91)	–	6.8 (1.3, 35.08)
	Placebo	0.09 (0.04, 0.15)	0.13 (0.04, 0.39)	0.15 (0.03, 0.77)	–
Anorexia, OR (95% CI)	Anlotinib	–	0.92 (0.48, 1.74)	1.43 (0.77, 2.6)	1.65 (1.12, 2.46)
	Anlotinib plus ICIs	1.09 (0.58, 2.07)	–	1.55 (0.64, 3.75)	1.8 (0.86, 3.84)
	ICIs	0.7 (0.38, 1.3)	0.64 (0.27, 1.57)	–	1.16 (0.73, 1.86)
	Placebo	0.61 (0.41, 0.89)	0.56 (0.26, 1.17)	0.87 (0.54, 1.37)	–
Hand-foot syndrome, OR (95% CI)	Anlotinib	–	0.61 (0.35, 1.04)	–	9.05 (5.2, 17.07)
	Anlotinib plus ICIs	1.65 (0.96, 2.85)	–	–	15.02 (6.9, 34.33)
	Placebo	0.11 (0.06, 0.19)	0.07 (0.03, 0.15)	–	–
Nausea, OR (95% CI)	Anlotinib	–	1.14 (0.56, 2.32)	3.19 (0.91, 11.88)	4.19 (1.15, 16.42)
	Anlotinib plus ICIs	0.88 (0.43, 1.79)	–	2.8 (0.99, 8.38)	3.68 (1.24, 11.58)
	ICIs	0.31 (0.08, 1.1)	0.36 (0.12, 1.01)	–	1.32 (0.96, 1.81)
	Placebo	0.24 (0.06, 0.87)	0.27 (0.09, 0.81)	0.76 (0.55, 1.04)	–

PFS, progression-free survival; OS, overall survival; ORR, objective response rate; DCR, disease control rate; TRAE, treatment-related adverse event; TRAE ≥3, TRAE grade 3 or higher; HR, hazard ratio; CI, confidence interval; OR, odds ratio; ICIs, immune checkpoint inhibitors.

Table 4 SUCRA ranking result based on network consistency model

Outcomes	Anlotinib	Anlotinib plus ICIs	ICIs	Placebo
PFS	0.6	1	0.4	0
OS	0.57	0.98	0.43	0.01
ORR	0.74	0.92	0.34	0
DCR	0.62	1	0.38	0
TRAE	1	–	0.5	0
TRAE ≥3	0.92	0.66	0.29	0.13
Hypertension	0.71	0.96	0.09	0.25
Fatigue	0.67	0.99	0.29	0.05
Diarrhea	0.88	0.79	0.32	0.01
Thyroid abnormalities	0.85	0.6	0.54	0
Anorexia	0.75	0.79	0.34	0.11
Hand-foot syndrome	0.52	–	0.98	0
Nausea	0.86	0.77	0.34	0.02

SUCRA, surface under the cumulative ranking; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; DCR, disease control rate; TRAE, treatment-related adverse event; TRAE ≥3, TRAE grade 3 or higher; ICIs, immune checkpoint inhibitors.

patients, three regimens were compared as third-line treatment: anlotinib monotherapy, anlotinib plus ICIs, and ICI monotherapy. For efficacy, anlotinib plus ICIs showed superior PFS over anlotinib or ICIs monotherapy. For OS, anlotinib plus ICIs demonstrated marginally significant improvement versus anlotinib (HR =0.79, 95% CI: 0.54, 1.01) and versus ICIs (HR =0.72, 95% CI: 0.47, 1.01). Anlotinib plus ICIs had comparable ORR to anlotinib monotherapy and better ORR than ICI monotherapy. Anlotinib plus ICIs also improved DCR over monotherapy. SUCRA rankings suggested anlotinib plus ICIs may prolong survival in NSCLC. For safety, studies of anlotinib plus ICIs reported adverse reactions by type, limiting TRAE analysis. Hypertension is a common anlotinib-associated adverse event in NSCLC. SUCRA rankings showed anlotinib plus ICIs conferred a higher incidence of hypertension, fatigue, and anorexia. Interestingly, some studies indicate anlotinib-induced hypertension may improve PFS (32), although the mechanism requires further study. The incidence of TRAE ≥3, diarrhea, thyroid dysfunction, and nausea was higher with anlotinib monotherapy than combination therapy or ICI monotherapy. Overall, no significant differences existed between regimens, indicating combination therapy was well tolerated. In recent decades, treatment of NSCLC has improved considerably with the development of ICIs and TKIs. ICIs have demonstrated efficacy as first- and second-line NSCLC treatments. ICIs activate effector T cells to normalize tumor vasculature and downregulate VEGF through feedback to increase T cell infiltration and cytotoxicity (41). As a novel small molecule TKIs, anlotinib has multiple targets and can effectively inhibit tyrosine kinase activity, blocking receptor phosphorylation and downstream signaling, and promoting cancer cell apoptosis (42). For advanced NSCLC, third-line anlotinib significantly improved median PFS and OS versus placebo. Anlotinib may also confer superior survival over other TKIs (6). Some evidence indicates TKIs could impact the immune microenvironment and enhance immune responses. Collectively, these data provide a rationale for combined anlotinib and ICI therapy for lung cancer. In recent years, studies have assessed anlotinib plus ICIs for NSCLC, with most supporting improved outcomes with combination therapy over monotherapy, although some studies found no significant differences or increased adverse events with combination treatment. Therefore, this meta-analysis aimed to compare the efficacy and safety of anlotinib plus ICIs versus monotherapy for NSCLC.

In this study, we found that compared to placebo, anlotinib plus ICIs, anlotinib monotherapy, and ICIs monotherapy all demonstrated improved PFS, OS, ORR, and DCR. For PFS, anlotinib plus ICIs showed greater improvement versus anlotinib alone (HR =0.64; 95% CI: 0.43, 0.89) and ICIs alone (HR =0.55; 95% CI: 0.39, 0.73). For OS, anlotinib plus ICIs trended towards greater benefit over anlotinib (HR =0.79; 95% CI: 0.54, 1.01) and ICIs (HR =0.72; 95% CI: 0.47, 1.01). For ORR, anlotinib plus ICIs did not differ significantly from anlotinib (OR =1.21; 95% CI: 0.72, 2.03) but was superior to ICIs (OR =2.43; 95% CI: 1.63, 3.68). Similarly for DCR, no difference was seen between combination therapy and anlotinib, while ICIs alone were most efficacious. No significant differences in TRAE ≥3 were observed between regimens. Chen found that combined anti-CTLA4 and anti-PD-1 immunotherapy with stereotactic radiotherapy for metastatic NSCLC improved patient survival, with 18-month PFS of 23% in the anti-PD-1 group (37%) versus 63% in the anti-CTLA4 group (24%) (P=0.02), and 18-month OS of 39% and 66% (P=0.08), respectively. Anti-PD-1 demonstrated greater efficacy (43). Liu *et al.* showed anti-CTLA4 plus PD-1/PD-L1 immunotherapy had superior effectiveness over chemotherapy, with improved OS (HR =0.77, 95% CI: 0.66, 0.91) and PFS (HR =0.77, 95% CI: 0.70, 0.85) (44). A meta-analysis by Zhang *et al.* comparing four multi-targeted TKIs for NSCLC found anlotinib had the best ORR (OR =39.26; 95% CI: 2.36, 2,748.06), DCR (OR =8.69; 95% CI: 1.70, 50.18) and PFS (HR =0.27; 95% CI: 0.10, 0.78) versus placebo (9). TKIs, PD-1/PD-L1, anti-CTLA4 immunotherapy, and chemotherapy are all effective therapies for NSCLC. This study demonstrates anlotinib plus ICIs is a promising combination regimen that significantly improves patient survival and response rates compared to monotherapy. Further research into alternative combination approaches for NSCLC is warranted.

This study has some limitations. First, the lack of randomized controlled trials of anlotinib plus ICIs for NSCLC necessitated the inclusion of real-world and retrospective analyses. The inconsistent populations and lack of high-quality randomized data may have impacted results. Second, some studies suggest factors like EGFR mutations (32), treatment line (11), brain metastasis (21), and PD-L1 expression (34) could affect efficacy, but detailed data were insufficient for subgroup analyses. Moving forward, new methods like model-based meta-analysis (45) or random controlled clinical trials could help explore these factors.

Recently, combination regimens have demonstrated

improved efficacy over monotherapy for NSCLC (46-48). Here, we preliminarily showed anlotinib plus ICIs improves efficacy and safety versus monotherapy for NSCLC. A phase Ib trial reported efficacy and safety for first-line sintilimab plus anlotinib in advanced NSCLC. Additional clinical trials may provide further evidence supporting anlotinib and ICIs for NSCLC.

Conclusions

Our study demonstrated superior efficacy for anlotinib combined with ICIs versus anlotinib or ICI monotherapy in NSCLC patients, without increased adverse event risk.

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Footnote

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