Drug Design, Development and Therapy

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ORIGINAL RESEARCH

Effectiveness and Safety of Anlotinib-Related Therapeutic Regimens in Patients with Previously Immune Checkpoint Inhibitors-Treated Advanced NSCLC: A Real-World Exploratory Study

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Objective: This study aimed to identify the effectiveness and safety of anlotinib-related therapeutic regimens in patients with previously immune checkpoint inhibitors (ICIs)-treated advanced non-small cell lung cancer (NSCLC).

Methods: A total of 107 patients with previously ICIs-treated advanced NSCLC who received anlotinib-related regimens or single-agent chemotherapy in clinical practice were included in this study retrospectively. The anlotinib group (AG) included 54 patients who received anlotinib-related regimens, and the chemotherapy group (CG) consisted of 53 patients who received single-agent chemotherapy. This study retrospectively collected the efficacy and safety data during the patients' therapeutic process and performed regular follow-up to obtain long-term survival data. Clinical outcomes and safety profiles between AG and CG were analyzed and compared.

Results: Best overall response of the 107 patients with previously ICIs-treated advanced NSCLC suggested that objective response rates of AG and CG were 24.1% and 11.3%, respectively; no statistically significant difference was observed (P = 0.084). Disease control rates were 79.6% and 54.7%, respectively (P = 0.006). Furthermore, the median PFS of AG and CG were 6.3 months (95% CI = 0.91–11.69) and 2.8 months (95% CI = 2.32–3.28), respectively, which showed a statistically significant difference (P = 0.002). The median OS in AG and CG were 16.1 months (95% CI = 12.28–19.92) and 10.1 months (95% CI = 3.99–16.21), respectively, which also exhibited a statistically significant difference (P = 0.015). Incidence of adverse reactions with all grades in AG and CG were 85.2% and 83.0%, respectively, grade ≥3 adverse reactions occurred in 40.7% and 45.3%, respectively. Common adverse reactions of patients in AG included fatigue, hypertension, nausea and vomiting, and hematologic toxicity, while patients in CG commonly experienced fatigue, hematologic toxicity, nausea and vomiting, and liver toxicity.

Conclusion: Among patients with previously ICIs-treated advanced NSCLC, anlotinib-related therapeutic regimens demonstrated encouraging efficacy and a tolerable safety profile compared with the single-agent chemotherapy regimen. This conclusion still needs further validation in prospective clinical trials.

Keywords: NSCLC, anlotinib, immunotherapy, chemotherapy, effectiveness, safety

Introduction

Globally, lung cancer ranks second in incidence and first in mortality among malignancies of the respiratory system with over 2.48 million new cases and approximately 1.82 million deaths each year.[1] In China, lung cancer is the most prevalent malignancy, accounting for approximately 820,000 new cases and 720,000 deaths annually.[2] Non-small cell lung cancer (NSCLC) represents the predominant histological subtype, comprising roughly 85% of all lung cancer cases. Despite significant advancements in diagnosis and treatment in recent years, the prognosis of patients with advanced

Received: 20 April 2025
Accepted: 9 August 2025
Published: 29 August 2025

NSCLC remains poor.[3] Particularly, advanced NSCLC patients lacking identifiable driver gene mutations demonstrate a significant clinical challenge due to the absence of clear molecular therapeutic targets. Recent studies indicate that the 5-year survival rate for advanced NSCLC patients without driver gene mutations ranges between 9.7% and 19.4%.[4]

In recent years, immunotherapy, notably programmed cell death protein 1 (PD-1) inhibitors, have introduced new therapeutic possibility for these patients.[5] PD-1 inhibitors activate the body's immune system to eliminate cancer cells by reversing immune suppression mediated by tumor cells. Due to promising outcomes in clinical trials, combinations of PD-1 inhibitors with chemotherapy have gradually become established as the first-line standard treatment for advanced NSCLC.[6] In China, pembrolizumab, sintilimab, camrelizumab, tislelizumab, toripalimab, atezolizumab, penpulimab, and sugemalimab have been successively approved for first-line treatment indications in advanced NSCLC, significantly improving patient access and treatment outcomes.[7] Consequently, immunotherapy combined with chemotherapy has become the prevailing first-line treatment strategy for NSCLC domestically. With further price reductions, patients' accessibility has been significantly improved, allowing most patients with advanced NSCLC be able to receive immunotherapy combined with chemotherapy as the first-line treatment regimen in clinical practice.[8] However, immunotherapy might not be effective for all NSCLC patients, and some could experience disease progression after initial therapy. For these patients who failed prior immunotherapy, selecting the appropriate subsequent treatments remains an urgent clinical challenge.[9]

Current guidelines recommend single-agent chemotherapy such as docetaxel, pemetrexed, or paclitaxel as the primary standard of care for advanced NSCLC patients who have failed prior immunotherapy.[10] Phase III trials have demonstrated that docetaxel monotherapy yields an objective response rate (ORR) of approximately 9.0%, a median progression-free survival (PFS) of 3–4 months, and a median overall survival (OS) of approximately 8.5 months.[11] Evidently, chemotherapy with agents like docetaxel offer limited efficacy with suboptimal survival and response rates that fail to meet clinical expectations. Additionally, chemotherapy often induces significant side-effects – including myelosuppression, gastrointestinal adverse reactions and alopecia – that considerably diminish patients' quality of life.[12] Therefore, exploring more efficacious and safe treatment regimens for patients who progressafter immunotherapy holds substantial clinical importance.

Anlotinib, a novel small-molecule multi-targeted tyrosine kinase inhibitor with anti-angiogenic properties, has demonstrated promising anti-tumor activity against various malignancies in recent years.[13] It inhibits tumor growth by concurrently blocking multiple signaling pathways associated with angiogenesis and tumor cell proliferation. A prior study indicated that anlotinib, either as monotherapy or combined with other treatments, offers favorable efficacy and tolerability in advanced NSCLC patients.[14] An ALTER0303 study demonstrated the superior efficacy of anlotinib over placebo, reporting a median PFS of 5.4 months, median OS of 9.6 months, an ORR of 9.2%, and a disease control rate (DCR) of 81.0%.[15] These findings underscored anlotinib's efficacy in extending survival and improving quality of life in patients with advanced NSCLC. Furthermore, previous studies have confirmed that anlotinib exhibited synergistic effects with various therapeutic modalities.[16] Recent research into tumor microenvironment remodeling has indicated that anlotinib might regulate tumor cell reprogramming and vascular matrix remodeling, thus enhancing chemotherapy drug delivery. Additionally, anlotinib might modulate the tumor immune microenvironment, facilitating synergy with PD-1/PD-L1 inhibitors.[17] Thus, exploring combinations of anlotinib with chemotherapy or immunotherapy might offer improved therapeutic outcomes for patients with advanced NSCLC who have failed after previous immunotherapy.

This study innovatively investigated the effectiveness and safety of anlotinib-based treatment regimens in advanced NSCLC patients previously treated with immunotherapy. Through retrospective analysis comparing anlotinib-based regimens with single agent chemotherapy in clinical practice, this study aimed to identify efficacious and tolerable treatment options for patients with previously ICIs-treated advanced NSCLC.

Methods and Materials

Study Design and Eligible Criteria

Due to the relatively widespread use of anlotinib-based regimens and chemotherapy such as docetaxel in clinical practice among patients with previously ICIs-treated advanced NSCLC, this study was designed as a retrospective analysis. Patients with previously ICIs-treated advanced NSCLC who received either anlotinib-related regimens or chemotherapy monotherapy from January 2019 to December 2024 in clinical practice were selected for eligibility. Inclusion criteria were as follows: (1)

histologically confirmed diagnosis of advanced NSCLC; (2) eastern cooperative oncology group (ECOG) performance status of 0–2 score; (3) age ≥18 years; (4) previous failure of immunotherapy-based treatment (including PD-1, PD-L1, or CTLA-4 inhibitors, administered either as monotherapy or combination therapy) due to disease progression or intolerance; (5) patients who failed prior immunotherapy and subsequently received anlotinib-based regimens (anlotinib combined with immunotherapy or chemotherapy) were deemed the anlotinib group (AG); patients who failed prior immunotherapy and subsequently received chemotherapy with docetaxel, pemetrexed, or paclitaxel monotherapy were considered as chemotherapy group (CG); (6) availability of complete baseline demographic characteristics and sufficient clinical treatment data to allow assessment of therapeutic efficacy and prognosis. Exclusion criteria included: (1) patients were concomitant with other malignancies; (2) patients with severe, life-threatening comorbidities (eg, severe cardiac conditions or severe hepatic or renal dysfunction that might interfere study outcomes); and (3) patients who received other systemic anticancer treatments concurrently with the regimen of AG and CG. However, patients who underwent local palliative treatments (such as radiotherapy for localized lesions) were eligible for analysis. According to the eligible criteria of this, a total of 107 patients (54 patients in AG and 53 patients in CG) with previously ICIs-treated advanced NSCLC were enrolled in this study ultimately and the flowchart of this study was illustrated in Figure 1.

The primary objective of this study was to evaluate and compare the effectiveness and safety of anlotinib-based regimens versus single-agent chemotherapy (eg, docetaxel) in advanced NSCLC patients previously treated with ICIs. The primary endpoint was PFS, other endpoints included ORR, DCR, OS, and safety profile. The study was approved by the Ethics Committee of the Fourth Medical Center of Chinese PLA General Hospital, and informed consent was obtained from each patient included in this analysis. The entire study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Sample Size Calculation

Although this study was designed as a retrospective study, sample size calculation was also taken into consideration to determine how many subjects should be screened. Sample size was calculated based on the primary endpoint of PFS in each group using PASS 15 software. As the previous study reported, the chemotherapy monotherapy (docetaxel) might

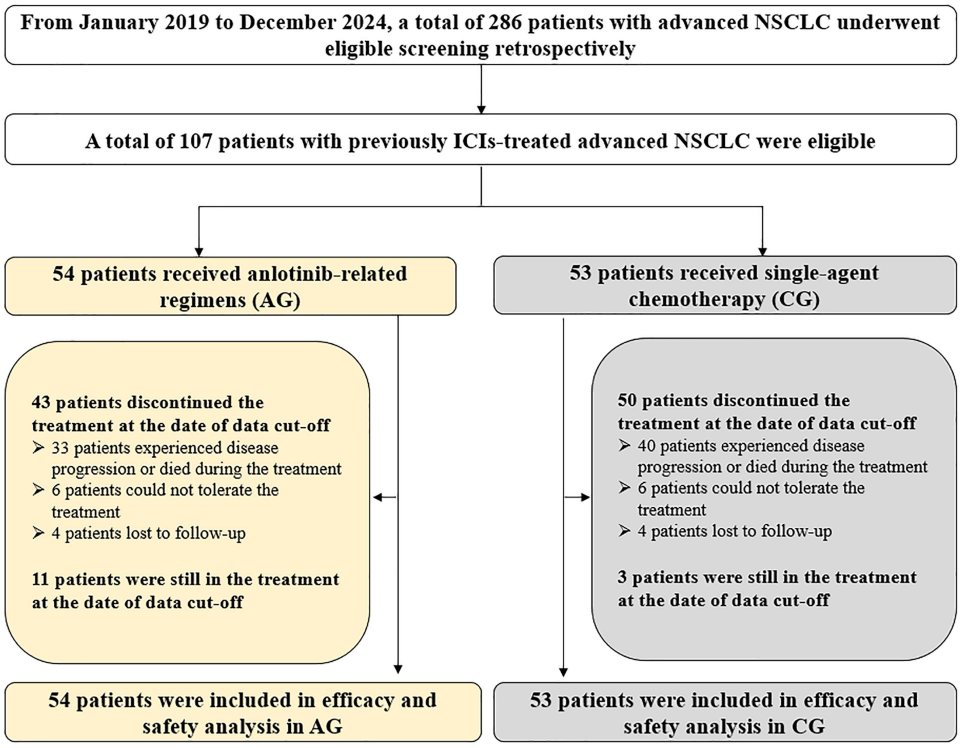

Figure 1 Flowchart of this real-world exploratory study.

https://doi.org/10.2147/DDDT.S535615

achieve a median PFS of approximately 3 months,[18] assuming that the anlotinib-related regimens might improve the median PFS from 3 months to 6 months based on the previous study.[19] Using the two survival curves of Log rank test in PASS 15.0, we estimated that 44 patients in each group might provide 80% power to detect an improvement in median PFS from 3 months (CG) to 6 months (AG), at a two-sided α of 0.05. As PFS was the primary endpoint, the statistical power was also driven by the number of PFS events. According to PASS 15.0, 66 PFS events (38 PFS events in CG and 28 PFS events in AG) were required to achieve a difference in median PFS between groups with 80% power at a two-sided α of 0.05. Considering a 15% dropout, 52 patients should be enrolled in each group. Finally, 54 patients and 53 patients were screened and included in AG and CG in our study, respectively.

Therapeutic Regimens According to the Eligible Criteria

This study was designed as a retrospective clinical analysis. Patients in AG were selected from those receiving anlotinib-based treatment regimens in clinical practice, including anlotinib combined with chemotherapy or immunotherapy. Specifically, anlotinib was administered orally at a dosage ranging from 8 mg to 12 mg once daily in the morning on an empty stomach for 14 consecutive days, followed by a 7-day rest period, every 21 days was deemed as one cycle. The chemotherapy agents used in AG included docetaxel, pemetrexed, or paclitaxel, administered intravenously on day 1 of each 21-day cycle, continuing treatment until disease progression (PD) or intolerable toxicity occurred. The immunotherapy agents combined with anlotinib included PD-1 inhibitors (tislelizumab, sintilimab, and camrelizumab) administered intravenously at a fixed dosage of 200 mg on day 1 of each 21-day cycle, infused over 30–60 minutes, and continued until PD or unacceptable toxicity. In cases where patients were unable to tolerate the combination therapy, treatment could be adjusted to single drug treatment with either agent.

Patients in CG received single-agent chemotherapy, including docetaxel (75 mg/m²), pemetrexed (500 mg/m²) or paclitaxel (175 mg/m²), administered intravenously every 21 days (one cycle), and treatment continued until disease progression or intolerable toxicity.

Data Collection and Effectiveness Assessment Protocol

In this study, data collection followed routine clinical practice, utilizing departmental medical records and the hospital's electronic medical record system to compile detailed baseline and treatment-related patient characteristics. Given that OS was the secondary endpoint of the study, regular monthly follow-up was conducted for patients after progression of the disease (PD). Follow-up was primarily conducted via telephone communication with patients or their relatives, aiming to document subsequent treatment regimens following progression on anlotinib-based therapy or chemotherapy monotherapy. In cases of patient death, the exact date of death was recorded. The data cut-off date for this study was set as May 15, 2025.

Secondary endpoints included ORR, DCR, and OS. To evaluate treatment efficacy, radiological assessments (CT or MRI) were performed every two therapeutic cycles after initiation of anlotinib-based regimens or chemotherapy monotherapy, or adjusted according to the clinical circumstances. Tumor responses in both the AG and CG were assessed according to RECIST 1.1 criteria. The definition of study endpoints was adopted from a previous study.[20]

Safety Profile Assessment

Safety profile was assessed by collecting treatment related adverse events (TRAEs) throughout the treatment period both in AG and CG, which was classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The incidence and severity of TRAEs was recorded, and the grade of each TRAEs was determined by the investigator. TRAEs of each patient who received anlotinib-based regimens or chemotherapy monotherapy was documented and the maximum toxicity of the patients was recorded as detailed as possible to present the safety profile of the assigned regimens. Incidence of TRAEs and Grade ≥3 TRAEs was recorded and presented in this study.

Statistical Analysis

All data collected in this study were analyzed using SPSS (version 25.0). Continuous variables were presented as median and ranges, while categorical variables were described using frequency and percentages. Baseline characteristics were

compared using the chi-square test or Fisher's exact test for categorical variables, and the Wilcoxon rank-sum test for continuous variables. ORR was defined as the proportion of patients achieving complete response (CR) or partial response (PR) as the best response during the treatment. DCR was defined as the proportion of patients achieving CR, PR, or stable disease (SD) as their best treatment response. Patients lacking evaluable response data were considered non-responders and were included in the denominator when calculating these rates. Survival data were presented with Kaplan-Meier curves using Stata 14.0 software. PFS and OS were defined according to the previous study.[21] Differences in PFS and OS between the AG and CG were compared using the Log rank test. Hazard ratios (HRs) were estimated using Cox proportional hazards models and stepwise multivariable Cox regression analysis was performed. $P < 0.05$ was considered as statistically significant.

Results

Comparison of Baseline Clinical Characteristics between AG and CG

As described previously, a total of 107 patients with previously ICIs-treated advanced NSCLC were included in this study. Fifty-four patients received anlotinib-based regimens and were assigned to AG, while 53 patients received chemotherapy monotherapy were assigned to CG. Baseline clinical characteristics of both groups were shown in Table 1. The median age of

Table 1 Comparison of Baseline Clinical Characteristics between AG and CG

Baseline Clinical Characteristics	AG (N = 54)	CG (N = 53)	Statistics	*P*
Age (years)				
Median (range)	64 (19–79)	63 (21–80)	NA	0.731
Gender				
Male	36 (66.7)	34 (64.2)	0.075	0.784
Female	18 (33.3)	19 (35.8)		
ECOG Performance Status				
0–1	39 (72.2)	36 (67.9)	0.236	0.627
2	15 (27.8)	17 (32.1)		
Smoking Status				
Non-smoker	12 (22.2)	11 (20.8)	0.034	0.853
Smoker	42 (77.8)	42 (79.2)		
Histological Type				
Adenocarcinoma	30 (55.6)	28 (52.8)	0.080	0.777
Squamous carcinoma	24 (44.4)	25 (47.2)		
Pathological Staging				
III	5 (9.3)	5 (9.4)	0.001	0.975
IV	49 (90.7)	48 (90.6)		
Previous treatment lines				
1	12 (22.2)	13 (24.5)	0.079	0.778
2	42 (77.8)	40 (75.5)		
Previous immunotherapy failure types	37 (68.5)	39 (73.6)	0.334	0.564
Progression				
Intolerance	17 (31.5)	14 (26.4)		
Previous ICIs regimens				
PD-1	45 (83.3)	47 (88.7)	0.634	0.426
PD-L1	9 (16.7)	6 (11.3)		
Number of metastatic lesions				
≤ 3	39 (72.2)	36 (67.9)	0.236	0.627
> 3	15 (27.8)	17 (32.1)		

Abbreviations: AG, anlotinib-related group; CG, chemotherapy group; ECOG, Eastern Cooperative Oncology Group; ICIs, immune checkpoint inhibitors; PD-1, Programmed cell death protein 1; PD-L1, Programmed cell death ligand 1.

https://doi.org/10.2147/DDDT.S535615

the two groups was 64 and 63 years, respectively, and 12 patients in AG and 19 patients in CG had an ECOG score of 2. Overall, the two groups were well balanced in terms of other baseline characteristics, including gender, smoking status, histological type, pathological staging, previous treatment lines, previous immunotherapy failure types, previous ICIs regimens, and number of metastatic lesions, and no significant statistical differences were observed ($P > 0.05$). Furthermore, in AG (54 patients receiving anlotinib-based treatment), 23 patients received anlotinib combined with chemotherapy, and 31 patients received anlotinib combined with PD-1 inhibitors (15 received tislelizumab, 11 received sintilimab, and 5 received camrelizumab). In CG (53 patients receiving chemotherapy monotherapy), 31 patients received docetaxel monotherapy, 13 received paclitaxel monotherapy, and 9 received pemetrexed monotherapy.

Comparison of Efficacy between AG and CG

This study retrospectively collected efficacy assessment data during the treatment process. Based on the best efficacy during treatment, the response of patients was assessed. In AG, there were 0 patients with CR, 13 patients with PR, 30 patients with SD, 6 patients with PD, and 5 patients did not have available assessment data. In CG, there were 0 patients with CR, 6 patients with PR, 23 patients with SD, 18 patients with PD, and 6 patients did not have available assessment data. Consequently, ORRs in AG and CG were 24.1% (95% CI = 13.5–37.6%) and 11.3% (95% CI = 4.3–23.0%), respectively, no significant statistical difference was observed (P=0.084). DCRs in AG and CG were 79.6% (95% CI = 66.4–89.4%) and 54.7% (95% CI = 40.4–68.4%), respectively, and a statistically significant difference was found (P=0.006). Observably, the waterfall plots of the changes in target lesions before and after treatment with AG and CG are shown in Figure 2. Forty-nine patients in AG demonstrated a more significant reduction in target lesions compared with 47 patients in CG (mean reduction = −13.12% vs 12.02%). Additionally, one amazing case was a 42-year-old female patient who had squamous carcinoma and received camrelizumab combined with chemotherapy for three cycles previously, then she was intolerant to this regimen. In this study, she received anlotinib combined with sintilimab for over 1 year, then the CT results demonstrated the patient's target lesions showed a significant reduction of over 80%. The CT scan comparison before and after treatment is shown in Figure 3, exhibiting an encouraging benefit from the anlotinib plus sintilimab treatment.

Comparison of Prognosis between AG and CG

As mentioned previously, the data cutoff date of this study was May 15, 2025. The long-term follow-up data in AG and CG demonstrated that the median follow-up durations were 15.3 months (range = 1.1–36.5 months) and 9.2 months (range = 0.9–34.2 months), respectively. The PFS curves of the AG and CG are shown in Figure 4. Obviously, the median PFS for patients who received anlotinib-based regimens and chemotherapy monotherapy were 6.3 months (95% CI = 0.91–11.69) and 2.8 months

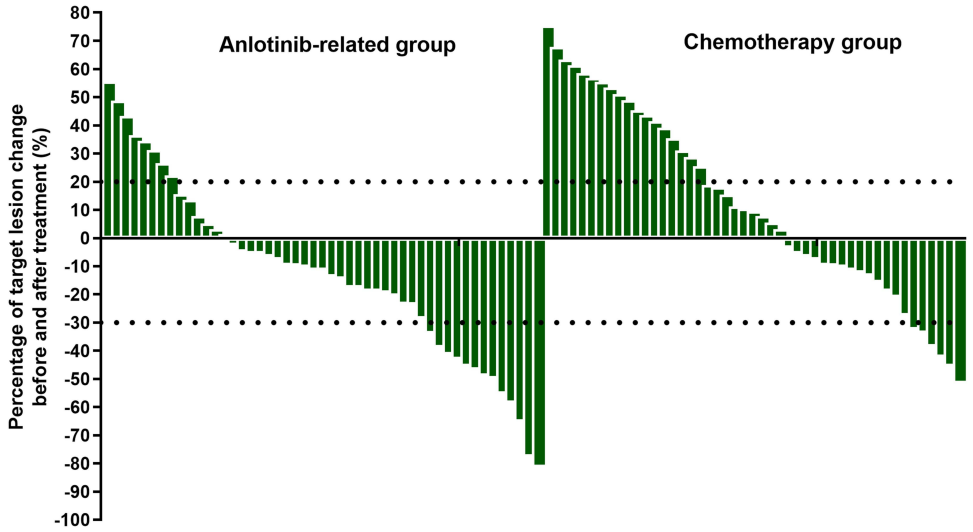

Figure 2 Comparison of the change in waterfall plot of target lesion changes before and after treatment between AG and CG.

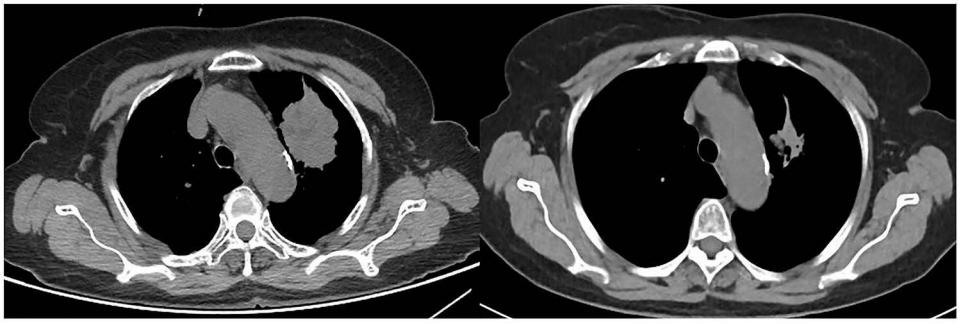

Figure 3 CT scan results of the changes for target lesions in the lung site of a female patient with advanced NSCLC before and after the treatment of anlotinib plus sintilimab.

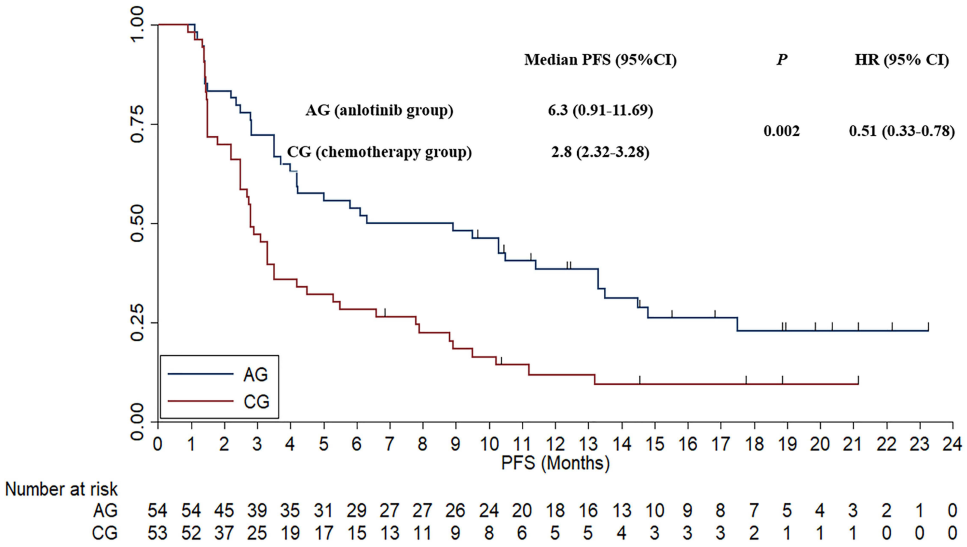

Figure 4 Comparison of Kaplan-Meier progression free survival curve between AG and CG.

(95% CI = 2.32–3.28), respectively. And the 12-month PFS rates were 22.8% (95% CI = 11.8–36.1%) and 9.5% (95% CI = 3.3–19.8%), which showed a statistically significant difference [$\chi^2 = 10.05$, $P = 0.002$. HR = 0.51 (95% CI = 0.33–0.78)].

At the date of data cutoff, OS data in AG and CG were mature enough (64.8% in AG and 84.9% in CG). The OS curves of AG and CG are illustrated in Figure 5. The median OS for patients who were treated with anlotinib-based regimens and chemotherapy monotherapy were 16.1 months (95% CI = 12.28–19.92) and 10.1 months (95% CI = 3.99–16.21), respectively, which also showed a statistically significant difference [$\chi^2 = 5.87$, $P = 0.015$. HR = 0.58 (95% CI = 0.38–0.91)].

Comparison of PFS and OS According to Different Anlotinib-Related Regimens in AG

As described previously, among the 54 patients who were treated with anlotinib-related regimens, 23 patients received anlotinib combined with chemotherapy and 31 patients were treated with anlotinib combined with PD-1 inhibitors. This study also analyzed the prognostic differences between these two treatment regimens in the previously ICIs-treated population, as shown in Figure 6. The median PFS of patients receiving anlotinib combined with immunotherapy and those receiving anlotinib combined with chemotherapy were 6.3 months (95% CI = 0.00–13.87) and 8.9 months (95% CI = 0.61–17.20), respectively, and no statistically significant difference was detected [$\chi^2 = 0.315$, $P = 0.575$, HR = 1.20 (95% CI = 0.64–2.25)]. The median OS for the two groups were 16.8 months (95% CI = 12.37–21.23) and 13.4 months (95% CI = 6.02–20.78), respectively, with a marginally significant difference [$\chi^2 = 1.482$, $P = 0.223$, HR = 1.50 (95% CI = 0.77–2.92)].

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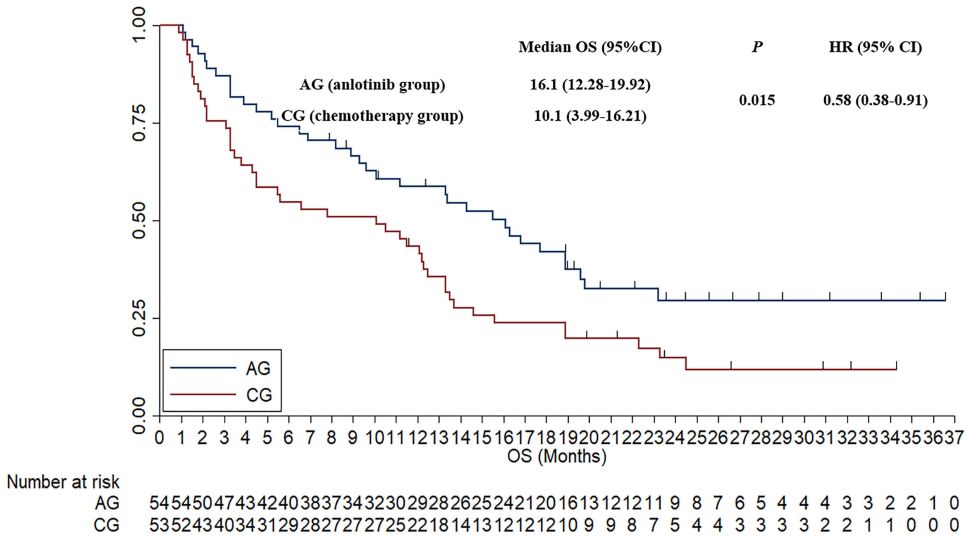

Figure 5 Comparison of Kaplan-Meier overall survival curve between AG and CG.

Safety Profile between AG and CG

Safety profile data during the treatment process for patients in both AG and CG were retrospectively collected, as shown in Table 2. In AG, 46 patients experienced TRAEs of varying severity with an incidence rate of 85.2%, and the incidence of grade ≥ 3 TRAEs was 40.7%. In CG, 44 patients underwent all grade of TRAEs with an incidence rate of 83.0%, and the incidence of grade ≥ 3 TRAEs was 45.3%. The common TRAEs (incidence > 10%) among the 54 patients receiving anlotinib-related regimens were fatigue (51.9%), hypertension (50.0%), nausea and vomiting (38.9%), hematologic toxicity (33.3%), hepatotoxicity (27.8%), hand-foot syndrome (20.4%), and oral mucositis (13.0%). And the main TRAEs (incidence > 10%) among the 53 patients who received chemotherapy monotherapy were hematologic toxicity (47.2%), fatigue (45.3%), nausea and vomiting (35.8%), hepatotoxicity (35.8%), alopecia (24.5%), oral mucositis (17.0%), and constipation (11.3%). Overall, the safety profile during the treatment process in both the anlotinib-related regimen and chemotherapy monotherapy groups were acceptable and manageable.

Discussion

This study retrospectively analyzed and compared the effectiveness and safety of anlotinib-related regimens versus chemotherapy monotherapy in patients with previously ICIs-treated advanced NSCLC in clinical practice. Results suggested that anlotinib-related regimens might significantly improve DCR and extend PFS and OS, providing long-term survival benefits for these patients. Additionally, anlotinib-related regimens seemed to be tolerable and manageable in patients previously treated with ICIs, offering meaningful real-world evidence to support their use in later-line therapeutic settings.

To our knowledge, several PD-1 inhibitors – including pembrolizumab, sintilimab, camrelizumab, tislelizumab, toripalimab, atezolizumab, penpulimab, and sugemalimab – had been successively approved in China as first-line treatment for advanced NSCLC currently.[22] These agents, whether administered as monotherapy or in combination with chemotherapy, had demonstrated positive outcomes in clinical trials, progressively reshaping the therapeutic landscape for advanced NSCLC.[23] Consequently, PD-1 inhibitors in combination with chemotherapy had become the new standard of care as first-line treatment for advanced NSCLC. With the inclusion of PD-1 inhibitors in national insurance systems, most advanced NSCLC patients might receive PD-1 inhibitor treatment in clinical practice without bearing too much economic burden.[24] Unfortunately, in clinical practice, more than 60% of patients experienced disease progression or intolerable adverse events within 10 months of PD-1 inhibitor combined with chemotherapy.[25] According to current guidelines, subsequent treatment options for patients with advanced NSCLC who had previously undergone immunotherapy predominantly involved chemotherapy. Nevertheless, these regimens, exemplified by docetaxel, often

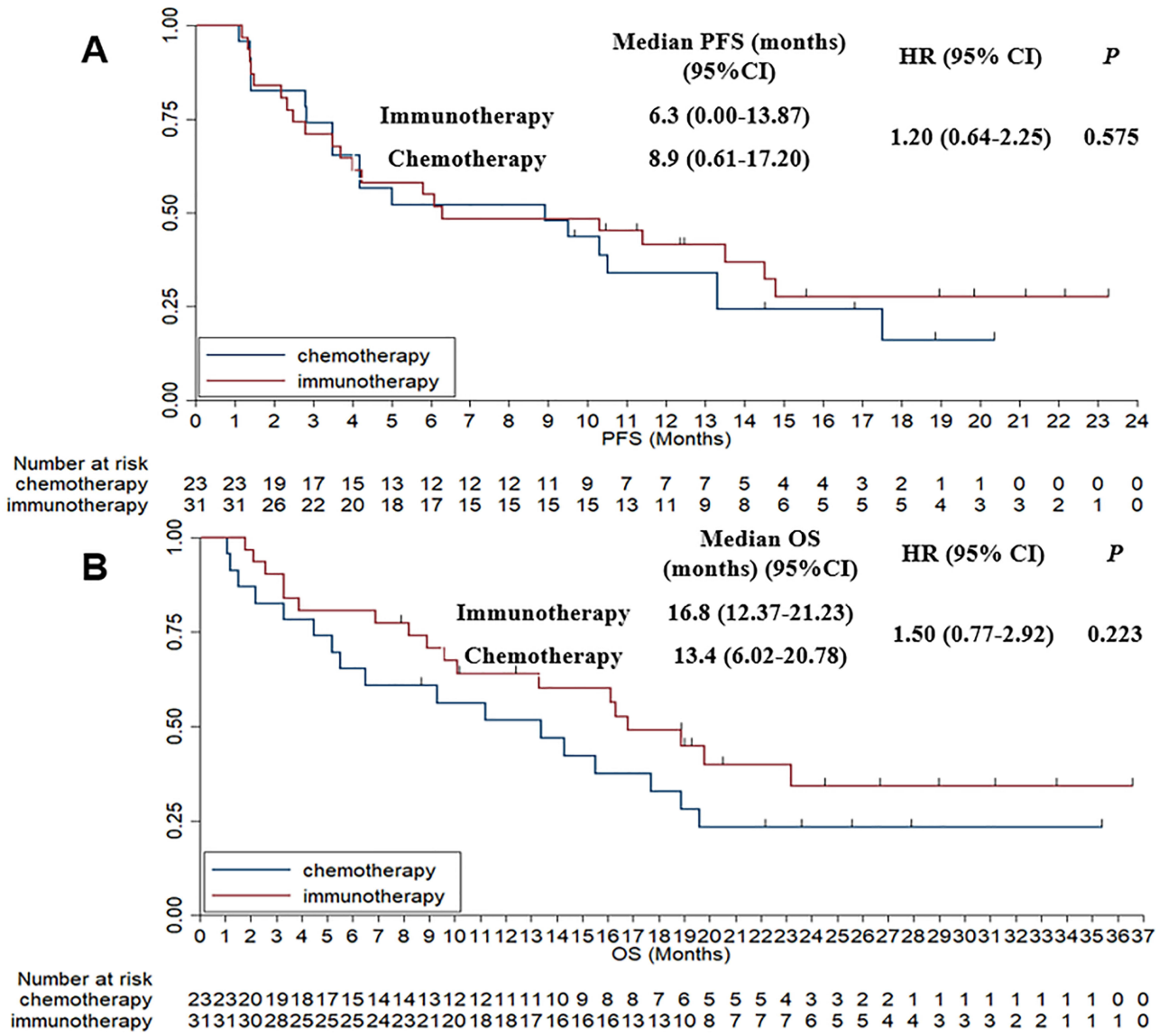

Figure 6 Comparison of Kaplan-Meier progression-free survival (**A**) and overall survival (**B**) curves between anlotinib combined with chemotherapy and anlotinib combined immunotherapy in AG.

exhibited limited efficacy and substantial toxicity, failing to meet clinical expectations.[26] Based on the results of the ALTER0303 study, anlotinib monotherapy had been established as a standard third-line or later treatment for patients with advanced NSCLC. Therefore, the therapeutic potential of anlotinib-related regimens in patients with advanced NSCLC who had previously received immunotherapy warranted further clinical investigation.

Table 2 Safety Profile of Patients in AG and CG During the Treatment

Adverse events	AG (N = 54)		CG (N = 53)	
	All grades (N, %)	Grade ≥3 (N, %)	All grades (N, %)	Grade ≥3 (N, %)
Any grade	46 (85.2)	22 (40.7)	44 (83.0)	24 (45.3)
Fatigue	28 (51.9)	7 (13.0)	24 (45.3)	6 (11.3)
Hypertension	27 (50.0)	8 (14.8)	3 (5.7)	0 (0.0)

(*Continued*)

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Table 2 (Continued).

Adverse events	AG (N = 54)		CG (N = 53)	
	All grades (N, %)	Grade ≥3 (N, %)	All grades (N, %)	Grade ≥3 (N, %)
Nausea and vomiting	21 (38.9)	6 (11.1)	19 (35.8)	5 (9.4)
Hematologic toxicity	18 (33.3)	3 (5.6)	25 (47.2)	10 (18.9)
Hepatotoxicity	15 (27.8)	3 (5.6)	19 (35.8)	6 (11.3)
Hand-foot syndrome	11 (20.4)	2 (3.7)	2 (3.8)	0 (0.0)
Alopecia	5 (9.3)	0 (0.0)	13 (24.5)	5 (9.4)
Oral mucositis	7 (13.0)	0 (0.0)	9 (17.0)	1 (1.9)
Constipation	5 (9.3)	0 (0.0)	6 (11.3)	0 (0.0)
Pneumonia	5 (9.3)	0 (0.0)	5 (9.4)	0 (0.0)

Abbreviations: AG, anlotinib-related group; CG, chemotherapy group.

In this study, a total of 107 patients with previously ICIs-treated advanced NSCLC were enrolled. The median age of the patients was 63–64 years, and most patients had received second-line treatment (over 75%) previously. The majority of patients had failed immunotherapy due to disease progression (over 68%), and most of the previous immunotherapies were PD-1 inhibitors (over 83%). The baseline characteristics of patients in this study were consistent with the baseline characteristics of patients included in an exploratory clinical study initiated by Professor Dou.[27] Notably, the majority of patients had previously received PD-1 inhibitors, which was consistent with the current clinical therapeutic trend of immunotherapy in advanced NSCLC patients.[28] Noteworthy, over 26% of patients in this study had failed the ICI therapy due to intolerance, highlighting that immune-related toxicities remain a significant concern in clinical settings. Since the approval and inclusion of immunotherapy drugs in China's national insurance system in 2018, their clinical application was expanded substantially, particularly after 2021. This shift underscored the evolving treatment landscape for advanced NSCLC, transitioning from traditional chemotherapy to immunotherapy-based approaches clinically.[29]

In this study, ORR was 24.1% in the anlotinib-related treatment group and 11.3% in the chemotherapy monotherapy group, showing no statistically significant difference ($P = 0.084$). This might be attributed to the relatively small sample size and potential patient heterogeneity, such as prior treatment history or immune-related adverse event profiles. Nevertheless, the numerical trend suggested a potential clinical benefit of anlotinib-based regimens in tumor response, which warranted further validation in larger, adequately powered prospective trials. However, the DCR was significantly higher in the AG (79.6%) compared to that in CG (54.7%) ($P = 0.006$). These findings suggested that anlotinib-related regimens might offer superior tumor control among patients with advanced NSCLC who had previously undergone immunotherapy.[16] Regarding survival outcomes, the median PFS was 6.3 months in the AG versus 2.8 months in CG. Furthermore, the median OS was 16.1 months for patients who received the anlotinib-related regimen compared to 10.1 months for patients who received chemotherapy monotherapy. These results indicated that combining anlotinib with chemotherapy or immunotherapy might provide synergistic benefits, leading to both improved short-term efficacy and extended survival. These findings were consistent with previous research, such as the study by Professor Ren, which involved 40 patients with advanced NSCLC who failed prior immunotherapy.[21] In their study, patients received a combination of famitinib (a tyrosine kinase inhibitor similar to anlotinib) and camrelizumab (PD-1 inhibitor), resulting in an ORR of 7.5%, a DCR of 80.0%, a median PFS of 5.4 months, and a median OS of 12.1 months. However, it should be noted that their study was a single-arm clinical trial without a control group, which was a limitation inherently. Moreover, in our study, the outcomes observed in the chemotherapy monotherapy group – ORR, DCR, and PFS – were comparable to those reported in the CheckMate 017 and CheckMate 057 clinical trials, which evaluated nivolumab versus docetaxel in previously treated NSCLC patients.[30] The OS in CG was slightly longer, possibly reflecting advancements in supportive care or patient selection.[30] Nonetheless, these results also underscored that chemotherapy monotherapy continued to offer limited benefits in the current treatment landscape for advanced NSCLC.[31] Interestingly, the ORR, PFS, and OS observed in the AG group appeared to be more favorable than those reported in the ALTER0303 trial, where anlotinib monotherapy achieved an ORR of 9.2%, a median PFS of 5.4 months, and a median OS of 9.6 months.[15] This discrepancy might be attributed to differences in patient populations: in our study, 25.6% of patients received anlotinib-related

regimen as the second-line treatment, whereas the ALTER0303 trial focused exclusively on third-line or later treatments.[32] Additionally, since its approval in 2018, anlotinib had been the subject of extensive research exploring its mechanisms of action. Initially recognized for its anti-angiogenic properties, recent studies had revealed that anlotinib also modulated the tumor microenvironment.[33] It facilitated vascular normalization and extracellular matrix remodeling, enhancing drug delivery and potentially overcoming resistance to immunotherapy to some extent.[34] These effects might improve the infiltration and function of immune cells within tumors, thereby augmenting the efficacy of both chemotherapy and PD-1 inhibitors.[35] As a result, anlotinib-based regimens demonstrated significant clinical benefits in patients with advanced NSCLC who had previously been treated with immunotherapy. These findings supported the further exploration of anlotinib combination treatment strategies to improve outcomes in this patient population.

Additionally, this study also explored the efficacy differences between anlotinib combined with chemotherapy and anlotinib combined with PD-1 inhibitors in patients with previously ICIs-treated advanced NSCLC. The results showed that anlotinib combined with PD-1 inhibitors and anlotinib combined with chemotherapy demonstrated similar PFS (median PFS = 6.3 months vs 8.9 months, $P = 0.575$), which suggested that anlotinib plus chemotherapy seemed to have a similar disease control compared with anlotinib plus immunotherapy.[36] Interestingly, the Kaplan-Meier curve of OS illustrated that the anlotinib plus immunotherapy regimen appeared to have a superior OS compared with anlotinib plus chemotherapy (median OS = 16.8 months vs 13.4 months), although the difference was not statistically significant ($P = 0.223$). This result might be attributed to several factors: (1) Limited sample size: the subgroup included a relatively small number of patients (N = 54), which reduced the statistical power and increased the chance of a type II error, thus potentially obscuring a meaningful survival benefit; (2) Patient heterogeneity: variability in prior treatments, PD-L1 expression, performance status, and comorbidities might have contributed to survival differences, diluting the observable effect; and (3) Follow-up duration: although sufficient for PFS analysis, the median follow-up duration might not yet fully capture long-term survival differences between two groups. To validate this finding and allow robust multivariate subgroup analysis, future studies should involve larger, more homogeneous patient cohorts. And prospective multicenter trials with stratified randomization based on key prognostic variables might help confirm whether the combination regimen conferred a true OS benefit. Consequently, OS analysis suggested that anlotinib combined with PD-1 inhibitors might offer significant clinical benefits as an immune re-challenge strategy for patients with immune treatment failure. These findings aligned with previous research by Levra MG, who reported that NSCLC patients who underwent a second course of PD-1 inhibitor therapy after discontinuing nivolumab experienced a median OS of 18.4 months, particularly among those with an initial treatment duration of $\geq$ 3 months.[37] In summary, both anlotinib-based combination therapies (anlotinib plus chemotherapy and anlotinib plus immunotherapy) showed promising outcomes, determining the optimal regimen for patients with advanced NSCLC who had previously undergone immunotherapy required additional research with larger patient cohorts. Given the observed clinical benefits, anlotinib-based combination therapies might represent a viable and potentially preferred option for patients with advanced NSCLC who had progressed after ICI-based treatments. In particular, combinations with chemotherapy or immunotherapy might be considered based on patient performance status, prior toxicity profile, and treatment accessibility. These findings supported the consideration of anlotinib-based regimens as a rational component of subsequent treatment sequencing strategies in real-world clinical practice.

Ultimately, the safety profile analysis showed that the incidence of TRAEs in AG was 85.2%, with 40.7% of patients experiencing grade 3 or higher TRAEs. In CG, 83.0% of patients experienced TRAEs, and 45.3% experienced grade 3 or higher TRAEs. These results were in line with a previous study evaluating the safety profiles of anlotinib and chemotherapy in similar patient populations.[38] Specific to anlotinib-based regimens, the most common TRAEs included hypertension and hand-foot syndrome (HFS). Hypertension was reported in approximately 50.0% of patients with grade $\geq$ 3 hypertension occurring in 14.8% of cases. HFS was observed in 20.4% of patients with grade $\geq$ 3 events in 3.7% of cases. These incidence rates aligned with those reported in prior clinical trials, indicating a predictable and manageable safety profile for anlotinib.[39] In clinical practice, management of hypertension involved close blood pressure monitoring and timely initiation of antihypertensive therapy. Commonly used agents included calcium channel blockers, ACE inhibitors, or angiotensin receptor blockers.[40] Treatment interruption and dose reduction of anlotinib were applied in cases of uncontrolled $\geq$ 3 grade hypertension. This approach effectively prevented hypertensive complications while allowing continued treatment. For HFS, preventive and therapeutic strategies included patient education on hand and foot

care, prophylactic application of urea-containing creams, topical corticosteroids, and avoidance of mechanical friction.[41] In moderate-to-severe cases (grade ≥ 2), temporary dose reduction or brief treatment interruption might alleviate symptoms. Although these TRAEs might impact patient quality-of-life, their management was typically straightforward and reversible. In our study, no patients permanently discontinued treatment due to either hypertension or HFS. This suggested that, with appropriate early intervention and supportive care, these toxicities were manageable and did not pose a major barrier to long-term adherence. In the chemotherapy monotherapy group, alopecia was a prominent AE, consistent with the known toxicity profile of agents such as docetaxel. Alopecia was a well-documented toxicity of docetaxel, often impacting patients' quality-of-life.[42] Overall, the safety profile associated with anlotinib-related regimens in patients with previously ICIs-treated advanced NSCLC were manageable and controllable.

This study had several limitations that warranted consideration. As a retrospective observational study, it might be subject to inherent biases, including selection bias due to non-randomized treatment allocation, potential confounding factors, and incomplete documentation in medical records. Although efforts were made to balance baseline characteristics between groups, unmeasured variables might still influence outcomes. Additionally, the single-center design limited generalizability. Therefore, our findings should be interpreted cautiously and further validated through large-scale, prospective, multicenter randomized controlled trials. Due to the retrospective nature of the study, data on patients' social economic status were not available. However, we acknowledged that socioeconomic status might influence treatment selection and access, and future prospective studies should consider collecting and analyzing these variables. Despite these limitations, the study provided preliminary evidence supporting that anlotinib-related regimens might offer superior efficacy and improved prognosis compared to chemotherapy monotherapy in patients with previously ICIs-treated advanced NSCLC. These findings contributed valuable insights into treatment strategies for this patient population and underscored the need for prospective, randomized controlled phase III clinical trials with larger sample sizes to validate and expand upon these results subsequently.

Disclosure

The authors declare that there are no conflicts of interest.

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