Original Article

A cohort study of the efficacy and safety of immune checkpoint inhibitors plus anlotinib versus immune checkpoint inhibitors alone as the treatment of advanced non-small cell lung cancer in the real world

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Background: Anlotinib is a new multi-target tyrosine kinase inhibitor (TKI) and has been shown to have antitumor effects and synergistic antitumor effects with immunotherapy only in animal studies and in the 2nd-line treatment in small clinical trials. A real-world study with large sample to compare the efficacy and safety of anlotinib plus immune checkpoint inhibitors (ICIs) with ICIs alone in the multiline treatment of advanced non-small cell lung cancer (NSCLC) was urgently needed.

Methods: The data of 535 advanced NSCLC patients were collected from January 1, 2018, to December 31, 2021. The patients were divided into 2 groups: (I) ICI monotherapy (230 patients); (II) ICI + anlotinib (305 patients). After propensity-score matching (PSM) to reduce the effects of biases and confounding variables, the progression-free survival time (PFS), occurrence of adverse events, disease control rate (DCR), and objective response rate (ORR) of the 2 groups were compared. The effects of clinical factors, including age, gender, gene mutations, tumor proportion score, metastases, and combined radiotherapy, were also analyzed.

Results: After PSM, the baseline clinical characteristics were well balanced and the 2 group had a good comparability. Patients in the ICI + anlotinib group had significantly longer median PFS in both the 2nd-line treatment (7.73 *vs.* 4.70 months; P=0.003) and 3rd-line treatment (5.90 *vs.* 3.37 months; P=0.020), but the difference lacked statistical significance in the 1st-line treatment (8.40 *vs.* 5.20 months; P=0.229). The overall

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median PFS of patients in the ICI + anlotinib group was also much longer than that of patients in the ICI monotherapy group (6.37 *vs.* 3.90 months; P<0.001). The ICI + anlotinib group also tended to have a higher DCR, a higher ORR, and a higher probability of severe adverse drug reactions during the treatment than the ICI monotherapy group, but the differences were not statistically significant. Combining ICI + anlotinib could improve the outcomes of patients with bone metastasis.

Conclusions: Anlotinib + ICI therapy could have greater efficacy in the treatment of advanced NSCLC patients than ICI monotherapy. The probability of adverse events might increase in the combined treatment, but could be controlled.

Keywords: Non-small cell lung cancer (NSCLC); immunotherapy; combined therapy; anlotinib

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Introduction

Lung cancer has become the leading cause of cancer-related deaths due to its aggressiveness and high mortality rate (1). In 2015 alone, approximately 610,200 patients died from lung cancer in China, a figure that accounts for 22% of all cancer-related deaths (2,3). Non-small cell lung cancer (NSCLC) is the principal subtype of lung cancer, and accounts for about 85% of all types of lung cancer (4). In addition to traditional platinum-based drug chemotherapy, targeted therapy and immunotherapy are also vital treatments (5) for advanced NSCLC. With increased options of therapeutic drugs and the continuous progress of individualized treatment strategies, the prognosis of patients with advanced NSCLC has improved significantly, and treatment with dual-drug or multi-drug comprehensive therapy has become widely accepted (6).

Immune checkpoint inhibitors (ICIs) are new treatments for lung cancer in which inhibitors of programmed cell death-1 (PD-1) and its programmed cell death-ligand 1 (PD-L1) release the restriction of T-cell immune function by PD-1/PD-L1 such that the cells activated by tumor stimulation can play anti-tumor roles. Multiple large-scale clinical trials have shown that ICIs significantly prolong the median overall survival (OS) of patients with lung cancer and improve the objective response rate (ORR) of anti-tumor therapy (7-9). At present, ICIs have been approved as 1st-line treatment for those with advanced NSCLCs that have no driver gene and show positive PD-L1 expression. However, while immunotherapy has promising outcomes for lung cancer with great prospects, its sustained effectiveness is low, where PD-L1 inhibitors cure solid tumors in only 10–30% (10).

Anti-angiogenic drugs achieve anti-tumor effects by changing the tumor microenvironment, degenerating tumor blood vessels, and inhibiting the formation of new blood vessels. Anlotinib is a new multi-target tyrosine kinase inhibitor (TKI) that was independently developed in China. The inhibition of tumor-related angiogenesis, mediated by vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), and platelet derived growth factor receptor (PDGFR), effectively inhibits tumor growth. Large randomized clinical trials, such as ALTER0302 and ALTER0303, have shown that anlotinib has significant anti-tumor efficacy, and its efficacy in the 3rd-line or multi-line treatment of NSCLC has also been confirmed by landmark studies (11-13).

In recent years, combined therapy that includes anti-angiogenic drugs has become a new strategy for treating various solid tumors, including lung cancers. Anti-angiogenic drugs not only block the formation of new blood vessels, but also reverse the immunosuppressive state of the tumor microenvironment, thereby enhancing the anti-tumor effect (14,15). Research conducted with mouse models of lung cancer has shown that Anlotinib combined with PD-1 inhibitors promote the infiltration of innate immune cells and enhance the potential synergistic anti-tumor activity (15). Furthermore, anlotinib monotherapy has been shown to downregulate the expression of PD-L1 to improve the tumor immune microenvironment (14). In a multicenter, randomized clinical trial, a new humanized monoclonal antibody against PD-L1, combined with anlotinib in second-line therapy significantly reduced the risk of disease progression or death in patients with stage IIIB to IV NSCLC compared with TQ-B2450

monotherapy and was safely tolerated (16). Anlotinib plus immunotherapy may also be beneficial compared to immunotherapy monotherapy in other solid tumors (17).

Compared with randomized controlled trials, real world studies can reflect the actual clinical efficacy of drugs and the gap between guidelines and practice, while real world studies involving large sample sizes to analyze the efficacy of anlotinib + ICIs are scarce now. Thus, using real medical cases, we conducted a retrospective study to examine the efficacy and safety of anlotinib combined with PD-1 inhibitors in treating patients with advanced NSCLC to provide reliable reference for patients with advanced NSCLC in choosing feasible treatment options. We present the following article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-350/rc).

Methods

Study population

During this cohort study, which was conducted at Jiangsu Cancer Hospital, we collected the data of 535 patients with advanced NSCLC from January 1, 2018, to December 31, 2021. The patients included those who had received combined therapy of Anlotinib with PD-1 inhibitors and those who had received PD-1 inhibitor monotherapy. To be eligible for inclusion in the study, the patients had to meet the following inclusion criteria: (I) aged >18 years; (II) stage IIIB or stage IV lung adenocarcinoma or squamous carcinoma as confirmed by cytology or histology; (III) Eastern Cooperative Oncology Group (ECOG) score of 0–2 points; (IV) at least 1 target lesion that could be measured by radiographic imaging; (V) undergone at least 2 courses of treatment of ICI + anlotinib or ICI monotherapy, which they had continued until their condition improved or they could not tolerate the drug (if the adverse events became severe, the drugs were discontinued); (VI) no serious organ diseases, such as heart, liver, or kidney diseases; and (VII) complete and accurate medical records.

Any patient with a past record of hemorrhage or hemoptysis, current coagulation abnormalities [i.e., an international normalized ratio (INR) >1.5 or prothrombin time (PT) > ULN + 4 s], or radiographic test results suggesting the tumor invasion of important blood vessels was excluded from the study. The last follow-up date was December 31, 2021. Patients who were lost to follow-up were not included in the study. The sample size of this study was determined by the number of patients who met the inclusion and exclusion criteria.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Jiangsu Cancer Hospital (No. 2021-008), and all participants signed an informed consent form.

Treatment methods

Under the 3-week course of treatment, an oral dosage of Anlotinib Hydrochloride Capsules (12 mg qd), was consecutively administered for 2 weeks, and then stopped for 1 week. Adverse events were closely monitored during the treatment (18) and the dose is recommended to be adjusted under the guidance of a physician according to the degree of adverse events. The dosage was adjusted to 10 mg qd for the first time, administered for 2 weeks, and usage was stopped for 1 week; the dosage was adjusted to 8 mg qd for the second time, and used for 2 weeks, and usage was stopped for 1 week; if the patient remained unable to tolerate the adjustment to the dosage of 8 mg qd, it was permanently discontinued. For non-hemorrhagic (without bleeding) events, if a grade 3–4 adverse event occurred, the medications were suspended until the adverse event returned to a grade 2, and the treatment was then reduced to 1 dosage of the drug or permanently discontinued; if the patient did not recover after 2 weeks of suspending the medication, it was permanently discontinued. For hemorrhagic adverse events, if a grade 2 event occurred, the medication was suspended and symptomatic treatment was continued until the adverse event returned to below a grade 2 in 2 weeks, and the drug dosage was further reduced; if bleeding re-occurred, the drug was permanently discontinued; if the hemorrhagic adverse reaction was > grade 3, symptomatic treatment was administered, and the drug was permanently discontinued.

The ICIs were as follows: 1,200 mg of atezolizumab every 3 weeks via intravenous injection; 10 mg/kg of durvalumab every 2 weeks via intravenous injection; 2 mg/kg of pembrolizumab every 3 weeks via intravenous injection; 3 mg/kg of nivolumab every 2 weeks via intravenous injection; 200 mg of sintilimab every 3 weeks via intravenous injection; 200 mg of tislelizumab every 3 weeks via intravenous injection; and 200 mg of camrelizumab every 3 weeks via intravenous injection. During the whole treatment, the immune-related adverse events were treated symptomatically and respectively until the condition of the

patients improved or degenerated to intolerable toxicity, which can result in the death of patients.

Efficacy assessment

During treatment, a tumor assessment was performed every 6 weeks. According to the evaluation criteria for the efficacy of solid tumors (RECIST 1.1) (19), the efficacy evaluation of tumor treatment can be divided into 4 indicators; that is, complete response (CR); partial response (PR), stable disease (SD), and progressive disease (PD). The researchers conducted symptom assessments based on the respective changes in the lung cancer-related symptoms.

Progression-free survival (PFS) was defined as the time from the 1st medication treatment to the first tumor progression or death (whichever occurred first). The disease control rate (DCR) was defined as the proportion of patients whose tumors had shrunk or stabilized and were maintained for a certain period during the therapeutic treatment. The ORR was defined as the proportion of patients whose tumors had shrunk to a predetermined degree within the minimum time limit (i.e., the sum total of the proportion of patients who achieved a CR or PR).

Safety evaluation

Under the Common Terminology Criteria for Adverse Events (CTCAE 4.0 version) (18), the severity of the adverse events were graded, and any adverse drug reactions (ADR) > grade 3 in patients taking medication were recorded to analyze their respective relationship to the drugs taken.

Statistical methodology

R i386 4.1.2 statistical analysis software, SPSS 23.0 software, and EXCEL365 software were used to process the collected data, and visualize the statistical results.

The patients were divided into the following 2 groups based on the treatment they received: (I) the ICI monotherapy group; and (II) the ICI + anlotinib group. All the baseline clinical characteristics, including gender, age, education, body mass index (BMI), ECOG score, history of hypertension or diabetes, pathology, metastases, gene mutations including epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 receptor tyrosine kinase (ROS), and Kirsten rat sarcoma viral oncogene (KRAS), tumor proportion score (TPS), treatment lines, surgery history, and combined radiotherapy during ICI treatment were recorded. The PFS and the final treatment outcomes were the main observation and comparison indexes. To address any potential sources of bias and confounding variables between the 2 groups, the baseline clinical characteristics of the 2 groups were compared using the standardized mean difference (SMD) and were subjected to propensity-score matching (PSM) method using the package "nonrandom" and the package "tableone". The findings after PSM were more statistically robust.

The quantitative variables in this study included age, BMI, and TPS. The patients were further divided into 3 groups (i.e., <60, 60–75, and ≥75 years old) based on age, as the number of new lung cancer cases and deaths peak in patients aged 60–75 years (2). The BMI was calculated using the following formula: body weight (kg)/height $(m)^2$. Patients were further divided into 4 groups (i.e., <18.5, 18.5–24, 24–28, ≥28 kg/m^2) based on the BMI according to the obesity standards for Asian populations developed by the World Health Organization (20). The TPS was calculated using the following formula: number of tumor cells with positive PD-L1 staining/number of viable tumor cells in the sample ×100%. The TPS provided an evaluation of patients' PD-L1 expression levels before commencing ICI therapy. The patients were further divided into 4 groups based on the TPS (i.e., 0%, 0–1%, 1–50%, and 50–100%), as determined by the Youden Index used in previous studies, which has been widely used as the dividing standard in many worldwide large clinical trials (21,22).

Univariate and multivariate Cox regression analyses were conducted to analyze the effects of possible factors on prognosis. The log-rank test was used to compare differences in the survival curves, and the chi-square test was used to compare differences in proportions. A 2-tailed P value <0.05 indicated a statistically significant discrepancy. The packages "ggplot2", "survival", and "survminer" were used to draw survival curves and otherwise visualize the statistical results.

Results

Baseline clinical characteristics and PSM matching

After screening 1,428 patients treated at the Jiangsu Cancer Hospital up to December 31, 2021, 535 NSCLC patients met the inclusion criteria for this study, including 305 patients treated with ICI + anlotinib, and 230 patients

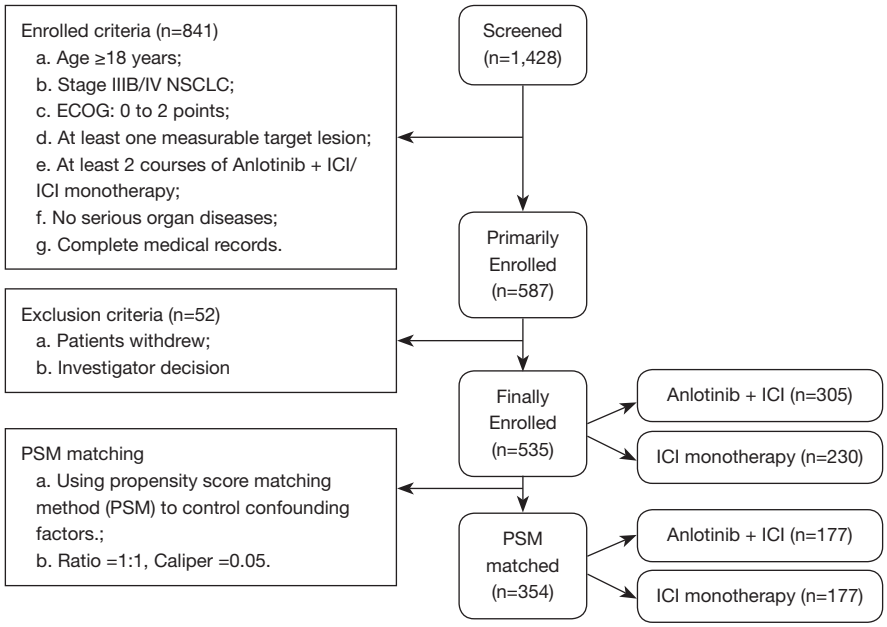

Figure 1 Screening and enrollment of patients. NSCLC, non-small cell lung cancer; EOCG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; PSM, propensity-score matching.

treated only with ICI monotherapy (*Figure 1*). At the end of this study, 354 patients met the criteria for disease progression. The average follow-up time was 7.10 months, and the longest follow-up time was 33.7 months for a patient treated with ICI + anlotinib.

The 2 groups of patients differed from each other in terms of age, pathological type, clinical stage, lung lobe with primary lesions, brain metastasis, bone metastasis, intrapulmonary metastasis, EGFR mutation, ALK mutation, KRAS mutation, and treatment line, and the chi-square test showed that these differences were statistically significant (P<0.05). The SMD of most clinical baseline indicators were >0.1 (10%), indicating the poor balance of the 2 groups' baseline data. The baseline data and statistical results are set out in *Table 1*.

Using PSM to reduce the effects of the biases and the confounding variables between the 2 groups, 2 highly comparable control groups were created based on the ratio of 1:1 and a caliper value of 0.05. Of the 354 patients, 177 were allocated to each group to achieve a baseline-data balance (*Figure 1*), in which the final model evaluation of PSM was good (*Figure 2*), and the SMD control was close to 10% (*Figure 3*). The baseline clinical characteristics of the 2 new groups after PSM were well balanced and showed no significant differences (P>0.05) (*Table 1*).

Factors affecting the PFS of patients diagnosed with advanced NSCLC

Univariate and multivariate analyses of overall group including the ICI monotherapy group and the ICI + anlotinib group were conducted before PSM, and among all the baseline characteristics and the treatment group (ICI monotherapy group *vs.* ICI + anlotinib group) also as an analysis variable, the treatment group [hazards ratio (HR) =0.571; P<0.001], gender (HR =1.531; P=0.002), BMI (HR =0.752; P=0.001), pathological type (HR =0.723; P=0.017), bone metastasis (HR =1.503; P=0.002), and liver metastasis (HR =1.703; P=0.001) were found to be associated with the PFS of the ICI treated patients. Univariate and multivariate analyses were then conducted after PSM, and the treatment group (ICI monotherapy group *vs.* ICI + anlotinib group; HR =0.549; P<0.001), BMI (HR =0.808; P=0.032), bone metastasis (HR =1.416; P=0.028), and liver metastasis (HR =1.797; P=0.003) were found to be independent relevant factors, associated with the PFS of advanced NSCLC patients and the P value of the treatment group (ICI + anlotinib group *vs.* ICI monotherapy group) was the smallest among all these significant factors (*Table 2*). Regardless of the treatment group, advanced NSCLC patients with bone metastasis or liver metastasis had shorter median PFS than those who did not have any bone or liver

Table 1 A comparison of the baseline clinical characteristics of patients before/after PSM

Items	Before PSM				After PSM			
	ICI + anlotinib (n=305)	ICI monotherapy (n=230)	P	SMD	ICI + anlotinib (n=177)	ICI monotherapy (n=177)	P	SMD
Gender, n (%)			0.129	0.152			0.898	0.014
Male	233 (76.39)	183 (79.57)			137 (77.40)	138 (77.97)		
Female	82 (26.89)	47 (20.43)			40 (22.60)	39 (22.03)		
Age, n (%)			0.006	0.272			0.677	0.048
<60 years	139 (45.57)	74 (32.17)			66 (37.29)	67 (37.85)		
60–75 years	149 (48.85)	137 (59.57)			98 (55.37)	101 (57.06)		
≥75 years	17 (5.57)	19 (8.26)			13 (7.34)	9 (5.08)		
BMI (kg/m^2), n (%)			0.267	0.113			0.526	0.084
<18.5	33 (10.82)	27 (11.74)			14 (7.91)	17 (9.60)		
18.5–24	191 (62.62)	126 (54.78)			115 (64.97)	103 (58.19)		
24–28	72 (23.61)	66 (28.70)			42 (23.73)	47 (26.55)		
≥28	9 (2.95)	11 (4.78)			6 (3.39)	10 (5.65)		
Educational background, n (%)			0.151	0.166			0.493	0.027
≤ Elementary	78 (25.57)	71 (30.87)			48 (27.12)	55 (31.07)		
Junior and senior	172 (56.39)	130 (56.52)			108 (61.02)	97 (54.80)		
≥ College	55 (18.03)	29 (12.61)			21 (11.86)	25 (14.12)		
ECOG, n (%)			0.061	0.125			0.113	0.121
0	1 (0.33)	6 (2.61)			0 (0.00)	1 (0.56)		
1	297 (97.38)	219 (95.22)			176 (99.44)	171 (96.61)		
2	7 (2.30)	5 (2.17)			1 (0.56)	5 (2.82)		
Hypertension, n (%)			0.998	<0.001			0.300	0.110
No	240 (78.69)	181 (78.70)			143 (80.79)	135 (76.27)		
Yes	65 (21.31)	49 (21.30)			34 (19.21)	42 (23.73)		
Diabetes, n (%)			0.283	0.093			1.000	<0.001
No	279 (91.48)	204 (88.70)			156 (88.14)	156 (88.14)		
Yes	26 (8.52)	26 (11.30)			21 (11.86)	21 (11.86)		
Pathological type, n (%)			0.002	0.276			0.914	0.011
Adenocarcinoma	209 (68.52)	127 (55.22)			106 (59.89)	105 (59.32)		
Squamous carcinoma	96 (31.48)	103 (44.78)			71 (40.11)	72 (40.68)		
Clinical stage, n (%)			<0.001	0.381			0.291	0.112
IIIB stage	15 (4.92)	38 (16.52)			15 (8.47)	21 (11.86)		
IV stage	290 (95.08)	192 (83.48)			162 (91.53)	156 (88.14)		
Lung lobe, n (%)			0.023	0.198			0.915	0.011
Left	129 (42.30)	120 (52.17)			92 (51.98)	91 (51.41)		
Right	176 (57.70)	110 (47.83)			85 (48.02)	86 (48.59)		

Table 1 (*continued*)

Table 1 (*continued*)

Items	Before PSM				After PSM			
	ICI + anlotinib (n=305)	ICI monotherapy (n=230)	P	SMD	ICI + anlotinib (n=177)	ICI monotherapy (n=177)	P	SMD
Location, n (%)			0.401	0.006			0.427	0.024
Superior	170 (55.74)	131 (56.96)			101 (57.06)	102 (57.63)		
Middle	25 (8.20)	12 (5.22)			15 (8.47)	9 (5.08)		
Inferior	110 (36.07)	87 (37.83)			61 (34.46)	66 (37.29)		
Meningeal metastasis, n (%)			0.356	0.141			1.000	<0.001
No	302 (99.02)	230 (100.00)			177 (100.00)	177 (100.00)		
Yes	3 (0.98)	0 (0.00)			0 (0.00)	0 (0.00)		
Brain metastasis, n (%)			0.002	0.271			0.894	0.014
No	219 (71.80)	191 (83.04)			142 (80.23)	141 (79.66)		
Yes	86 (28.20)	39 (16.96)			35 (19.77)	36 (20.34)		
Bone metastasis, n (%)			0.004	0.253			0.588	0.057
No	164 (53.77)	152 (66.09)			103 (58.19)	108 (61.02)		
Yes	141 (46.23)	78 (33.91)			74 (41.81)	69 (38.98)		
Liver metastasis, n (%)			0.648	0.040			0.887	0.015
No	250 (81.97)	192 (83.48)			148 (83.62)	147 (83.05)		
Yes	55 (18.03)	38 (16.52)			29 (16.38)	30 (16.95)		
Peritoneum metastasis, n (%)			0.150	0.128			0.238	0.125
No	276 (90.49)	216 (93.91)			170 (96.05)	165 (93.22)		
Yes	29 (9.51)	14 (6.09)			7 (3.95)	12 (6.78)		
Urogenital metastasis, n (%)			0.424	0.069			0.660	0.047
No	261 (85.57)	191 (83.04)			151 (85.31)	148 (83.62)		
Yes	44 (14.43)	39 (16.96)			26 (14.69)	29 (16.38)		
Pleural metastasis, n (%)			0.073	0.157			0.393	0.091
No	162 (53.11)	140 (60.87)			92 (51.98)	100 (56.50)		
Yes	143 (46.89)	90 (39.13)			85 (48.02)	77 (43.50)		
Intrapulmonary metastasis, n (%)			0.010	0.225			0.230	0.127
No	107 (35.08)	106 (46.09)			63 (35.59)	74 (41.81)		
Yes	198 (64.92)	124 (53.91)			114 (64.41)	103 (58.19)		
PD-L1 TPS, n (%)			0.134	0.095			0.120	0.098
0	3 (0.98)	0 (0.00)			3 (1.69)	0 (0.00)		
(0, 1%]	13 (4.26)	18 (7.83)			10 (5.65)	10 (5.65)		
(1%, 50%]	2 (0.66)	1 (0.43)			2 (1.13)	0 (0.00)		
(50%, 100%]	3 (0.98)	4 (1.74)			1 (0.56)	2 (1.13)		
Unknown	284 (93.11)	207 (90.00)			161 (90.96)	165 (93.22)		

Table 1 (*continued*)

Table 1 (*continued*)

Items	Before PSM				After PSM			
	ICI + anlotinib (n=305)	ICI monotherapy (n=230)	P	SMD	ICI + anlotinib (n=177)	ICI monotherapy (n=177)	P	SMD
Gene mutation, n (%)			0.371	0.060			0.899	0.006
No	155 (50.82)	126 (54.78)			99 (55.93)	101 (57.06)		
Yes	76 (24.92)	78 (33.91)			26 (14.69)	23 (12.99)		
Unknown	74 (24.26)	76 (33.04)			52 (29.38)	53 (29.94)		
EGFR mutation, n (%)			0.001	0.043			0.873	0.006
No	165 (54.10)	136 (59.13)			105 (59.32)	107 (60.45)		
Yes	66 (21.64)	18 (7.83)			20 (11.30)	17 (9.60)		
Unknown	74 (24.26)	76 (33.04)			52 (29.38)	53 (29.94)		
ALK mutation, n (%)			0.047	0.191			0.907	0.012
No	230 (75.41)	154 (66.96)			125 (70.62)	124 (70.06)		
Yes	1 (0.33)	0 (0.00)			0 (0.00)	0 (0.00)		
Unknown	74 (24.26)	76 (33.04)			52 (29.38)	53 (29.94)		
ROS mutation, n (%)			0.053	0.203			0.919	0.019
No	228 (74.75)	150 (65.22)			122 (68.93)	120 (67.80)		
Yes	3 (0.98)	4 (1.74)			3 (1.69)	4 (2.26)		
Unknown	74 (24.26)	76 (33.04)			52 (29.38)	53 (29.94)		
KRAS mutation, n (%)			0.023	0.216			0.927	0.006
No	226 (74.10)	146 (63.48)			121 (68.36)	121 (68.36)		
Yes	5 (1.64)	8 (3.48)			4 (2.26)	3 (1.69)		
Unknown	74 (24.26)	76 (33.04)			52 (29.38)	53 (29.94)		
Treatment lines, n (%)			<0.001	0.557			0.643	0.030
1st line	8 (2.62)	22 (9.57)			8 (4.52)	6 (3.39)		
2nd line	54 (17.70)	83 (36.09)			46 (25.99)	53 (29.94)		
3rd line and above	243 (79.67)	125 (54.35)			123 (69.49)	118 (66.67)		
Surgery history, n (%)			0.697	0.034			0.380	0.093
No	233 (76.39)	179 (77.83)			139 (78.53)	132 (74.58)		
Yes	72 (23.61)	51 (22.17)			38 (21.47)	45 (25.42)		
Radiotherapy during immunotherapy, n (%)			0.411	0.072			1.000	<0.001
No	249 (81.64)	194 (84.35)			148 (83.62)	148 (83.62)		
Yes	56 (18.36)	36 (15.65)			29 (16.38)	29 (16.38)		

ICI, immune checkpoint inhibitor; PSM, propensity-score matching; BMI, body mass index; EOCG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; ROS, ROS proto-oncogene 1 receptor tyrosine kinase; KRAS, Kirsten rat sarcoma viral oncogene; SMD, standardized mean difference.

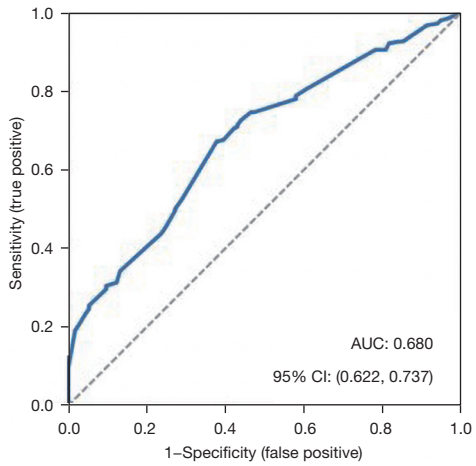

Figure 2 The final model evaluation using PSM. AUC, area under the curve; CI, confidence interval; PSM, propensity-score matching.

metastasis according to the log-rank tests both before and after PSM (*Figure 4*).

Efficacy evaluation

Before PSM, the median PFS of the ICI + anlotinib group was significantly longer than that of the ICI monotherapy group (5.90 *vs.* 4.10 months; P=0.003) (*Figure 5A*). After PSM, the addition of anlotinib prolonged the median PFS of advanced NSCLC patients receiving ICI treatment (ICI + anlotinib group *vs.* ICI monotherapy group; 6.37 *vs.* 3.90 months; P<0.001) (*Figure 5B*).

A stratified analysis of the different treatment lines was conducted (*Figure 6*). The median PFS of the ICI + anlotinib group was much longer than that of the ICI monotherapy group in the 1st-line treatment, but the

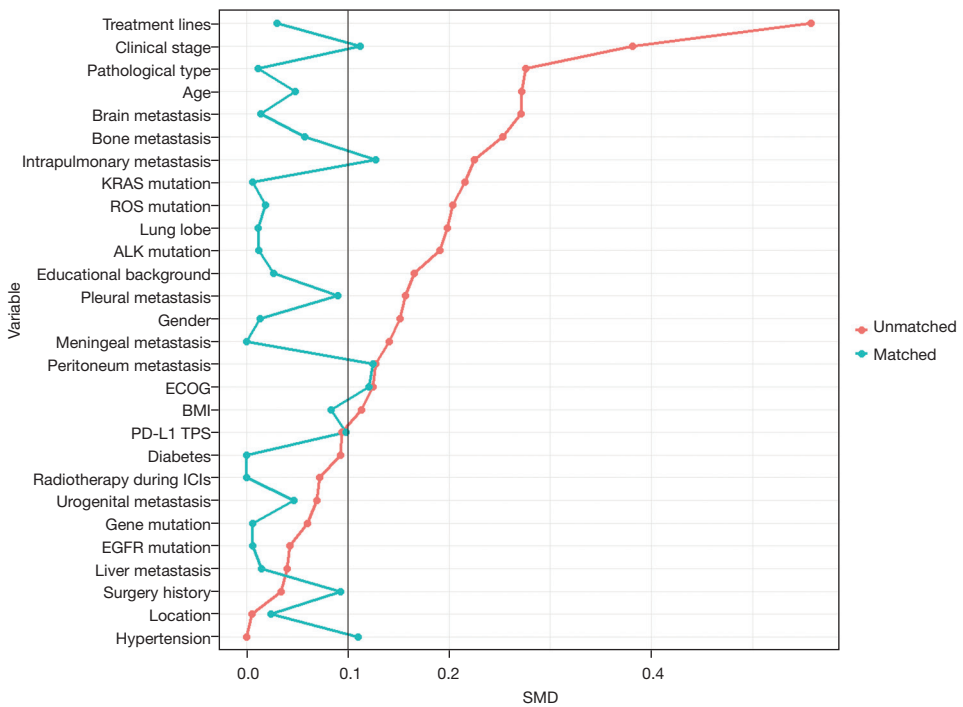

Figure 3 The fluctuation of SMD before/after PSM. SMD, standardized mean difference; PSM, propensity-score matching; BMI, body mass index; EOCG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; ROS, ROS proto-oncogene 1 receptor tyrosine kinase; KRAS, Kirsten rat sarcoma viral oncogene.

Table 2 Univariate and multivariate analyses of the factors associated with the efficacy of ICI treatment before/after PSM

Items	Before PSM				After PSM			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)
Treatment group	0.003	0.727 (0.588–0.899)	<0.001***	0.571 (0.448–0.727)	<0.001	0.630 (0.487–0.815)	<0.001***	0.549 (0.418–0.721)
Gender	0.000	1.556 (1.230–1.968)	0.002**	1.531 (1.169–2.004)	0.041	1.357 (1.013–1.818)	0.069	1.385 (0.975–1.968)
Age	0.989	0.999 (0.834–1.196)	0.817	0.978 (0.806–1.185)	0.826	0.975 (0.778–1.222)	0.836	0.974 (0.763–1.245)
BMI	0.000	0.740 (0.640–0.855)	0.001**	0.752 (0.640–0.883)	0.007	0.788 (0.662–0.938)	0.032*	0.808 (0.666–0.982)
Education	0.633	0.962 (0.820–1.128)	0.806	1.022 (0.857–1.219)	0.776	1.030 (0.840–1.263)	0.432	1.096 (0.872–1.376)
ECOG	0.392	0.774 (0.431–1.391)	0.150	0.642 (0.352–1.173)	0.494	0.736 (0.306–1.771)	0.117	0.450 (0.166–1.220)
Hypertension	0.440	1.106 (0.856–1.430)	0.181	1.226 (0.909–1.653)	0.183	1.237 (0.905–1.690)	0.257	1.259 (0.846–1.875)
Diabetes	0.749	1.058 (0.749–1.494)	0.315	1.225 (0.825–1.818)	0.584	1.112 (0.761–1.623)	0.426	1.209 (0.757–1.932)
Pathological type	0.001	0.692 (0.665–0.861)	0.017*	0.723 (0.554–0.944)	0.032	0.751 (0.577–0.976)	0.082	0.755 (0.550–1.036)
Clinical stage	0.208	1.277 (0.873–1.868)	0.637	0.896 (0.569–1.412)	1.188	1.371 (0.857–2.192)	0.797	0.930 (0.533–1.622)
Lung lobe	0.792	0.972 (0.789–1.199)	0.359	0.896 (0.708–1.134)	0.491	0.915 (0.709–1.179)	0.380	0.877 (0.653–1.176)
Location	0.364	1.052 (0.943–1.175)	0.724	1.022 (0.906–1.154)	0.242	1.085 (0.946–1.244)	0.195	1.107 (0.949–1.290)
Meningeal metastasis	0.437	1.570 (0.503–4.899)	0.747	1.224 (0.359–4.177)	–	–	–	–
Brain metastasis	0.056	1.261 (0.994–1.599)	0.967	0.994 (0.743–1.329)	0.383	1.148 (0.842–1.566)	0.691	0.927 (0.638–1.347)
Bone metastasis	0.000	1.656 (1.343–2.042)	0.002**	1.503 (1.168–1.935)	0.003	1.474 (1.142–1.903)	0.028*	1.416 (1.039–1.928)
Liver metastasis	0.000	1.843 (1.401–2.425)	0.001**	1.703 (1.241–2.338)	0.001	1.724 (1.235–2.406)	0.003**	1.797 (1.222–2.644)
Peritoneum metastasis	0.007	1.733 (1.159–2.591)	0.198	1.346 (0.856–2.114)	0.023	2.032 (1.105–3.740)	0.298	1.473 (0.710–3.054)
Urogenital metastasis	0.332	1.159 (0.861–1.560)	0.921	0.983 (0.697–1.386)	0.477	0.871 (0.596–1.273)	0.234	0.772 (0.504–1.182)
Pleural metastasis	0.127	1.177 (0.955–1.451)	0.519	1.080 (0.855–1.363)	0.335	1.134 (0.878–1.464)	0.966	0.994 (0.744–1.327)
Intrapulmonary metastasis	0.417	1.093 (0.882–1.354)	0.091	1.244 (0.966–1.602)	0.619	1.069 (0.822–1.391)	0.507	1.114 (0.809–1.534)
PD-L1 TPS	0.897	0.993 (0.896–1.101)	0.271	1.072 (0.947–1.212)	0.786	1.018 (0.893–1.161)	0.422	1.073 (0.904–1.273)
Gene mutation	0.305	0.939 (0.833–1.059)	0.976	1.011 (0.490–2.086)	0.414	0.943 (0.819–1.086)	0.937	1.048 (0.323–3.405)
EGFR mutation	0.261	0.934 (0.829–1.052)	0.663	1.180 (0.561–2.482)	0.360	0.937 (0.814–1.078)	0.677	1.289 (0.390–4.255)
ALK mutation	0.032	0.877 (0.778–0.989)	0.176	0.490 (0.174–1.378)	0.100	0.888 (0.771–1.023)	0.660	0.631 (0.081–4.905)
ROS mutation	0.073	0.897 (0.796–1.010)	0.140	1.994 (0.798–4.982)	1.163	0.905 (0.786–1.041)	0.311	1.842 (0.565–6.000)
KRAS mutation	0.056	0.890 (0.790–1.003)	0.619	0.803 (0.338–1.907)	0.104	0.889 (0.772–1.025)	0.504	0.586 (0.122–2.811)
Treatment lines	0.441	1.073 (0.896–1.286)	0.738	0.967 (0.793–1.179)	0.562	1.067 (0.856–1.330)	0.378	0.896 (0.703–1.143)
Surgery history	0.025	0.748 (0.580–0.964)	0.167	0.821 (0.620–1.086)	0.061	0.749 (0.553–1.013)	0.203	0.785 (0.540–1.140)
Radiotherapy	0.983	0.997 (0.765–1.300)	0.117	0.792 (0.592–1.060)	0.396	1.158 (0.826–1.624)	0.364	0.837 (0.569–1.230)

*, P<0.05; **, P<0.01; ***, P<0.001. ICI, immune checkpoint inhibitor; PSM, propensity-score matching; SMD, standardized mean difference; HR, hazards ratio; CI, confidence interval; BMI, body mass index; EOCG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; ROS, ROS proto-oncogene 1 receptor tyrosine kinase; KRAS, Kirsten rat sarcoma viral oncogene.

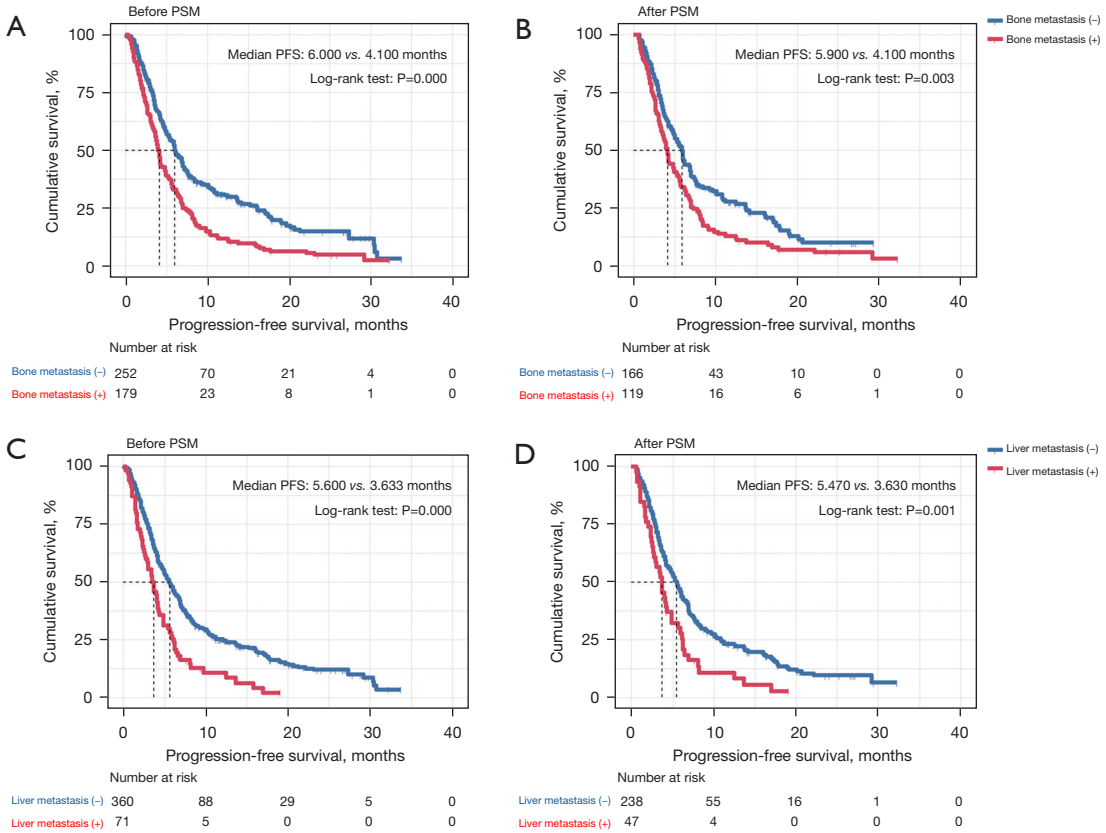

Figure 4 Effect of bone metastasis and liver metastasis on the efficacy of ICIs in the treatment advanced NSCLC patients. (A) The survival curves of ICIs in patients with or without bone metastasis before PSM; (B) the survival curves of ICIs in patients with or without bone metastasis after PSM; (C) the survival curves of ICIs in patients with or without liver metastasis before PSM; (D) the survival curves of ICIs in patients with or without liver metastasis after PSM. ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; PSM, propensity-score matching; PFS, progression-free survival.

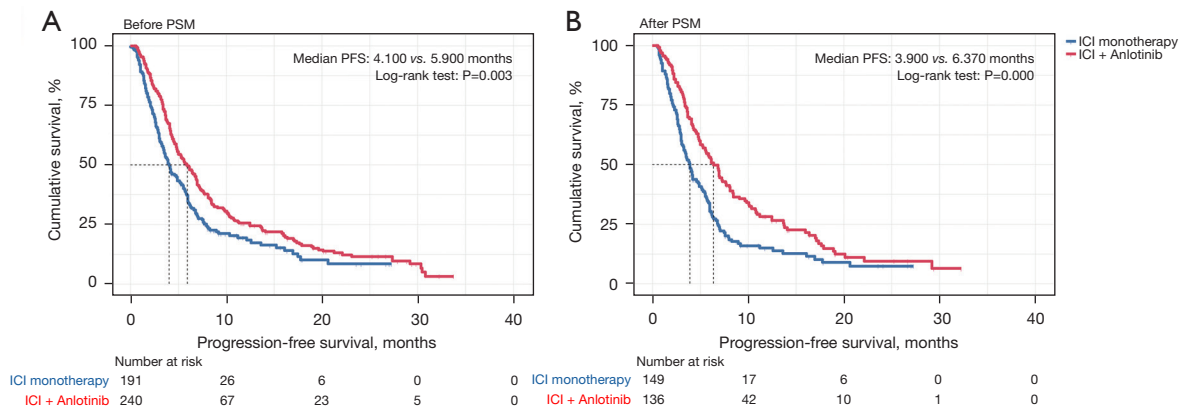

Figure 5 The survival curves of the ICI monotherapy/ICI + anlotinib groups in advanced NSCLC patients. (A) The survival curves before PSM; (B) the survival curves after PSM. ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; PSM, propensity-score matching; PFS, progression-free survival.

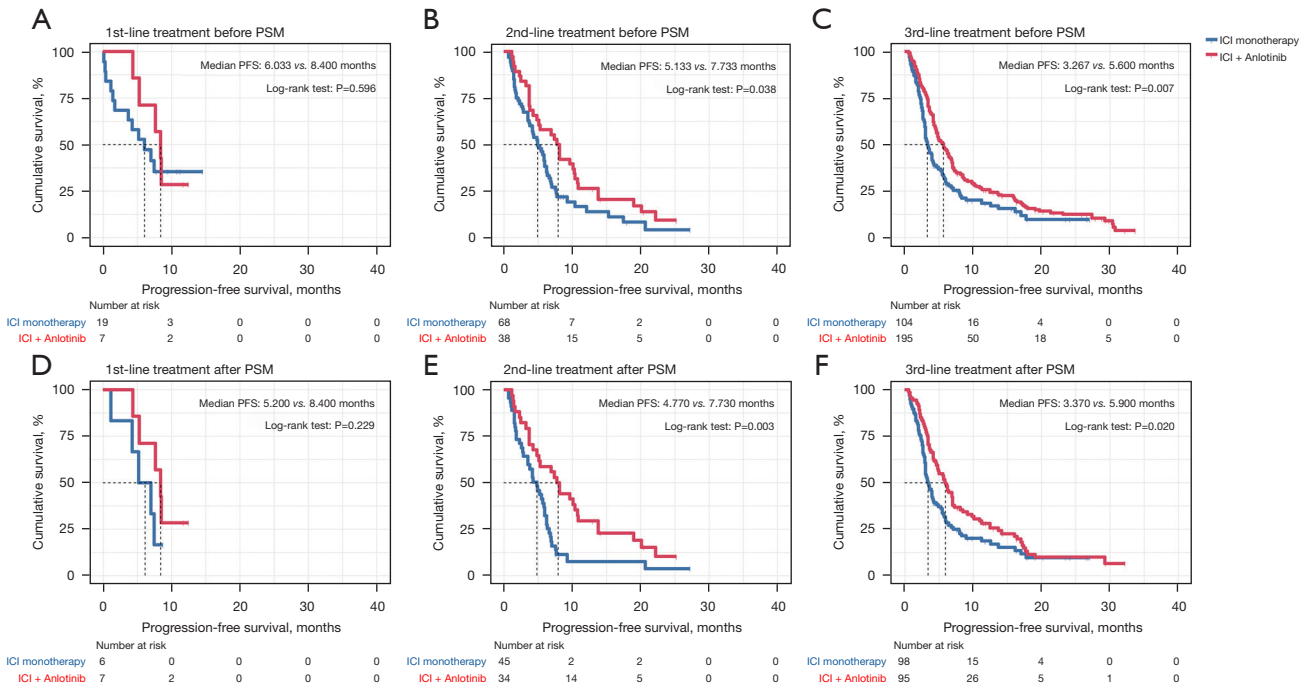

Figure 6 The survival curves of the ICI monotherapy/ICI + anlotinib groups in advanced NSCLC patients in a stratified analysis of different treatment lines. (A) The survival curves for the 1st-line treatment before PSM; (B) the survival curves for the 2nd-line treatment before PSM; (C) the survival curves for the 3rd-line treatment before PSM; (D) the survival curves for the 1st-line treatment after PSM; (E) the survival curves for the 2nd-line treatment after PSM; (F) the survival curves for the 3rd-line treatment after PSM. ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; PSM, propensity-score matching; PFS, progression-free survival.

difference was not statistically significant (before PSM: 8.40 *vs.* 6.03 months, P=0.596; after PSM: 8.40 *vs.* 5.20 months, P=0.229). Patients treated with ICI + anlotinib had a better prognosis than those using ICI monotherapy alone in the 2nd-line treatment (before PSM: 7.73 *vs.* 5.13 months, P=0.038; after PSM: 7.73 *vs.* 4.70 months, P=0.003), and in the 3rd-line treatment (before PSM: 5.60 *vs.* 3.27 months, P=0.007; after PSM: 5.90 *vs.* 3.37 months, P=0.020).

Among the 305 patients in the ICI + anlotinib group, 36 patients achieved a PR, 243 achieved SD, and only 26 did not progress to SD. Conversely, in the ICI monotherapy group, 21 patients had their lesions reduced by >30% after treatment, while 29 did not achieve SD before disease progression. Both the ORR (before PSM: 11.80% *vs.* 9.13%; after PSM: 14.12% *vs.* 9.04%) and the DCR (before PSM: 91.48% *vs.* 87.39%; after PSM: 90.96% *vs.* 88.14%) of the ICI + anlotinib group were higher than those of the ICI monotherapy group (*Table 3*).

A comparison of patients with liver metastasis or bone metastasis revealed that ICI + Anlotinib improved the prognosis of patients with bone metastasis significantly more than ICI monotherapy (before PSM: 4.23 *vs.* 3.27 months; P=0.036; after PSM: 4.90 *vs.* 3.27 months; P=0.012), but the differences between the 2 therapies in patients with liver metastasis was not significant (before PSM: 3.70 *vs.* 2.67 months, P=0.739; after PSM: 4.23 *vs.* 2.67 months, P=0.333) (*Figure 7*).

Adverse events

After different treatments in this study of 535 patients, we recorded and evaluated severe ADRs > Grade 3, including immune related pneumonitis (3.36%), hypothyroidism (2.80%), bone marrow suppression (2.62%), hand-foot syndrome (0.93%), dental ulcer (0.93%), pulmonary embolism (0.56%), hemoptysis (0.75%), nausea and vomiting (0.37%), arrhythmia (0.56%), and renal insufficiency (0.37%). Comparing the data of patients from the 2 groups before PSM, the probability of severe ADRs in the ICI + anlotinib group was significantly higher than that of the ICI monotherapy group. Conversely, after PSM, patients in the ICI + anlotinib group tended to develop

Table 3 Comparison of the efficacy of the different treatments in 2 groups before/after PSM

Groups	N	CR	PR, n (%)	SD, n (%)	PD, n (%)	ORR, %	DCR, %
Before PSM							
Anlotinib + ICI, n (%)	305	0	36 (11.80)	243 (79.67)	26 (8.52)	11.80	91.48
ICI monotherapy, n (%)	230	0	21 (9.13)	180 (78.26)	29 (12.61)	9.13	87.39
P						0.321	0.124
After PSM							
Anlotinib + ICI, n (%)	177	0	25 (14.12)	136 (76.84)	16 (9.04)	14.12	90.96
ICI monotherapy, n (%)	177	0	16 (9.04)	140 (79.10)	21 (11.86)	9.04	88.14
P						0.385	0.135

PSM, propensity-score matching; ICI, immune checkpoint inhibitor; CR, complete disease; PR, partial disease; SD, stable disease; PD, progression disease; ORR, objective response rate; DCR, disease control rate.

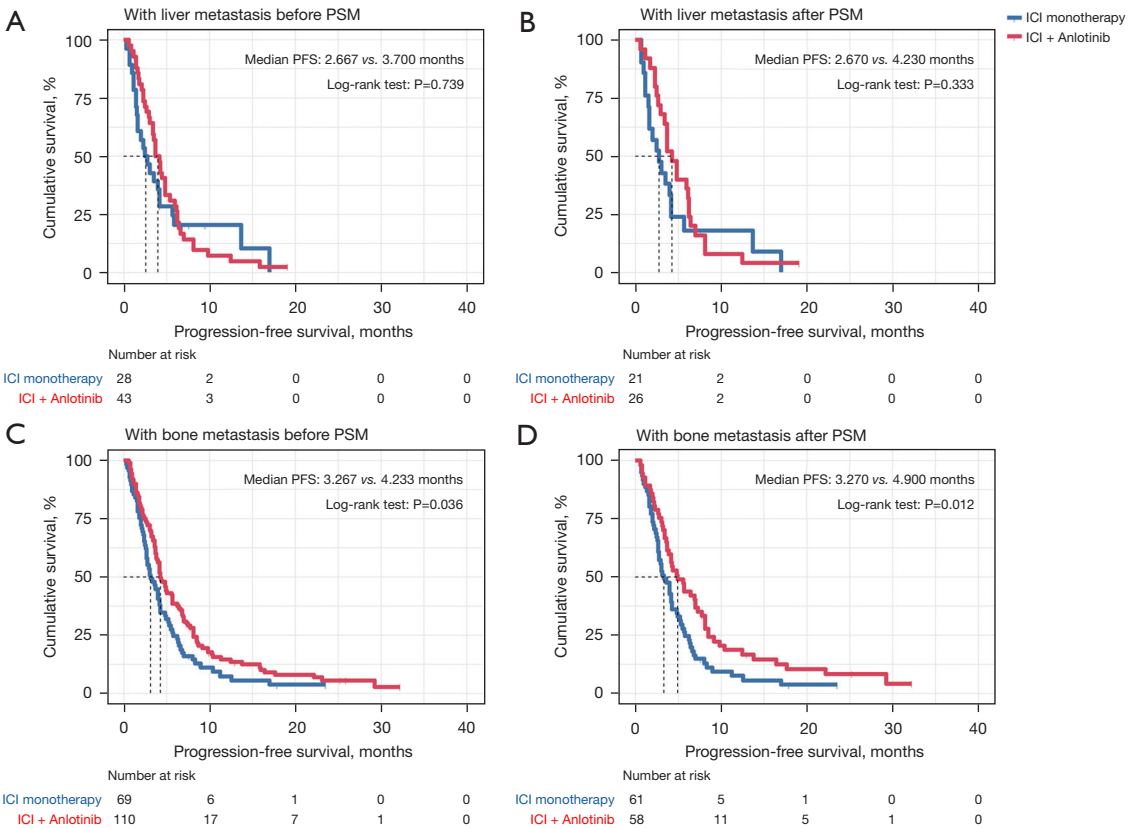

Figure 7 The survival curves for the ICI monotherapy/ICI + anlotinib groups in advanced NSCLC patients with bone metastasis or liver metastasis. (A) The survival curves for the patients with liver metastasis before PSM; (B) the survival curves for the patients with liver metastasis after PSM; (C) the survival curves for the patients with bone metastasis before PSM; (D) the survival curves for the patients with bone metastasis after PSM. ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; PSM, propensity-score matching; PFS, progression-free survival.

Table 4 Comparison of severe ADRs between the 2 groups before/after PSM

Items	Before PSM, n (%)			After PSM, n (%)		
	ICI + anlotinib (n=305)	ICI monotherapy (n=230)	P	ICI + anlotinib (n=177)	ICI monotherapy (n=177)	P
All severe ADRs	47 (15.41)	21 (9.13)	0.031	28 (15.82)	16 (9.04)	0.053
Immune pneumonia	11 (3.61)	7 (3.04)	0.721	8 (4.52)	4 (2.26)	0.240
Pulmonary embolism	3 (0.98)	0 (0.00)	0.356	2 (1.13)	0 (0.00)	0.499
Bone marrow suppression	8 (2.62)	6 (2.61)	1.000	4 (2.26)	6 (3.39)	0.748
Hemoptysis	3 (0.98)	0 (0.00)	0.356	1 (0.56)	0 (0.00)	1.000
Hand-foot syndrome	5 (1.64)	0 (0.00)	0.134	3 (1.69)	0 (0.00)	0.246
Dental ulcer	5 (1.64)	0 (0.00)	0.134	3 (1.69)	0 (0.00)	0.246
Hypothyroidism	10 (3.28)	5 (2.17)	0.443	5 (2.82)	4 (2.26)	1.000
Myocarditis	3 (0.98)	2 (0.87)	1.000	2 (1.13)	1 (0.56)	1.000
Arrhythmia	1 (0.33)	2 (0.87)	0.806	0 (0.00)	1 (0.56)	1.000
Nausea and vomiting	2 (0.66)	0 (0.00)	0.509	1 (0.56)	0 (0.00)	1.000
Renal insufficiency	1 (0.33)	1 (0.43)	1.000	0 (0.00)	1 (0.56)	1.000
Hypohepatia	3 (0.98)	1 (0.43)	0.824	1 (0.56)	0 (0.00)	1.000

ADR, adverse drug reaction; PSM, propensity-score matching; ICI, immune checkpoint inhibitor.

severe ADRs, but there was no significant difference between the 2 groups (*Table 4* and *Figure 8*).

In addition, in this study, in the ICI + anlotinib group, 4 patients discontinued the drug due to the severe ADRs of immune-related pneumonitis, 3 due to pulmonary embolism, 3 due to immune-related myocarditis, and 1 due to severe renal insufficiency. Conversely, in the ICI monotherapy group, only 2 patients discontinued the treatment due to immune-related pneumonia, and 2 due to immune-related myocarditis. These patients were still included in the statistical analysis as well. The adverse events experienced by the other patients in this study were able to be alleviated via active symptomatic treatments or dosage adjustments, which enabled the predetermined treatment to be continued.

Discussion

With advancements in diagnostic and therapeutic methods, the treatment options for malignant tumors are becoming increasingly diverse, and immunotherapy has revolutionized the landscape of lung cancer treatment. Tumor cells can escape the immune system by evading recognition by T cells and antigen-presenting cells through a variety of mechanisms, one of which is combining PD-1 with PD-L1 in order to inhibit T cell activation and promote T cell apoptosis. Thus, by blocking the combination of PD-1 and PD-L1, ICIs can improve the recognition and clearance of tumor cells by immune cells (23). ICIs have better therapeutic effects and more controllable adverse events than standard chemotherapy (8,24). However, the sustained efficacy of immunotherapeutic agents alone remains low (25). The therapeutic approaches that combine immunotherapy with other anti-tumor agents have shown promising results. In particular, the additional of anti-angiogenic drugs has demonstrated remarkable therapeutic effect and high safety in a range of solid tumors.

Angiogenesis encourages tumor growth, as it provides a suitable microenvironment for tumors to enlarge and invade aggressively, and participates in all aspects of tumor development (26). The vascular endothelial growth factor (VEGF) family is one of the main regulators of tumor angiogenesis. Anti-angiogenic drugs block tumor growth by inhibiting the VEGF and other factors. A number of anti-angiogenic drugs have been legally approved in China for the treatment of advanced NSCLC, including anlotinib, Bevacizumab and Recombinant Human Endostatin. More specifically, anlotinib is a multi-target TKI. When used in

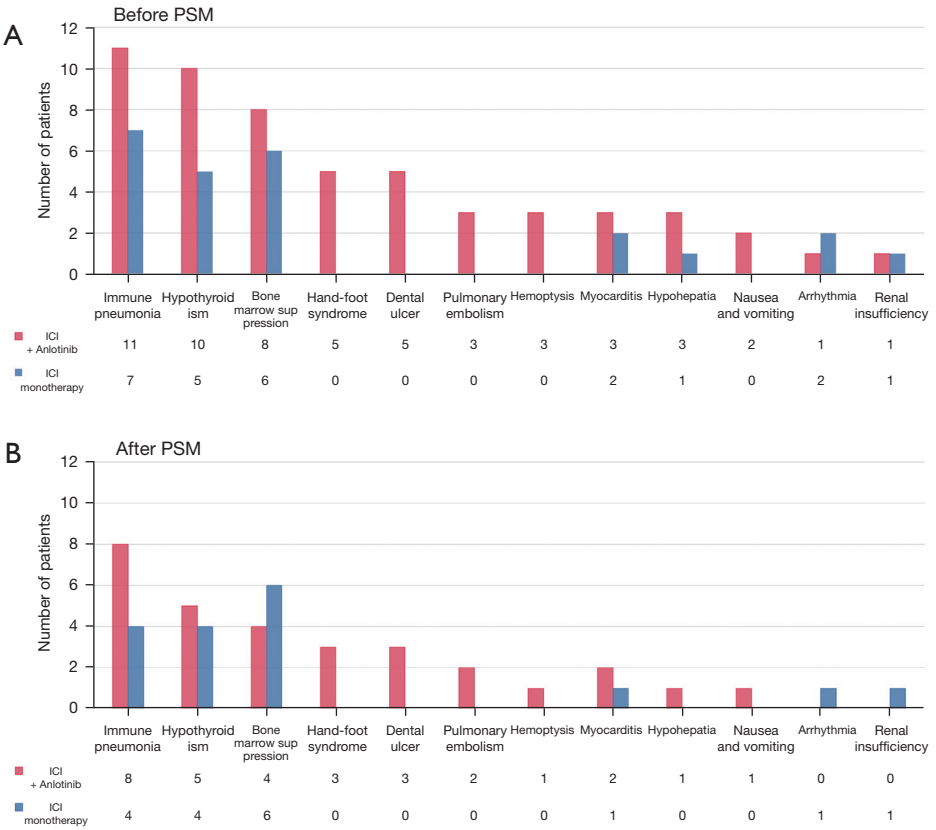

Figure 8 The severe ADRs in the ICI monotherapy/ICI + anlotinib groups. (A) The number of different ADRs before PSM; (B) the number of different ADRs after PSM. ADR, adverse drug reaction; ICI, immune checkpoint inhibitor; PSM, propensity-score matching.

the 3rd-line treatment of patients with advanced NSCLC, it achieves a significantly longer median PFS and OS for patients than placebo group (27).

A previous study has shown that TKIs may affect the immune microenvironment, and enhance the immune response (28). ICIs normalize tumor blood vessels by activating effector T cells and reduce the VEGF via feedback regulation to increase the infiltration and killing functions of the effector T cells (29). Such evidence provides a solid basis for combining TKIs with ICIs to treat lung cancer. At present, the efficacy and safety of anti-angiogenic drugs combined with ICIs have been evaluated and proven by a number of leading studies (30-33). For example, the IMpower150 study (33) showed that the anti-angiogenic drug Bevacizumab combined with the PD-L1 inhibitor Atezolizumab and chemotherapy significantly prolonged the PFS and OS of patients with advanced non-squamous NSCLC with negative driver genes, and significantly enhanced the ORR and DCR. This research laid a solid foundation for the combined use of anti-angiogenic drugs, chemotherapy, and immunotherapy treatment in the 1st-line treatment of patients with advanced NSCLC.

The use of 2-drug combination therapies of anti-angiogenic drugs and immunotherapy is still under research and evaluation. An early JVDF study (34) examined the use of Ramucirumab plus pembrolizumab therapy in the treatment of advanced NSCLC. Additionally, data were released at the World Conference on Lung Cancer in 2019 on the use of Anlotinib combined with Sintilimab in the 1st-line treatment of advanced NSCLC. Thus, there is preliminary evidence of the efficacy and safety of immunotherapy combined with anti-angiogenic drugs. Anlotinib combined with ICIs, especially PD-1 inhibitors, have great potential in treating advanced NSCLC. However, large-sample analyses have not yet been conducted examining the real efficacy and safety of these combined therapies in clinical settings.

In this study, we collected and analyzed the clinical data of 535 patients, used PMS matching to reduce the possibility of biases, and re-analyzed the data. The research

results verified that compared to ICI monotherapy, ICI + anlotinib treatment effectively prolonged the PFS of patients with advanced NSCLC, especially in 2nd-line and 3rd-line treatments, and improved the ORR and DCR. Our findings support the results of previous randomized clinical trials (12,27). Additionally, we also showed that previous immunotherapy treatment failures have no effect on the efficacy of the combined therapy.

In relation to the safety of the combined therapy of immunotherapy + anlotinib, the increase in adverse events is an important issue that needs to be addressed. Generally, compared with patients with ICI monotherapy, the patients that received the ICI + anlotinib treatment were more likely to have a number of adverse reactions, including immune related pneumonitis, hypothyroidism, bone marrow suppression, hand-foot syndrome, dental ulcer, pulmonary embolism, and hemoptysis. The occurrence of these adverse events may result from the anti-angiogenic effect of Anlotinib. However, whether in combination treatment or monotherapy treatment, no significant difference was found in terms of the probability of serious adverse reactions. Thus, some adverse events may increase during the combination therapy, but they are largely controllable, and patients' overall drug tolerance of the combined therapy was good.

This study had a number of limitations. First, this was a retrospective study, and the patients included were not chosen randomly. Second, the patients included in this study came from different medical groups, and their corresponding treatment plans differed. In addition, the adverse events experienced by different patients may have been treated differently by physicians. Third, some patients had not finished their genetic testing or PD-L1 expression testing, which made it difficult to assess the biomarkers of their disease. Fourth, the follow-up time was rather short, and OS was not examined in the research analysis. Finally, as a single-center study, this study has certain corresponding limitations. However, the focus of this study was to compare the efficacy and adverse reactions of ICI monotherapy and ICI + anlotinib and we have used PSM method in order to minimize the bias and confounding variables between two treatment groups as much as possible.

Conclusions

The ICI + anlotinib therapy is an effective therapeutic strategy in advanced NSCLC. This combined therapy effectively prolonged the survival time of patients in the 2nd-line and 3rd-line treatments, improved the ORR and DCR, and led to good tolerance to adverse drug reactions. Based on a number of relevant clinical trials on anti-angiogenic drugs combined with ICIs conducted at home and abroad, we conclude that this ICI + anlotinib treatment is a feasible treatment option for patients with advanced NSCLC depending on their individual needs in clinical practice. Notably, during the medication process, physicians should pay close attention to monitoring drug-related adverse events to ensure they are dealt with in an appropriate and timely manner.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-350/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-350/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-350/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Jiangsu Cancer Hospital (No. 2021-008), and all participants signed an informed consent form.

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