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Efficacy and safety of anlotinib monotherapy or combination therapy in the treatment of patients with advanced non-small cell lung cancer: a retrospective real-world study conducted in East China

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Abstract

Background Non-small cell lung cancer (NSCLC) is one of the leading causes of cancer-related mortality worldwide. Despite significant advancements in chemotherapy, targeted therapy, and immunotherapy, the prognosis for advanced NSCLC remains poor. The development of resistance to standard treatments and the lack of effective therapeutic options for heavily pretreated patients underscore the urgent need for novel treatment strategies. Angiogenesis plays a pivotal role in tumor growth and metastasis, making it a critical target in cancer therapy. Anlotinib, a novel multi-target tyrosine kinase inhibitor, has demonstrated potent anti-tumor activity in patients with advanced NSCLC.

Methods The retrospective analysis was conducted on clinical data from 82 patients with advanced NSCLC who received either anlotinib monotherapy or combination therapy. Patients were divided into two groups based on different treatment modalities: anlotinib monotherapy group (30 patients) and anlotinib combination therapy group (52 patients). The anlotinib combination therapy group received anlotinib in combination with immune checkpoint inhibitors (ICIs), chemotherapy, or targeted drugs. The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), disease control rate (DCR), and adverse events.

Results Although the difference in ORR between the two groups was not statistically significant ($P > 0.05$), the DCR was notably higher in the combination therapy group compared to the monotherapy group (86.5% vs. 66.7%, $P < 0.05$). In the anlotinib combination therapy group, patients demonstrated a significantly longer PFS compared to those in the anlotinib monotherapy group (median PFS: 20.0 m vs. 9.3 m, $P = 0.030$). The PFS% at 12, 18, and 24 months in the anlotinib combination therapy group were 65.38%, 55.77%, and 28.85%, respectively, all significantly higher than in the anlotinib monotherapy group ($P < 0.05$). In the combination therapy regimen, anlotinib combined

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with ICIs significantly prolonged patients' PFS (median PFS: 25.4 m vs. 9.3 m, $P < 0.05$). Subgroup analysis results indicated that in subgroups of male patients, patients with a history of hypertension, patients with ≥ 3 lines of treatment, and patients without a history of anti-angiogenic therapy, the PFS in the anlotinib combination therapy group was significantly better than in the anlotinib monotherapy group ($P < 0.05$). Although the incidence of bleeding and skin adverse reactions was higher in the anlotinib combination therapy group compared to the monotherapy group, the difference was not statistically significant ($P > 0.05$).

Conclusion Anlotinib combination therapy was associated with improved PFS in advanced NSCLC patients, with a tolerable safety profile.

Keywords Anlotinib, Advanced NSCLC, Combination therapy, Efficacy, Safety

Introduction

Lung cancer remains a global health challenge as the leading cause of cancer-related mortality, with over 2.2 million reported cases and nearly 1.8 million fatalities in 2020 alone [1]. NSCLC includes squamous, adenocarcinoma, and large-cell carcinoma, accounting for 80-85% of all lung cancers, with an overall 5-year survival rate of 20% [2, 3]. Chemotherapy, the conventional treatment, yields limited advantages for advanced NSCLC due to its substantial side effects, often poorly tolerated by patients [4]. The emergence of targeted drugs and immunotherapy is promising for the treatment of NSCLC [5–7].

Angiogenesis plays an important role in tumor occurrence, proliferation, and metastasis [8, 9]. Anti-angiogenic drugs are considered to have promising therapeutic effects, especially in patients who cannot tolerate chemotherapy. Anlotinib, a multi-targeted tyrosine kinase inhibitor, is frequently used in clinical settings. It impedes the vascular growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR), thereby efficiently thwarting tumor angiogenesis [10, 11]. The phase III ALTER0303 study demonstrated that patients with advanced NSCLC receiving anlotinib as third or further line treatment had significantly longer overall survival (OS) (median OS: 9.6 m vs. 6.3 m) and PFS (median PFS: 5.4 m vs. 1.4 m) than patients receiving placebo [12].

Previous studies suggested the potential synergistic effects of anti-angiogenic drugs in combination with other types of therapy [7, 13, 14]. However, the real-world efficacy and safety of anlotinib in combination with other drugs for advanced NSCLC must be further explored. This study aimed to evaluate the efficacy and safety of anlotinib monotherapy or combination therapy in the treatment of patients with advanced NSCLC.

Materials and methods

Patients

This study retrospectively analyzed the clinical data of 82 patients with advanced NSCLC treated with anlotinib (monotherapy or combination therapy) at the Department of Respiratory and Critical Care Medicine, Nanjing Drum Tower Hospital Clinical College of Nanjing University of Chinese Medicine, from July 2018 to September 2021 (Fig. 1). The study was approved by the Medical Ethics Committee of Nanjing Drum Tower Hospital. (Ethics No. 2020-137-13).The inclusion criteria were as follows: (i) the presence of pathologically or cytologically confirmed NSCLC, (ii) pathological stage III-IV, (iii) PS score of 0–1, (iv) age ≥ 18 years old, (v) expected survival time ≥ 3 months, (vi) patients received either anlotinib monotherapy or combination therapy with ICIs, chemotherapy, or targeted drugs. Exclusion criteria: (i) with autoimmune and immunosuppressive diseases, (ii) combined with primary tumors at other sites, (iii) poor compliance and missed visits, (iv) no measurable lesions or lesions that could not be evaluated.

Patients were divided into two groups based on whether they received anlotinib alone or in combination with ICIs, chemotherapy, or targeted drugs. The dose of anlotinib was 8–12 mg once daily for 2 weeks, followed by 1-week discontinuation, with the clinician adjusting the dose during treatment based on the patient's response. ICIs included sintilimab [200 mg], camrelizumab [200 mg], and pembrolizumab [200 mg], which were given intravenously on the first day of each cycle (3 weeks for 1 cycle). Chemotherapeutic agents include pemetrexed [500 mg/m^2], docetaxel [75 mg/m^2], given intravenously on the first day of each cycle, and gemcitabine [1,250 mg/m^2], given intravenously on the first and eighth days of each cycle. Targeted agents included osimertinib (80 mg orally once daily), gefitinib (250 mg orally once daily), and erlotinib (150 mg orally once daily). Prior anti-angiogenic therapy included bevacizumab (Avastin) and recombinant human vascular endothelial inhibitor injection (Endostar).

Data collection

Clinical and survival data for all patients were analyzed retrospectively through medical records and telephone interviews. The following data were collected from medical records: age, gender, smoking history, histology, presence of metastases, presence of hypertension, and history

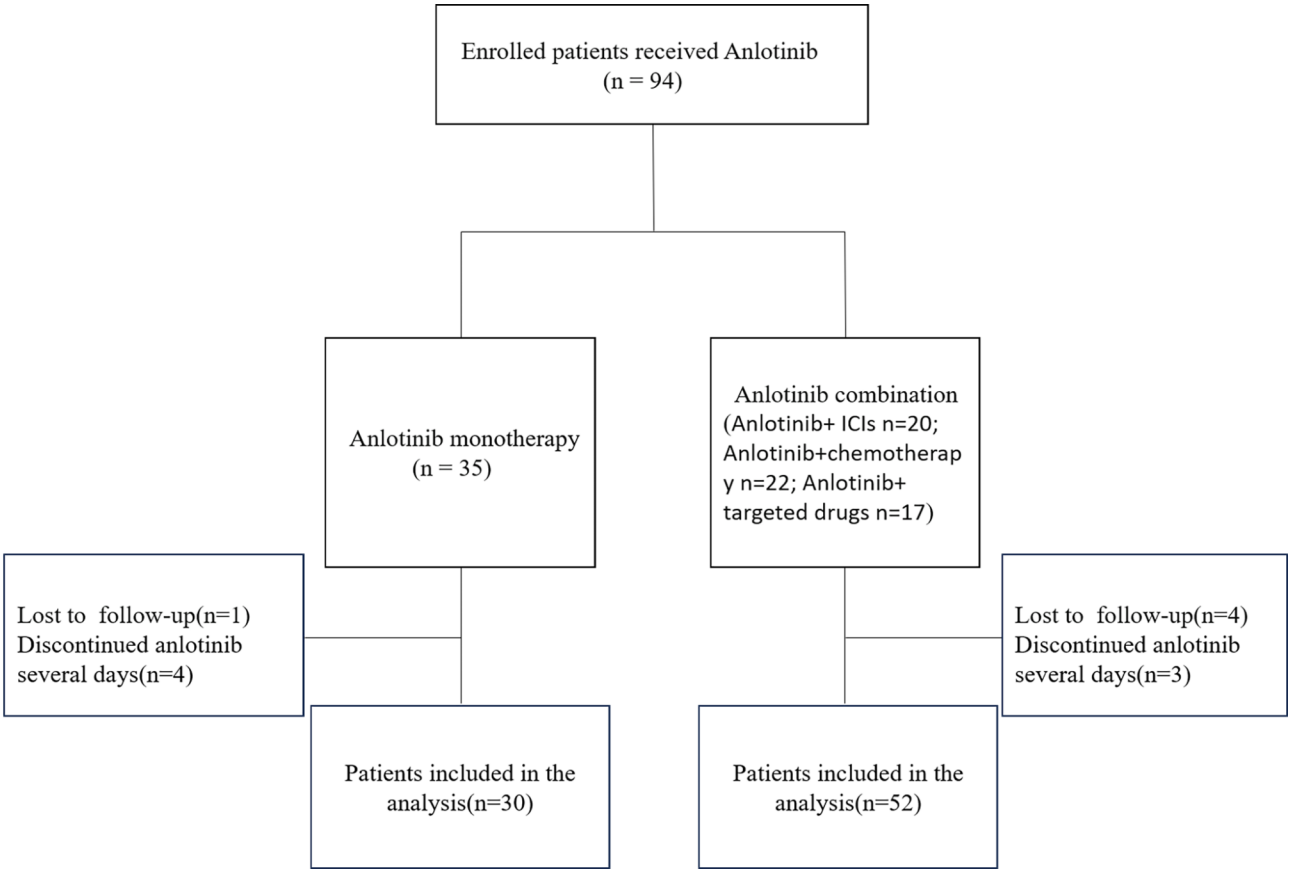

Fig. 1 Experimental group flow chart

of anti-angiogenic drug use. Follow-up visits were performed every two cycles.

Evaluation of efficacy and adverse events

Efficacy was assessed according to the criteria for evaluating the efficacy of solid tumors1.1 [15], including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). CR: Complete disappearance of all target lesions, with no new lesions emerging and normalization of tumor markers. PR: ≥30% reduction in the sum of the largest diameters of target lesions after treatment.SD: shrinkage of the sum of the largest diameters of the target lesions after treatment without reaching PR, or increase in the sum of the largest diameters of the target lesions before reaching PD.PD: increase of the sum of the largest diameters of the target lesions by at least ≥ 20% after treatment, or the emergence of new lesions.OS was defined as the time between the start of the study treatment and death from any cause. PFS was recorded as the time from the start of the treatment until the first documented progression of the disease, final follow-up, or any cause of death. ORR = (CR + PR)/total cases × 100%, DCR = (CR + PR + SD)/total cases × 100%. Adverse drug reactions in both groups during treatment were using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [16].

Statistical analysis

SPSS version 25.0, GraphPad Prism 9.0 were used for all statistical analyses. Differences in demographic and imaging response characteristics between groups were assessed by the chi-square ($\chi 2$) test for categorical or t-test for continuous variables. Survival curves were plotted by the Kaplan-Meier method, and the Log-rank test made comparisons. Cox regression models were used to find the prognostic factors associated with PFS. A value of $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

From 2018 to 2021, a total of 94 patients met the inclusion and exclusion criteria. Among them, 5 were lost to follow-up, and 7 were not on regular medication. Finally, 82 patients were included in the study. Among all eligible patients, males constituted the majority (79.3%), and 38 patients (46.3%) had a history of smoking. 12 patients were classified as stage III, while 70 patients were stage IV. 38 patients (46.3%) were diagnosed with squamous

Table 1 Baseline characteristics of two groups

characteristics	anlotinib monotherapy	anlotinib combination	*P* value
Age	68.1 ± 9.4	66.3 ± 10	0.464
Gender, n(%)			0.638
Male	24(80)	24(75)	
Female	6(20)	8(25)	
Histology, n(%)			0.328
Squamous cell carcinoma	15(50)	14(43.8)	
Non-squamous cell carcinoma	15(50)	18(56.2)	
ECOG, n(%)			0.328
0	18(60)	18(56.2)	
1	12(40)	14(43.8)	
Metastasis, n(%)			0.364
No	15(50)	11(34.4)	
Number of metastases = 1	9(30)	10(31.3)	
Number of metastases = 2	4(13.3)	10(31.2)	
Number of metastases ≥ 3	2(6.7)	1(3.1)	
Hypertension, n(%)			0.461
No	19(63.3)	17(53.1)	
Yes	11(36.7)	15(46.9)	
Treatment line, n(%)			0.526
First-line	5(16.7)	6(18.8)	
Second-line	6(20)	10(31.2)	
Third-line and above	19(63.3)	16(50)	
Pre-antiangiogenic therapy, n(%)			0.891
No	23(76.7)	25(78.1)	
Yes	7(23.3)	7(21.9)	
cTNM stage, n(%)			0.090
III	6(20)	1(3.1)	
IV	24(80)	31(96.9)	
Smoking habits, n(%)			0.023
Non-smoker	12(40)	22(68.8)	
ex-smoker	18(60)	10(31.2)	

carcinoma, and 44 patients (53.7%) had non-squamous carcinoma. Liver metastases were present in 8 patients (9.8%), brain metastases in 10 patients (12.2%), and bone metastases in 26 patients (31.7%). Anlotinib was administered as first-line therapy in 12 patients (14.6%), second-line therapy in 27 patients (32.9%), and third- or later-line therapy in 43 patients (52.4%). 30 patients received anlotinib monotherapy, while 52 patients received combination therapy. Among them, 18 patients received anlotinib in combination with ICIs, 20 patients in combination with chemotherapy, and 14 patients in combination with targeted drugs. The baseline characteristics of the patients are summarized in Table 1. There were no significant differences between the two groups in terms of gender, age, smoking history, histology, ECOG PS, metastases, hypertension, treatment regimen, history of antiangiogenic therapy, or cTNM staging, indicating comparability ($P > 0.05$).

Table 2 Short-term effects of two groups

	anlotinib monotherapy	anlotinib combination	*P* value
PR	2(6.7%)	5(9.6%)	
SD	18(60%)	40(76.9%)	
PD	10(33.3%)	7(13.5%)	
ORR	6.7%	9.6%	0.960
DCR	66.7%	86.5%	**0.033**

Boldness indicates *p* value less than 0.05

Efficacy

As shown in Table 2, in the anlotinib monotherapy group, the best response was observed as follows: 2 cases of PR (6.7%), 18 cases of SD (60%), and 10 cases of PD (33.3%). In the anlotinib combination therapy group, the best response was: 5 cases of PR (9.6%), 40 cases of SD (76.9%), and 7 cases of PD (13.5%). The ORR in the anlotinib combination therapy group was 9.6%, higher than the 6.7% in the monotherapy group, but the difference was not statistically significant ($P = 0.960$). The DCR was 86.5%, higher than the 66.7% in the monotherapy group, and the difference was statistically significant ($P = 0.033$).

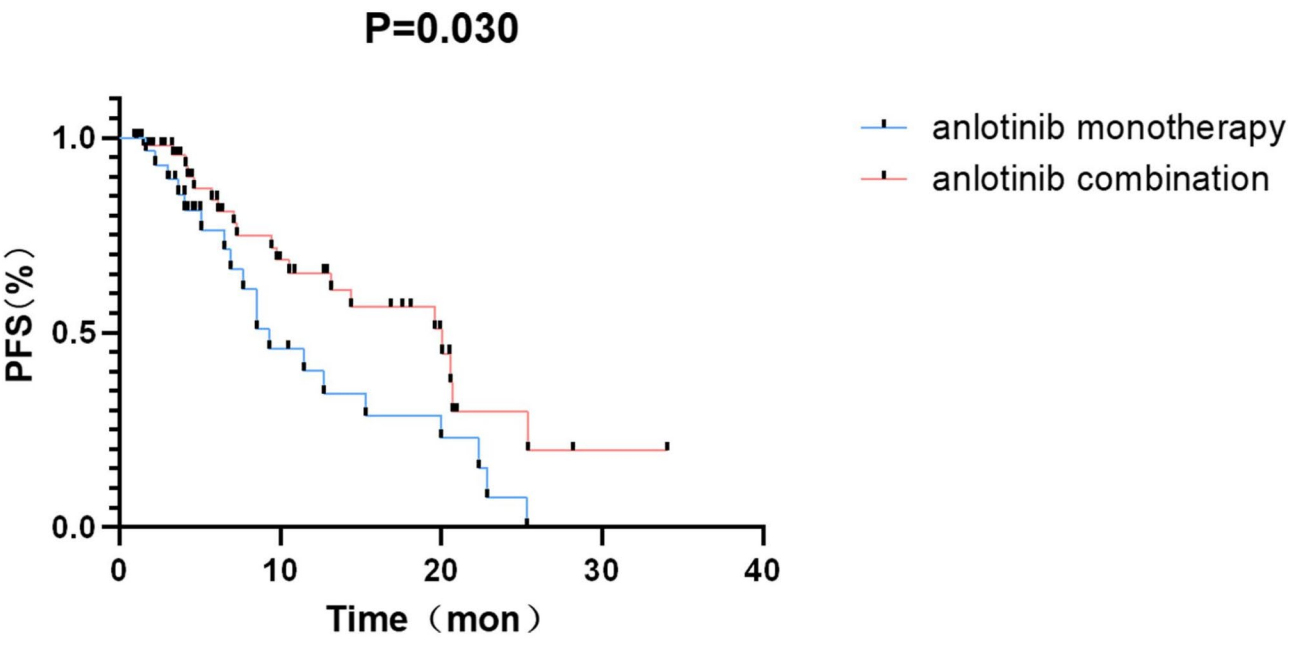

Fig. 2 Comparison of PFS between the two groups

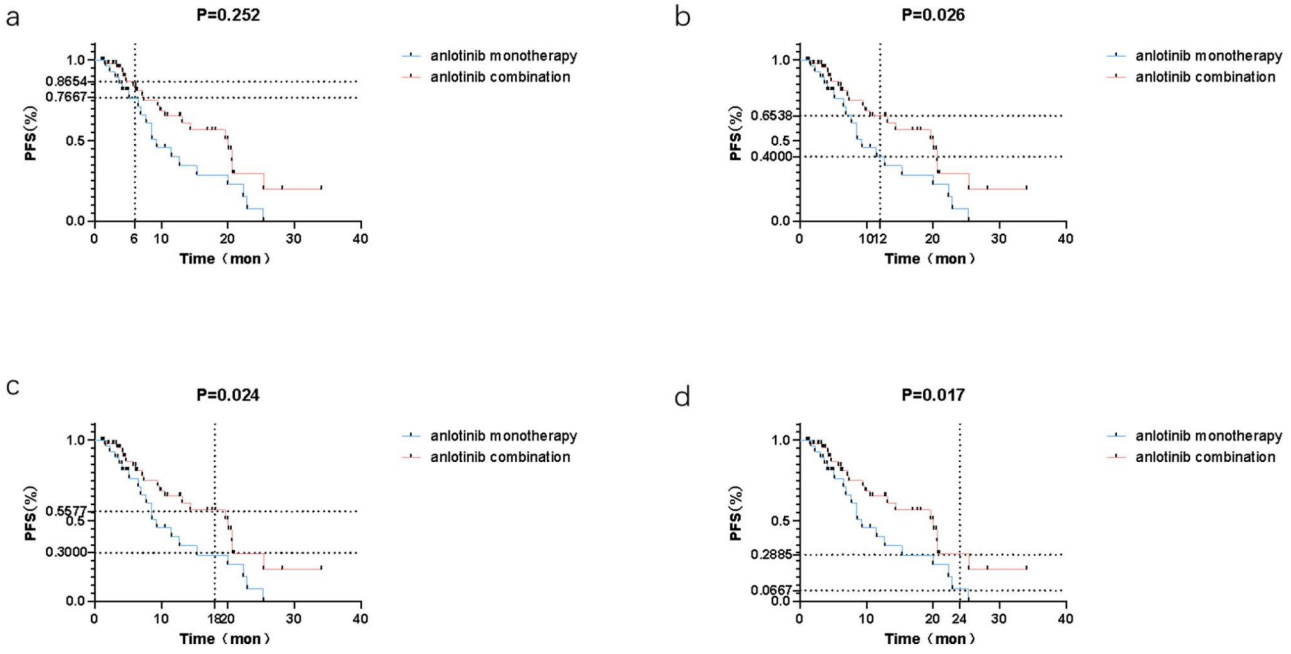

Fig. 3 Comparison of PFS% at 6- months (**a**), 12- months (**b**), 18- months (**c**), and 24- months (**d**) between the two groups

As of the statistical time (October 2022), the follow-up time for patients in the anlotinib monotherapy group ranged from 1.0 month to 24.5 months, while for patients in the anlotinib combination therapy group, it ranged from 1.4 months to 33.7 months. The PFS in the anlotinib combination therapy group was superior to that in the anlotinib monotherapy group (median PFS: 20.0 m vs. 9.3 m, $P=0.030$, Fig. 2). As shown in Fig. 3, the PFS% at 6 months in the anlotinib combination therapy group was 86.54%, compared to 76.67% in the anlotinib monotherapy group ($P=0.252$). The PFS% at 12, 18, and 24 months were 65.38%, 55.77%, and 28.85%, respectively, all significantly higher than in the anlotinib monotherapy group ($P=0.026$; $P=0.024$; $P=0.017$). Since the majority of patients (96.3%) were still alive at the last follow-up, OS analysis was not conducted.

The analysis of different combination regimens (with ICIs/chemotherapy/targeted drugs) demonstrated that

anlotinib combination therapy with ICIs significantly improved patients' PFS (median PFS: 25.4 m vs. 9.3 m, $P=0.043$, Fig. 4). Anlotinib combination therapy with chemotherapy (median PFS: 20.7 m vs. 9.3 m, $P=0.336$, Fig. 4) and with targeted drugs (median PFS: 19.3 m vs. 9.3 m, $P=0.119$, Fig. 4) showed trends toward prolonging PFS, albeit not statistically significant.

Subsequently, we conducted subgroup analysis to identify patients who were most likely to benefit from anlotinib combination therapy. The results indicated that in subgroups of male patients, patients with a history of hypertension, and patients without a history of anti-angiogenic therapy, the efficacy of anlotinib combination therapy was significantly better than that of anlotinib monotherapy ($P<0.05$, Table 3; Fig. 5). In addition, the subgroup of third-line and subsequent treatments also showed statistically significant differences. In order to evaluate the efficacy across different lines of therapy, we compared the PFS between the monotherapy and combination therapy groups in both the first/second line and third line or later treatments. The results indicated that the combination therapy group consistently exhibited a higher survival rate than the monotherapy group in the first and second line treatments, especially after 20 months, where the divergence became more pronounced. This suggests that patients in the first or second line of treatment may derive greater benefits from combination therapy. In the third line or subsequent treatments, the combination therapy group showed a slightly higher survival rate in the early stages, but the curves tended to converge in the mid-to-later stages.(Fig. 6).

Furthermore, we performed univariate analysis of PFS, and the results showed that PFS was not significantly associated with age, gender, smoking history, or pathological staging, but was associated with the treatment modality (Fig. 7).

Safety

The incidence of adverse reactions in the anlotinib combination therapy group (44.2%) was higher than that in the anlotinib monotherapy group (30%), but the difference was not statistically significant ($P=0.203$). The most common adverse reactions in the anlotinib combination therapy group were bleeding and skin tissue, including nasal mucosal bleeding, gum bleeding, rash and hand-foot syndrome. Other notable adverse reactions included fatigue, hypertension, decreased platelet count and deficiency of granules. Among them, four patients experienced grade 3–4 adverse reactions (1 case of hypertension, 1 case of hand-foot syndrome, 1 case of gastrointestinal reactions, and 1 case of hypothyroidism). Adverse reactions in the monotherapy group mainly included hypertension, pulmonary infections, and bleeding, with no patients experiencing grade 3–4 adverse reactions. Patients experiencing adverse reactions could alleviate symptoms through symptomatic treatment,

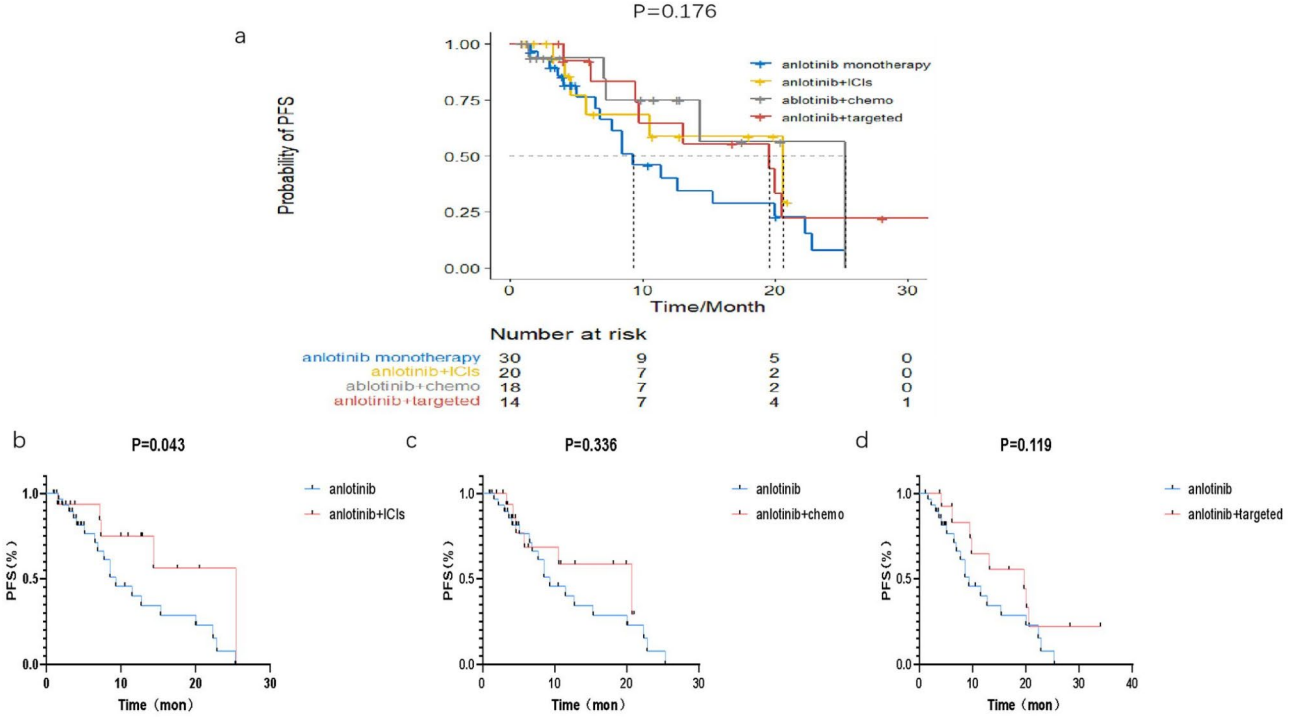

Fig. 4 Comparison of PFS of anlotinib alone and combination (**a**), anlotinib in combination with ICIs (**b**), anlotinib in combination with chemotherapy (**c**), and anlotinib in combination with targeted drugs (**d**)

Table 3 Subgroup analysis of PFS with anlotinib monotherapy or anlotinib combination therapy

characteristics	Total patients (*n* = 82)	mPFS		*P* value	HR (95% CI)
		anlotinib monotherapy (*n* = 30)	anlotinib combination (*n* = 52)		
Age					
< 65	25	9.3	20.7	0.296	0.458(0.106–1.983)
≥ 65	57	8.5	14.4	0.115	0.541(0.252–1.161)
Gender					
Male	65	8.5	20.7	**0.007**	0.341(0.157–0.740)
Female	17	22.3	13.1	0.430	1.526(0.359–6.485)
Histology					
Squamous cell carcinoma	38	9.3	14.4	0.060	0.367(0.129–1.042)
Non-squamous cell carcinoma	44	8.5	20.0	0.195	0.515(0.189–1.404)
ECOG					
0	51	9.3	20.0	0.581	0.777(0.317–1.903)
1	31	8.5	20.7	0.055	0.333(0.108–1.026)
Metastasis					
No	33	8.5	20.6	0.245	0.547(0.198–1.513)
Yes	49	9.3	19.6	0.053	0.375(0.139–1.013)
Hypertension					
No	47	8.5	19.6	0.419	0.688(0.277–1.706)
Yes	35	9.3	25.4	**0.024**	0.285(0.096–0.846)
Treatment line					
< 3	39	——	14.4	0.057	3.862(0.963–15.490)
≥ 3	43	5.1	19.6	**0.004**	0.321(0.148–0.699)
Pre-antiangiogenic therapy					
No	55	9.3	20.0	**0.014**	0.358(0.157–0.812)
Yes	27	9.6	19.6	0.874	0.905(0.264–3.105)
cTNM stage					
III	12	11.5	25.4	0.339	0.384(0.054–2.733)
IV	70	8.5	19.6	0.053	0.487(0.234–1.011)
Smoking habits					
Non-smoker	44	8.5	20.0	0.339	0.583(0.193–1.761)
ex-smoker	38	9.3	17.6	0.166	0.527(0.213–1.304)

Boldness indicates *p* value less than 0.05

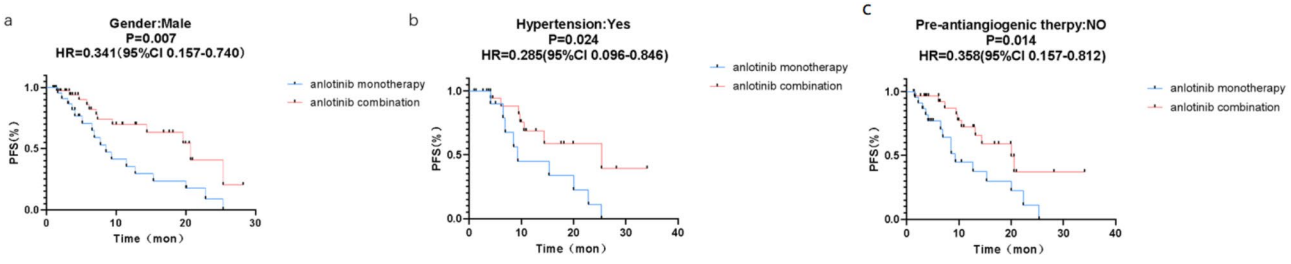

Fig. 5 Comparison of PFS in male patients (**a**), patients with a history of hypertension (**b**), and patients without a history of anti-angiogenic therapy (**c**), receiving anlotinib alone or in combination with other drugs

dose adjustments, or discontinuation of medication. There were no treatment-related deaths in either group (Table 4).

Discussion

The number of new cases of lung cancer in 2022 reached approximately 2.5 million, representing 12.4% of all new cancer cases worldwide, and it has surpassed female breast cancer as the most commonly diagnosed cancer. With about 1.8 million deaths, the mortality rate stands at a staggering 18.7%, making it the leading cause of cancer-related deaths globally [17]. In China, lung cancer is the primary cause of cancer-related deaths, with 820,000 new cases and 720,000 deaths reported in 2020 alone, accounting for 40% of global lung cancer fatalities [1].

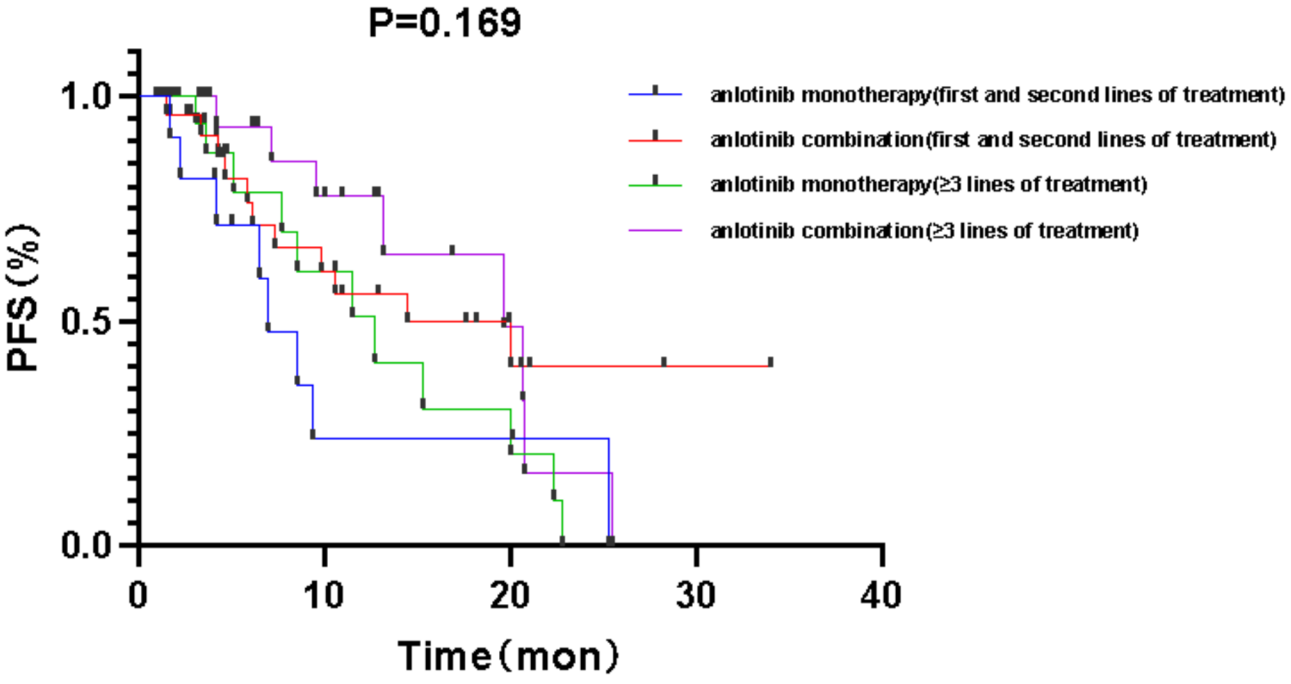

Fig. 6 Comparison of PFS between anlotinib monotherapy and combination therapy in first-and second-line treatment versus third-line and beyond treatment

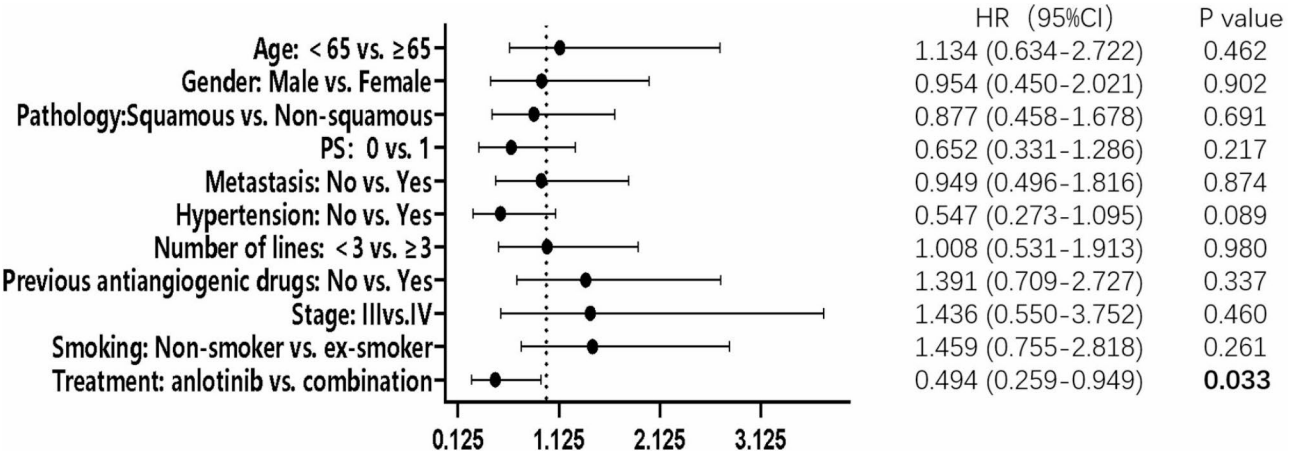

Fig. 7 Univariate analysis of factors associated with PFS, The bold font indicates $P < 0.05$, which is statistically significant

Anti-angiogenic therapy is increasingly recognized for its vital role in the treatment of lung cancer.

This retrospective study evaluated the efficacy and safety of anlotinib monotherapy or its combination with ICIs, chemotherapy, or targeted drugs in the treatment of advanced NSCLC. Compared to anlotinib monotherapy, the combination of anlotinib with ICIs, chemotherapy, or targeted drugs demonstrated promising efficacy.

Previous studies have shown that anti-angiogenic drugs, in combination with other antitumor drugs such as immunotherapy, chemotherapy, and targeted drugs, have a synergistic effect on tumor treatment. A trial comparing anlotinib monotherapy or in combination with ICIs, targeted drugs, and chemotherapy for advanced NSCLC observed that the DCR was higher in the anlotinib combination group (73.0%) than in the anlotinib monotherapy group (58.8%) [18]. Furthermore, Wang et al. reported that among EGFR negative patients, PFS for anlotinib monotherapy and anlotinib combination ICIs was 3.2 months and 5.0 months, respectively ($P = 0.012$). In the EGFR mutation group, the PFS for anlotinib and targeted drugs combination treatment indicated better efficacy than that of anlotinib monotherapy (1.83 m vs. 7.03 m, respectively, $P = 0.001$) [19]. In our study, the combination of drugs also prolonged PFS and improved DCR in patients. In addition, we compared the PFS rates

Table 4 Treatment-related adverse events in the two groups

AEs	anlotinib monotherapy ($n=30$)	anlotinib combination ($n=52$)	*P* value
Systemic disease (fatigue)	2	3	1.000
Cardiovascular diseases (hypertension)	2	3	1.000
Bleeding (hemoptysis, gum bleeding, nasal mucous membrane bleeding)	2	6	0.742
Gastrointestinal disease (abdominal pain)	1	1	1.000
Diseases of the skin and subcutaneous tissue (hand and foot syndrome, rash)	0	6	0.136
Respiratory disease (cough, lung infection)	2	2	0.969
Diseases of the blood system (decreased platelet count, deficiency of granules)	0	4	0.305
Endocrine system (hypothyroidism or hyperthyroidism)	1	2	1.000

at 6, 12, 18, and 24- months between the monotherapy and combination groups and showed that the combination group was higher than the monotherapy group.

One meta-analysis showed that ICI monotherapy had similar effects in patients aged ≥ 65 and < 65 years (HR: 0.64 vs. 0.68) [20], and another real-world data suggests that ICI + chemotherapy was more likely to be discontinued due to adverse effects and did not significantly improve survival compared with ICI treatment. Therefore, ICIs alone or ICIs plus other therapies such as antiangiogenic agents or other novel ICIs (ICIs) may be recommended for older cases of PD-L1-positive NSCLC [21]. In our analysis, Anlotinib in combination with ICIs was associated with prolonged PFS in patients, although the difference was not statistically significant in the ≥ 65 and < 65 subgroups. A phase III study showed a significantly longer PFS in hypertensive patients compared with those without hypertension in patients with SCC in the anlotinib arm (7.23 m vs. 3.23 m $P=0.001$) [22]. In our study, anlotinib in combination with other pharmacological treatments significantly prolonged PFS in patients with a history of hypertension ($P<0.05$).Next, our study also showed that anlotinib in combination with other medications significantly prolonged PFS in male patients, patients who received ≥ 3 lines of treatment ($P<0.05$). Most of the published meta-analyses compared the benefits of different genders in immunotherapy or immunotherapy plus chemotherapy, and there were different dominant groups in different groups. Our study discussed the survival of anlotinib monotherapy or in combination with different genders, with the aim of making it more accessible to more people. In addition, we found that the combination of anlotinib in combination with other therapies significantly prolonged PFS in patients without a history of anti-angiogenic therapy. The above results indicate that these patients may be more likely to benefit from anlotinib combination therapy, but larger, prospective studies are required to validate these observations.

Anlotinib, developed in China, exerts its effects by downregulating the expression of PD-L1 in vascular endothelial cells, thereby reversing the immune suppression in the tumor microenvironment. When used in combination with immunotherapy, Anlotinib demonstrates a synergistic effect, further enhancing the efficacy of immunotherapy [23]. Immune therapy not only has the function of stimulating the body's immune system but also has the function of regulating blood vessels [24]. Anti-angiogenic therapy may help normalize tumor blood vessels and improve the tumor immune microenvironment. ICIs can activate T lymphocytes to secrete IFN-γ, reduce local hypoxia, and promote tumor vascular normalization, demonstrating the synergistic effect of anti-PD-1/PD-L1 antibodies in combination with anti-angiogenic drugs [25]. A phase I study evaluated the efficacy and safety of sintilimab in combination with anlotinib as a first-line treatment for patients with stage IIIB/C or IV NSCLC. Among the 22 treated patients, the DCR was 100%, the median PFS was 15 months, and the 12-month PFS rate was 71.4% [26]. In our study, anlotinib in combination with ICIs significantly prolonged PFS (median PFS: 25.4 m vs. 9.3 m, $P=0.043$).

In addition to its anti-angiogenic and immunomodulatory effects, anlotinib can also interfere with tumor cell proliferation, invasion, and migration, thereby inhibiting tumor growth and metastasis [27]. Furthermore, an in vitro study demonstrated that anlotinib induces tumor cell apoptosis by suppressing downstream signaling pathways such as PI3K/AKT [28]. These mechanisms may collectively contribute to the efficacy of anlotinib as a monotherapy, although further research and exploration are still required to fully elucidate these effects.

While the incidence of adverse reactions related to skin tissue and bleeding increased in the combination therapy group, there were no treatment-related fatalities. Moreover, these adverse reactions could be managed with symptomatic treatment, dose adjustments, or discontinuation. Our study findings align with previous reports, showing a lower incidence of severe adverse reactions (≥ Grade 3). This could be attributed to the close monitoring of patients by clinicians throughout the treatment process and the timely management of adverse reactions. Treatment-related adverse reactions can be controlled through early and appropriate interventions.

The significance of this study lies in the discovery that the combination therapy of Anlotinib and ICIs is the

most important treatment regimen in terms of survival benefit, and it has also identified the population that may benefit from Anlotinib combination therapy. However, this study also has several limitations.Firstly, it is a single-center retrospective study with limited overall and subgroup sample sizes. Secondly, the follow-up time for patients was relatively short, precluding OS analysis. While our study demonstrated a longer PFS with combination therapy compared to monotherapy, the comparison with different treatment lines was limited due to the small sample size and heterogeneity of the population. Future studies with larger, more homogeneous cohorts are needed to validate these findings across different treatment lines.

In summary, The combination of ICIs, chemotherapy, or targeted drugs with anlotinib showed potential efficacy and acceptable tolerability in this study, although further validation in larger, prospective studies is needed.

Author contributions
J. Wei: Conceptualization, Data curation, Writing-original draft. Y. Zhang, Y. Zheng, C. Ma: Methodology, Investigation. Q. Zhao, Y.Wang: Formal analysis, Interpretation. L. Miao: Software, Visualization. j.Ding: Project administration, Supervision.

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Data availability
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). All the patients have been informed and the Written informed consent was obtained from all individual participants included in the study prior to enrollment. The study was approved by the Medical Ethics Committee of Nanjing Drum Tower Hospital. (Ethics No. 2020-137-13).

Consent to publish
All authors of the manuscript have read and agreed to its content and are accountable for all aspects of the accuracy and integrity of the manuscript in accordance with ICMJE criteria. This article is original, has not already been published in a journal, and is not currently under consideration by another journal. We agree to the terms of the BioMed Central Copyright and License Agreement.

Conflict of interest
All authors declare no conflicts of interest associated with this manuscript.

Competing interests
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