



The efficacy and safety of immune checkpoint inhibitors combined with chemotherapy or anti-angiogenic therapy as a second-line or later treatment option for advanced non-small cell lung cancer: a retrospective comparative cohort study

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Background: Although immune checkpoint inhibitor (ICI) monotherapy remains the standard of second-line treatment for patients with advanced non-small cell lung cancer (NSCLC), the objective response rate (ORR) is low. There is an urgent need to increase the response population of second-line immunotherapy, and ICI combination therapy may be a possible option. However, the evidence is insufficient.

Methods: We retrospectively collected the medical records of patients who received ICI monotherapy or ICI combination therapy as a second-line or later treatment option. We further analysed baseline clinical characteristics, evaluated treatment efficacy, assessed treatment-related adverse events (AEs) and followed up survival. The outcome variables assessed in the study were ORR, disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and AEs.

Results: A total of 145 patients were ultimately enrolled in this study, including the ICI monotherapy group (n=63) and ICI combination therapy group (n=82). The ICI combination therapy group was further divided into the ICI/chemotherapy group (n=57) and ICI/anti-angiogenic therapy group (n=25). The baseline was comparable among the three subgroups. The ICI combination therapy groups showed a higher ORR (29.3% vs. 11.1%, P=0.008) and DCR (85.4% vs. 61.9%, P=0.001) and a longer PFS (6.77 vs. 3.47 months, P<0.001) and OS (18.60 vs. 8.47 months, P<0.001) than the ICI monotherapy group. The ICI/chemotherapy group showed a significantly higher ORR (31.6% vs. 11.1%, P=0.006) and DCR (84.2% vs. 61.9%, P=0.006) and a longer PFS (6.37 vs. 3.47 months, P<0.001) and OS (18.60 vs. 8.47 months, P<0.001) than the ICI monotherapy group. The ICI/anti-angiogenic therapy group showed a significantly higher DCR (88.0% vs. 61.9%, P=0.021) and a longer PFS (8.17 vs. 3.47 months, P<0.001) and OS (19.20 vs. 8.47 months, P=0.005) than the ICI monotherapy group. Neither of the combined ICI therapy groups showed a significant increase in the incidence of AEs compared to the ICI monotherapy group.

Conclusions: ICI combined with chemotherapy or anti-angiogenic therapy as second-line or later treatment demonstrated superiority over ICI monotherapy in advanced NSCLC patients without prior

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immunotherapy. These results provide a potentially superior treatment strategy and require verification in prospective clinical trials.

Keywords: Immune checkpoint inhibitors (ICIs); chemotherapy; anti-angiogenic therapy; combined modality therapy; non-small cell lung cancer (NSCLC)

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Introduction

Lung cancer is the second most prevalent (11.4%) and deadliest (18%) cancer worldwide; non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases, with most patients already in the middle and advanced stages when diagnosed (1). Precision therapy for lung cancer has rapidly progressed, and immune checkpoint inhibitors (ICIs) have drawn considerable attention and have greatly improved lung cancer prognosis. Several clinical studies have demonstrated that programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors, such as pembrolizumab (2,3), nivolumab (4-8), and atezolizumab (9,10), outperformed docetaxel in the survival and prognosis of advanced NSCLC patients without prior therapy and thus have been approved by the Food and Drug Administration (FDA) as second-line treatments for advanced NSCLC. However, the objective response rate (ORR) in patients receiving ICI monotherapy is low (~15%), and only a limited proportion of advanced patients demonstrate long-term benefits from second-line immunotherapy. There is an urgent need to increase the response population of second-line immunotherapy, and ICI combination therapy may be a possible option. However, the evidence for choosing ICI combination therapy as a second-line treatment for NSCLC is insufficient.

Several trials have explored new modalities of combined immunotherapy as the first-line treatment for advanced NSCLC. They have demonstrated that chemotherapy combined with immunotherapy is superior to standard chemotherapy alone (11-21). In the second-line setting, the PROLUNG study found that pembrolizumab plus docetaxel substantially improved ORR and progression-free survival (PFS) with manageable toxicity than docetaxel alone in patients with previously treated advanced NSCLC (22). Anti-angiogenic agents can synergistically enhance the efficacy of ICIs by regulating the tumour immune microenvironment (23,24). Some clinical trials also suggested that ICI combined

with anti-angiogenic therapy demonstrated encouraging clinical activity and a manageable safety profile in previously treated patients with advanced NSCLC (25-27). Therefore, it is necessary to determine whether ICI combination therapy improves prognosis of previously treated advanced NSCLC patients compared with ICI monotherapy. This study aimed to explore the efficacy and safety of combined ICI/chemotherapy or ICI/anti-angiogenic therapy as second-line or later treatment options for advanced NSCLC patients. We present the following article in accordance with the STROBE reporting checklist (available at <https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-697/rc>).

Methods

Patient enrolment and study design

This was a retrospective comparative cohort study. Patients with lung cancer treated with immunotherapy at the Hunan Cancer Hospital between April 2016 and August 2021 were screened retrospectively. The last follow-up and data collection were by March 2022. The inclusion criteria were as follows: (I) patients aged 18–75 years; (II) patients who scored 0–2 on the Eastern Cooperative Oncology Group performance status (ECOG PS); (III) patients histologically or cytologically diagnosed with unresectable stage III/IV NSCLC; (IV) patients without epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) fusions; (V) patients who have received ICI monotherapy or ICI therapy combined with chemotherapy/anti-angiogenic therapy as second-line or later treatment; (VI) patients with at least one evaluable target lesion (except those with uncontrolled brain metastases) according to Response Evaluation Criteria In Solid Tumours (RECIST, version 1.1); (VII) patients who had undergone at least one efficacy evaluation during treatment. The exclusion criteria were as follows: (I) patients pathologically diagnosed with small-cell lung cancer (SCLC) mixed with NSCLC; (II)

patients previously treated with a PD-1 inhibitor, PD-L1 inhibitor, or any other antibody or drug targeting an immune checkpoint; (III) patients with other concurrent malignancy. Detailed clinical characteristics including sex, age, ECOG PS, smoking history, TNM stage, histology, metastasis sites, driver mutation status, PD-L1 expression level and therapeutic regimens were collected. The outcome variables assessed in the study were ORR, disease control rate (DCR), PFS, overall survival (OS) and adverse events (AEs). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics board of Hunan Cancer Hospital (No. 202257) and individual consent for this retrospective analysis was waived.

Efficacy and safety evaluation

Patients were followed up with computed tomography (CT) or magnetic resonance imaging (MRI) every six weeks during the treatment cycles. Disease assessments were performed according to RECIST, version 1.1. PFS was defined as the duration from the start of the ICI therapy to the onset of disease progression or any-cause of death (whichever occurred first). If no disease progression or death occurred, the date of the last imaging examination was used. OS was defined as the duration from the start of ICI therapy to any-cause death or date of the last follow-up if no death occurred. Treatment-related AEs were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0).

Statistical analyses

All statistical analyses were performed using R statistical software (version 3.6.1; The R Foundation of Statistical Computing, Vienna, Austria). Two-tailed tests were performed at a significance level of $\alpha=0.05$, with $P<0.05$ indicative of statistical significance. Inter-group comparisons of count data were performed using the chi-square test or Fisher's exact test. The relationship between the variables and survival was assessed using Kaplan-Meier curves and the log-rank test's inter-group differences in survival were assessed. The Cox proportional hazards model was used to calculate the hazard ratio (HR) and 95% confidence interval (CI) to determine the differences in survival. Multivariate Cox regression analysis was used to determine the independent prognostic factors for improved PFS and OS.

Results

Baseline patient characteristics

In total, 697 patients who underwent immunotherapy between April 2016 and August 2021 were screened in a procedure. Of the 697 patients, 371 underwent first-line immunotherapy, 112 were diagnosed with SCLC, and 69 did not have complete treatment records were excluded from the study. A total of 145 patients were ultimately enrolled in this study (*Figure 1*), consisting of 63 patients in the ICI monotherapy group. The remaining 82 (ICI combination therapy group) patients were divided into the ICI/chemotherapy combination (ICI + C) group (n=57) and the ICI/anti-angiogenic therapy combination (ICI + A) group (n=25).

Table 1 shows the baseline clinical characteristics of the three study groups. The baseline was comparable among the three subgroups. In the ICI monotherapy group, 84.1% were male (53/63), with 30.2% (19/63) of the patients aged ≥ 65 years. In the ICI + C group, 77.2% were male (44/57), with 28.1% (16/57) of the patients aged ≥ 65 years. The ICI + A group included 19 males (19/25, 76.0%), of whom 28.0% (7/25) were aged ≥ 65 years. The patients in each group mostly scored 0–1 on the ECOG PS. In the ICI, ICI + C, and ICI + A groups, respectively, the smoking rate was 81.0% (51/63), 71.9% (41/57), and 68.0% (17/25), while the proportion of patients in clinical stage IV was 88.9% (56/63), 84.2% (48/57), and 84.0% (21/25). Data relating to driver mutation and PD-L1 expression were also collected from each group, and no significant inter-group differences were detected. There was no significant difference in baseline metastatic site and first-line treatment among the three groups. Most patients in the three groups received second-line therapy, and few received third-line or higher treatment. Among the chemotherapeutic agents selected for the ICI + C group, docetaxel, nab-paclitaxel, gemcitabine, and pemetrexed were administered in 13 (22.8%), 30 (52.6%), 7 (12.3%), and 7 (12.3%) cases, respectively. In the ICI + A group, anlotinib and bevacizumab were administered in 20 (80.0%) and 5 (20.0%) cases, respectively.

Efficacy

ORR and DCR

ORR and DCR were significantly higher in the ICI combination therapy group than in the ICI monotherapy group (ORR: 29.3% *vs.* 11.1%, $P=0.008$ and DCR: 85.4%

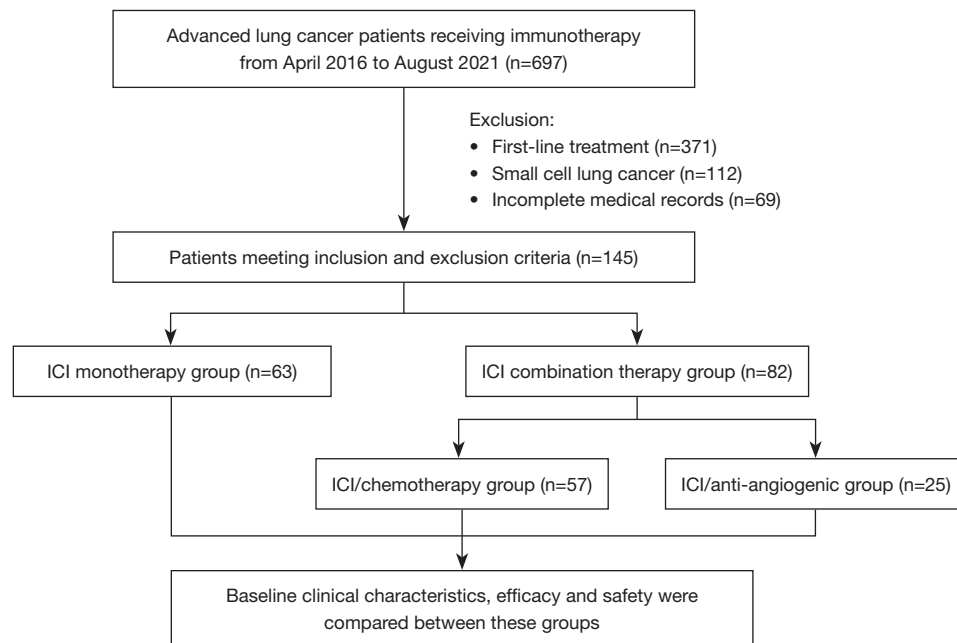


Figure 1 Flowchart of study design. ICI, immune checkpoint inhibitor.

Table 1 Baseline clinicopathological characteristics of patients

Characteristics	ICI Monotherapy (N=63)	ICI + C (N=57)	ICI + A (N=25)	P
Sex, n (%)				0.548
Male	53 (84.1)	44 (77.2)	19 (76.0)	
Female	10 (15.9)	13 (22.8)	6 (24.0)	
Age (years), n (%)				0.962
<65	44 (69.8)	41 (71.9)	18 (72.0)	
≥65	19 (30.2)	16 (28.1)	7 (28.0)	
ECOG PS, n (%)				1
0–1	59 (93.7)	54 (94.7)	24 (96.0)	
2	4 (6.3)	3 (5.3)	1 (4.0)	
Smoking history, n (%)				0.343
Ever smoker	51 (81.0)	41 (71.9)	17 (68.0)	
Never smoker	12 (19.0)	16 (28.1)	8 (32.0)	
TNM stage, n (%)				0.695
III	7 (11.1)	9 (15.8)	4 (16.0)	
IV	56 (88.9)	48 (84.2)	21 (84.0)	
Histology, n (%)				0.231
Squamous	33 (52.4)	21 (36.8)	11 (44.0)	
Non-squamous	30 (47.6)	36 (63.2)	14 (56.0)	

Table 1 (continued)

Table 1 (continued)

Characteristics	ICI Monotherapy (N=63)	ICI + C (N=57)	ICI + A (N=25)	P
Metastatic site, n (%)				
Lung	19 (30.2)	19 (33.3)	10 (40.0)	0.675
Pleura	12 (19.0)	8 (14.0)	3 (12.0)	0.720
Liver	8 (12.7)	5 (8.8)	3 (12.0)	0.776
Bone	17 (27.0)	19 (33.3)	7 (28.0)	0.734
Brain	10 (15.9)	11 (19.3)	4 (16.0)	0.918
Driver mutation, n (%)				0.909
KRAS	4 (6.3)	6 (10.5)	2 (8.0)	
BRAF	2 (3.2)	1 (1.8)	0 (0)	
None	57 (90.5)	50 (87.7)	23 (92.0)	
PD-L1 expression, n (%)				0.992
≥50%	4 (6.3)	3 (5.3)	1 (4.0)	
≥1%, <50%	7 (11.1)	7 (12.3)	3 (12.0)	
<1%	14 (22.2)	10 (17.5)	6 (24.0)	
Unknown	38 (60.3)	37 (64.9)	15 (60.0)	
First-line treatment, n (%)				0.932
Platinum-based chemotherapy	44 (69.8)	38 (66.7)	17 (68.0)	
Platinum-based chemotherapy plus bevacizumab	19 (30.2)	19 (33.3)	8 (32.0)	
Line of ICI therapy, n (%)				0.749
2	52 (82.5)	47 (82.5)	19 (76.0)	
≥3	11 (17.5)	10 (17.5)	6 (24.0)	
Selection of ICI, n (%)				0.954
Pembrolizumab	15 (23.8)	13 (22.8)	6 (24.0)	
Nivolumab	27 (42.9)	21 (36.9)	8 (32.0)	
Sintilimab	12 (19.0)	10 (17.5)	5 (20.0)	
Camrelizumab	8 (12.7)	11 (19.3)	5 (20.0)	
Toripalimab	1 (1.6)	2 (3.5)	1 (4.0)	

ICI, immune checkpoint inhibitor; ICI + C, ICI plus chemotherapy; ICI + A, ICI plus anti-angiogenic therapy; ECOG, Eastern Cooperative Oncology Group performance status.

vs. 61.9%, $P=0.001$). For patients who received second-line treatment, ORR and DCR remained significantly higher in the ICI combination therapy group than in the ICI monotherapy group (ORR: 31.7% vs. 11.5%, $P=0.01$ and DCR: 85.7% vs. 61.5%, $P=0.003$) (Table 2).

Moreover, when the differences in ORR and DCR between the three groups were evaluated, ORR and DCR

were significantly higher in the ICI + C group than in the ICI monotherapy group (ORR: 31.6% vs. 11.1%, $P=0.006$; DCR: 84.2% vs. 61.9%, $P=0.006$). For patients who received second-line treatment, ORR and DCR remained higher in the ICI + C combination group than in the ICI monotherapy group (ORR: 31.9% vs. 11.5%, $P=0.013$; DCR: 85.1% vs. 61.5%, $P=0.009$) (Table 3). DCR was significantly higher in

Table 2 ORR and DCR between the ICI monotherapy group and the ICI combination therapy group

Items	ICI monotherapy (%)	ICI combination therapy (%)	P
ORR			
Total	11.1	29.3	0.008
Second-line	11.5	31.7	0.01
DCR			
Total	61.9	85.4	0.001
Second-line	61.5	85.7	0.003

ORR, objective response rate; DCR, disease control rate; ICI, immune checkpoint inhibitor.

Table 3 ORR and DCR between the ICI monotherapy group and the ICI + C group

Items	ICI monotherapy (%)	ICI + C (%)	P
ORR			
Total	11.1	31.6	0.006
Second-line	11.5	31.9	0.013
DCR			
Total	61.9	84.2	0.006
Second-line	61.5	85.1	0.009

ORR, objective response rate; DCR, disease control rate; ICI + C, ICI plus chemotherapy; ICI, immune checkpoint inhibitor.

the ICI + A group than in the ICI monotherapy group (88.0% vs. 61.9%, $P=0.021$), while ORR was not significantly different (24.0% vs. 11.1%, $P=0.181$). For patients who received second-line treatment, ORR and DCR were not significantly different between the ICI + A therapy and ICI monotherapy groups (ORR: 31.3% vs. 11.5%, $P=0.113$; DCR: 87.5% vs. 61.5%, $P=0.069$) (Table 4). Additionally, ORR and DCR were not significantly different between the ICI + C and ICI + A groups (ORR: 31.6% vs. 24.0%, $P=0.487$; DCR: 84.2% vs. 88.0%, $P=0.748$) (Table 5).

PFS and OS

Median survival follow-up time was 20.83 months (95% CI: 17.49–24.17 months). PFS was significantly longer in the ICI combination therapy groups than in the ICI monotherapy group (mPFS: 6.77 vs. 3.47 months, $P<0.001$; HR =0.37, 95% CI: 0.26–0.53, $P<0.001$) (Figure 2A). OS

Table 4 ORR and DCR between the ICI monotherapy group and the ICI + A group

Items	ICI monotherapy (%)	ICI + A (%)	P
ORR			
Total	11.1	24.0	0.181
Second-line	11.5	31.3	0.113
DCR			
Total	61.9	88.0	0.021
Second-line	61.5	87.5	0.069

ORR, objective response rate; DCR, disease control rate; ICI + A, ICI plus anti-angiogenic therapy; ICI, immune checkpoint inhibitor.

Table 5 ORR and DCR between the ICI + C group and the ICI + A group

Items	ICI + C (%)	ICI + A (%)	P
ORR			
Total	31.6	24.0	0.487
Second-line	31.9	31.3	1.000
DCR			
Total	84.2	88.0	0.748
Second-line	85.1	87.5	1.000

ORR, objective response rate; DCR, disease control rate; ICI + C, ICI plus chemotherapy; ICI + A, ICI plus anti-angiogenic therapy; ICI, immune checkpoint inhibitor.

was also significantly longer in the ICI combination therapy groups than in the ICI monotherapy group (mOS: 18.60 vs. 8.47 months, $P<0.001$; HR =0.41, 95% CI: 0.27–0.62, $P<0.001$) (Figure 2B). For patients who received a second-line treatment, PFS and OS remained significantly longer in the ICI combination therapy groups than in the ICI monotherapy group (mPFS: 7.60 vs. 3.37 months, $P<0.001$; HR =0.33, 95% CI: 0.22–0.50, $P<0.001$; mOS: 20.60 vs. 8.00 months, $P<0.001$; HR =0.35, 95% CI: 0.22–0.57, $P<0.001$) (Figure 2C,2D).

Moreover, PFS and OS were significantly longer in the ICI + C group than in the ICI monotherapy group (mPFS: 6.37 vs. 3.47 months, $P<0.001$; HR =0.42, 95% CI: 0.29–0.63, $P<0.001$; mOS: 18.60 vs. 8.47 months, $P<0.001$; HR =0.40, 95% CI: 0.25–0.64, $P<0.001$) (Figure 3A,3B). For patients who received a second-line treatment, PFS and OS were also longer in the ICI + C group than in the ICI

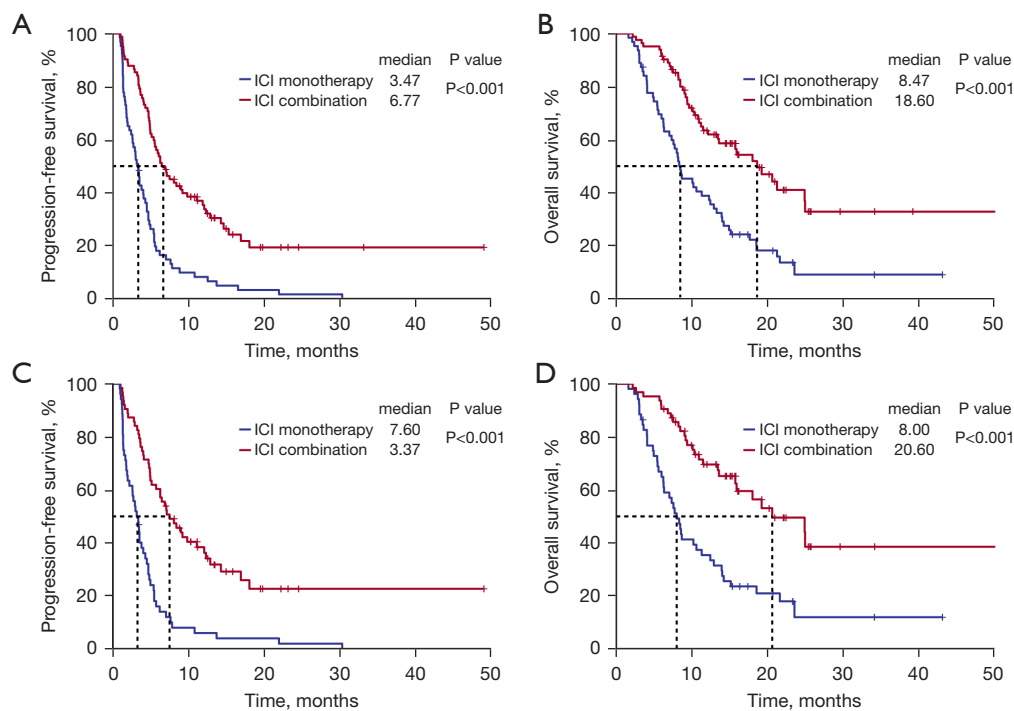


Figure 2 Progression-free survival and overall survival of patients treated with ICI combination therapy or ICI monotherapy. (A) Progression-free survival of patients treated with ICI combination therapy or ICI monotherapy as the second-line or later treatment. (B) Overall survival of patients treated with ICI combination therapy or ICI monotherapy as the second-line or later treatment. (C) Progression-free survival of patients treated with ICI combination therapy or ICI monotherapy as the second-line treatment. (D) Overall survival of patients treated with ICI combination therapy or ICI monotherapy as the second-line treatment. ICI, immune checkpoint inhibitor.

monotherapy group (mPFS: 6.57 vs. 3.37 months, $P < 0.001$; HR = 0.39, 95% CI: 0.25–0.60, $P < 0.001$; mOS: 20.60 vs. 8.00 months, $P < 0.001$; HR = 0.36, 95% CI: 0.21–0.62, $P < 0.001$) (Figure 3C,3D).

Furthermore, PFS and OS were significantly longer in the ICI + A group than in the ICI monotherapy group (mPFS: 8.17 vs. 3.47 months, $P < 0.001$; HR = 0.30, 95% CI: 0.17–0.53, $P < 0.001$; mOS: 19.20 vs. 8.47 months, $P = 0.005$; HR = 0.44, 95% CI: 0.24–0.80, $P = 0.007$) (Figure 4A,4B). For patients who received a second-line treatment, PFS and OS were also longer in the ICI + A group than in the ICI monotherapy group (mPFS: 14.73 vs. 3.37 months, $P < 0.001$; HR = 0.19, 95% CI: 0.09–0.42, $P < 0.001$; mOS: 24.87 vs. 8.00 months, $P = 0.003$; HR = 0.31, 95% CI: 0.14–0.70, $P = 0.005$) (Figure 4C,4D).

In contrast, PFS and OS were not significantly different between the ICI + C group and the ICI + A group (Figure S1A,S1B), with PFS of 6.37 vs. 8.17 months (HR = 1.46, 95% CI: 0.82–2.60, $P = 0.19$) and OS of 18.60 vs. 19.20 months (HR = 0.95, 95% CI: 0.49–1.83, $P = 0.88$).

Multivariate Cox regression analysis, including sex, age, ECOG PS score, smoking history, clinical stage, pathological type, treatment line, and therapeutic regimen, further confirmed that ICI combination therapy (PFS: HR = 0.35, 95% CI: 0.24–0.51, $P < 0.001$, Table S1; OS: HR = 0.39, 95% CI: 0.26–0.60, $P < 0.001$, Table S2), ICI + C (PFS: HR = 0.38, 95% CI: 0.25–0.57, $P < 0.001$, Table S3; OS: HR = 0.38, 95% CI: 0.24–0.62, $P < 0.001$, Table S4) and ICI + A (PFS: HR = 0.30, 95% CI: 0.17–0.53, $P < 0.001$, Table S5; OS: HR = 0.43, 95% CI: 0.23–0.80, $P = 0.008$, Table S6) were independent prognostic factors for improved PFS and OS compared to ICI monotherapy, respectively.

Safety

The number of patients with treatment-related AEs was 42 (66.6%), 44 (77.2%), and 17 (68.0%) in the ICI monotherapy, ICI + C and ICI + A groups, respectively, while the incidence of grade ≥ 3 treatment-related AEs in the same groups was 9.5%, 12.3%, and 8.0%, respectively.

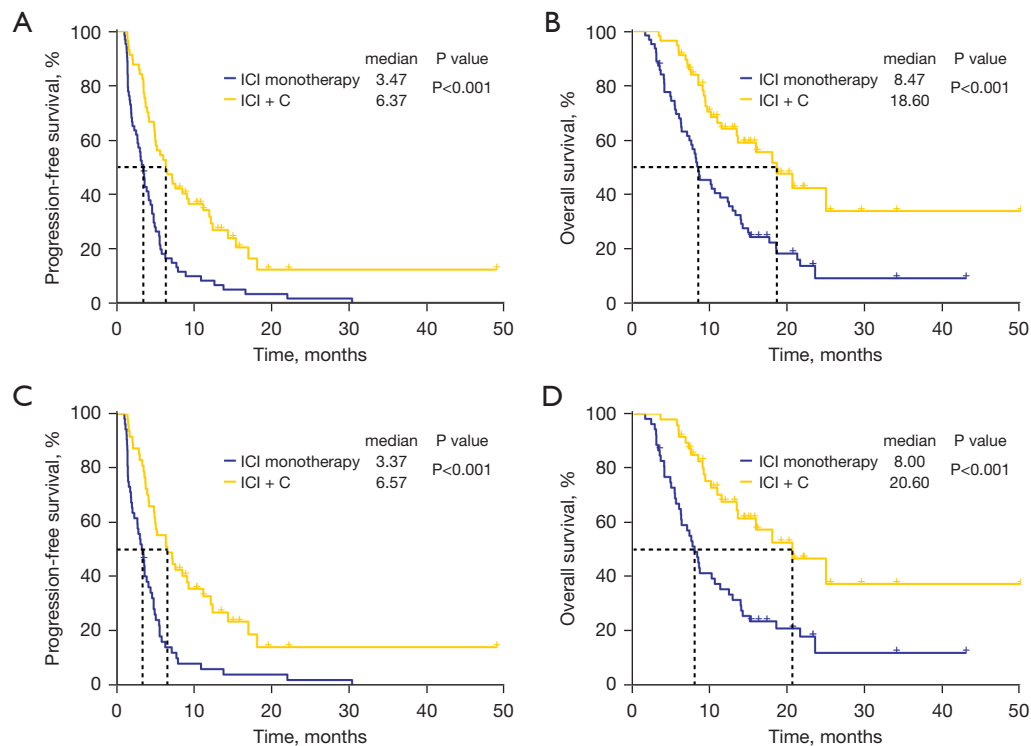


Figure 3 Progression-free survival and overall survival of patients treated with ICI/chemotherapy or ICI monotherapy. (A) Progression-free survival of patients treated with ICI/chemotherapy or ICI monotherapy as the second-line or later treatment. (B) Overall survival of patients treated with ICI/chemotherapy or ICI monotherapy as the second-line or later treatment. (C) Progression-free survival of patients treated with ICI/chemotherapy or ICI monotherapy as the second-line treatment. (D) Overall survival of patients treated with ICI/chemotherapy or ICI monotherapy as the second-line treatment. ICI, immune checkpoint inhibitor; ICI + C, ICI plus chemotherapy.

ICI combination therapy did not significantly increase the incidence of treatment-related AEs compared to ICI monotherapy (Table 6).

The incidence of immune-related AEs (irAEs) was 36.5% (23/63) in the ICI monotherapy group, 26.3% (15/57) in the ICI + C group, and 32.0% (8/25) in the ICI + A group, with the ICI + C group showing the lowest incidence. Most patients only developed grade 1–2 irAEs, while 4.8%, 5.3%, and 4.0% of patients in the three groups developed grade ≥ 3 treatment-related irAEs, respectively, without treatment discontinuation due to irAEs.

Discussion

This study explored the efficacy and safety of combined ICI/chemotherapy or ICI/anti-angiogenic therapy as second-line or later treatment for advanced NSCLC. ICI combination therapy exhibited good overall efficacy and safety; the ICI/chemotherapy combination or ICI/anti-

angiogenic therapy combination may be a novel second-line or later treatment for NSCLC patients who have not received prior immunotherapy.

On comparing the different combination therapy regimens, the following observations were made: (I) compared to ICI monotherapy, ICI/chemotherapy led to a significantly higher ORR and DCR, and ICI/anti-angiogenic therapy also had a favorable DCR; (II) ICI/chemotherapy and ICI/anti-angiogenic therapy were independent prognostic factors for improved PFS and OS compared to ICI monotherapy, respectively.

Immunotherapy has greatly improved the prognosis of driver gene-negative advanced NSCLC. Some regimens of ICI monotherapy (28–34), combined ICI/chemotherapy (11–21), ICI therapy combined with chemotherapy and anti-angiogenic therapy (35,36), dual immunotherapy combinations (37,38), and dual immunotherapy combined with chemotherapy (39) have been approved by the FDA and/or National Medical Products Administration for the

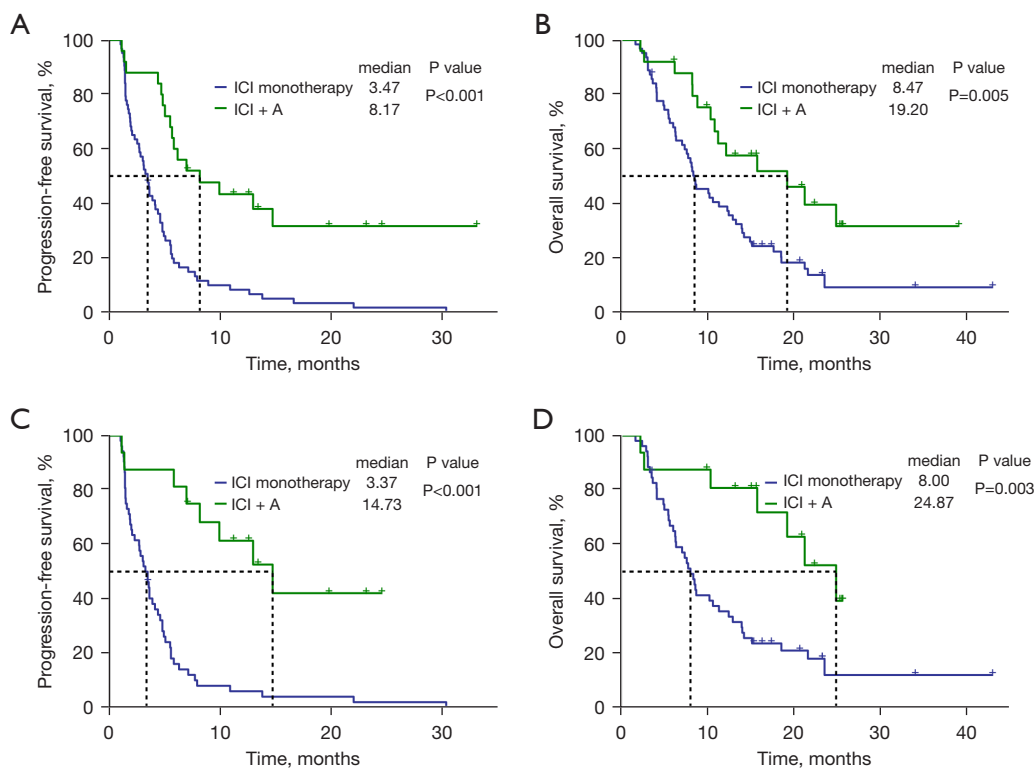


Figure 4 Progression-free survival and overall survival of patients treated with ICI/anti-angiogenic therapy or ICI monotherapy. (A) Progression-free survival of patients treated with ICI/anti-angiogenic therapy or ICI monotherapy as the second-line or later treatment. (B) Overall survival of patients treated with ICI/anti-angiogenic therapy or ICI monotherapy as the second-line or later treatment. (C) Progression-free survival of patients treated with ICI/anti-angiogenic therapy or ICI monotherapy as the second-line treatment. (D) Overall survival of patients treated with ICI/anti-angiogenic therapy or ICI monotherapy as the second-line treatment. ICI, immune checkpoint inhibitor; ICI + A, ICI plus anti-angiogenic therapy.

first-line treatment of advanced NSCLC. Nevertheless, many patients in China fail to receive first-line immunotherapy. In contrast, some phase III trials (2-10) have confirmed the effectiveness of ICI monotherapy as a second-line for advanced NSCLC. Although second-line treatment with ICI monotherapy improved the survival and prognosis of advanced NSCLC patients, the ORR in the population receiving ICI monotherapy remained low (~15%), and only a limited proportion of patients with advanced NSCLC derived longer-term benefit from second-line immunotherapy. To further improve the efficacy of second-line immunotherapy, several studies have explored combined immunotherapy regimens.

Zhang *et al.* showed that PD-1 inhibitors combined with chemotherapy and/or bevacizumab may be favorable for advanced NSCLC patients with prior therapy. The study included 22 patients who received combined immunotherapy and 33 treated with monotherapy group.

That study reported significant difference in DCR (95.5% *vs.* 46.7%, $P < 0.001$) and PFS (mPFS: 7.5 *vs.* 3.3 months, HR = 0.28, $P < 0.001$), and no significant difference in ORR (31.8% *vs.* 10.0%, $P = 0.075$) between the two groups (40). In our study, the pooled patients who received ICI immunotherapy combined with either chemotherapy or anti-angiogenic therapy showed a significantly improved ORR, DCR and PFS compared to those who received ICI immunotherapy alone. Moreover, the combined ICI therapy significantly prolonged OS.

In addition, Arrieta *et al.* reported in a phase II clinical trial that the ORR and PFS were significantly better in the combined Docetaxel/Pembrolizumab group than in the chemotherapy-only group (ORR: 42.5% *vs.* 15.8%, $P = 0.01$; mPFS: 9.5 *vs.* 3.9 months, HR = 0.24, $P < 0.001$) for advanced NSCLC in the second-line setting (41). Similarly, Mao *et al.* showed a significantly improved ORR (35.5% *vs.* 15.7%, $P = 0.039$), PFS (mPFS: 5.6 *vs.* 2.5 months, $P = 0.013$), and

Table 6 Conclusion of adverse events of patients

Events	Grade	ICI monotherapy (N=63)	ICI + C (N=57)	ICI + A (N=25)	P
Treatment-related AE, n (%)	Any grade	42 (66.6)	44 (77.2)	17 (68.0)	0.418
	Grade 3–5	6 (9.5)	7 (12.3)	2 (8.0)	0.877
Treatment-related irAE, n (%)	Any grade	23 (36.5)	15 (26.3)	8 (32.0)	0.488
	Grade 3–5	3 (4.8)	3 (5.3)	1 (4.0)	1.000
Nausea, n (%)	Any grade	2 (3.2)	3 (5.3)	1 (4.0)	0.864
	Grade 3–5	0 (0)	0 (0)	0 (0)	1.000
Vomiting, n (%)	Any grade	2 (3.2)	3 (5.3)	1 (4.0)	0.864
	Grade 3–5	0 (0)	0 (0)	0 (0)	1.000
Anemia, n (%)	Any grade	5 (7.9)	5 (8.8)	2 (8.0)	1.000
	Grade 3–5	2 (3.2)	1 (1.8)	1 (4.0)	0.824
Leukopenia, n (%)	Any grade	3 (4.8)	7 (12.3)	1 (4.0)	0.317
	Grade 3–5	0 (0)	2 (3.5)	0 (0)	0.469
Neutropenia, n (%)	Any grade	1 (1.6)	5 (8.8)	1 (4.0)	0.153
	Grade 3–5	0 (0)	1 (1.8)	0 (0)	0.566
Thrombocytopenia, n (%)	Any grade	2 (3.2)	3 (5.3)	1 (4.0)	0.864
	Grade 3–5	0 (0)	1 (1.8)	0 (0)	0.566
ALT/AST level increase, n (%)	Any grade	4 (6.3)	3 (5.3)	2 (8.0)	0.903
	Grade 3–5	1 (1.6)	1 (1.8)	0 (0)	1.000
irAEs					
Rash, n (%)	Any grade	5 (7.9)	3 (5.3)	2 (8.0)	0.755
	Grade 3–5	1 (1.6)	0 (0)	0 (0)	1.000
Hyperthyroidism, n (%)	Any grade	2 (3.2)	1 (1.8)	1 (4.0)	0.824
	Grade 3–5	0 (0)	0 (0)	0 (0)	1.000
Hypothyroidism, n (%)	Any grade	3 (4.8)	2 (3.5)	1 (4.0)	1.000
	Grade 3–5	1 (1.6)	0 (0)	0 (0)	1.000
Hypopituitarism, n (%)	Any grade	2 (3.2)	1 (1.8)	1 (4.0)	0.824
	Grade 3–5	0 (0)	0 (0)	0 (0)	1.000
Pneumonia, n (%)	Any grade	6 (9.5)	4 (7.0)	2 (8.0)	0.922
	Grade 3–5	1 (1.6)	1 (1.8)	1 (4.0)	0.574
Myocarditis, n (%)	Any grade	2 (3.2)	2 (3.5)	1 (4.0)	1.000
	Grade 3–5	0 (0)	0 (0)	0 (0)	1.000
Amylase level increase, n (%)	Any grade	1 (1.6)	1 (1.8)	0 (0)	1.000
	Grade 3–5	0 (0)	0 (0)	0 (0)	1.000
Lipase level increase, n (%)	Any grade	2 (3.2)	1 (1.8)	0 (0)	1.000
	Grade 3–5	0 (0)	0 (0)	0 (0)	1.000

ICI + C, ICI plus chemotherapy; ICI + A, ICI plus anti-angiogenic therapy; AE, adverse event; irAE, immune-related adverse event; ALT, alanine aminotransferase; AST, aspartate transaminase; ICI, immune checkpoint inhibitor.

OS (mOS: NE *vs.* 12.6 months, $P=0.038$) in another study that included NSCLC patients treated with combined ICI/chemotherapy compared to ICI monotherapy as second-line or later treatment (42). Moreover, a retrospective study found that the ORR, depth of response and PFS of ICIs plus chemotherapy were better than ICI monotherapy and ICIs plus anti-angiogenic therapy in patients with previously treated advanced NSCLC (43). In our study, the ICI/chemotherapy group showed a significantly higher ORR and DCR and a longer PFS and OS than the ICI monotherapy group. Meanwhile, there was no significant difference between the ICI/chemotherapy group and ICI/anti-angiogenic therapy group.

Introducing new drugs and combinations has also shown intriguing findings that favor using immunotherapy in combination. A recent phase I/II clinical trial evaluated the combination of camrelizumab/apatinib as the second-line for advanced squamous NSCLC and reported an ORR, DCR, mPFS, and mOS of 30.8%, 95%, 5.9 months, and 12.8 months, respectively; these data are superior to those presented by the registration studies of monotherapy with ICIs in the second line (44). In our study, the ICI/anti-angiogenic therapy group showed a significantly higher DCR and a longer PFS and OS than the ICI monotherapy group.

No new safety issues were observed in our analysis, consistent with previous studies (40–44). In the combined ICI/chemotherapy group, the AEs with an increased incidence were mostly related to hematologic toxicity, while the incidence of treatment-related irAEs did not increase. The ICI combination therapy did not significantly increase the incidence of treatment-related AEs compared to ICI monotherapy, suggesting that ICI combination therapy was well-tolerated.

This study has several limitations. First, the sample size of this study was relatively small, especially in the ICI/anti-angiogenic therapy combination group, which might affect the results. Second, this was a retrospective comparative cohort study, leading to inevitable selection bias. Third, the treatment regimen in this study involved five different ICIs, four different chemotherapeutic agents and two different anti-angiogenic agents, which may have a confounding effect on the efficacy.

Conclusions

Combined ICI/chemotherapy or ICI/anti-angiogenic therapy is well tolerated and has higher efficacy than ICI

monotherapy as a second-line or later treatment option for advanced NSCLC patients without prior immunotherapy, thereby providing a potentially superior treatment strategy. However, our findings require verification by prospective randomized controlled trials.

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Footnote

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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). The study was approved by the institutional ethics board of Hunan Cancer Hospital (No. 202257) and individual consent for this retrospective analysis was waived.

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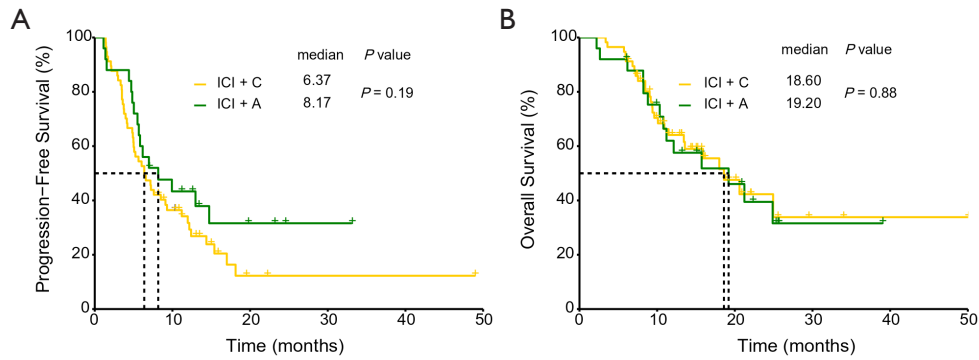


Figure S1 Progression-free survival and overall survival of patients treated with ICI/chemotherapy or ICI/anti-angiogenic therapy. (A) Progression-free survival of patients treated with ICI/chemotherapy or ICI/anti-angiogenic therapy as the second-line or later treatment. (B) Overall survival of patients treated with ICI/chemotherapy or ICI/anti-angiogenic therapy as the second-line or later treatment. ICI, immune checkpoint inhibitor.

Table S1 Univariate and multivariate Cox regression analyses of clinical parameters on PFS between ICI combination therapy and ICI monotherapy

Variable	Category	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P	HR (95% CI)	P
Sex	Male vs. female	0.99 (0.64-1.53)	0.973	0.64 (0.25-1.68)	0.366
Age (years)	≥65 vs. <65	0.75 (0.50-1.10)	0.140	0.66 (0.44-0.99)	0.043
ECOG PS	2 vs. <2	1.47 (0.72-3.01)	0.295	1.49 (0.72-3.11)	0.285
Smoking histology	Smoker vs. never smoker	1.19 (0.79-1.79)	0.409	1.77 (0.70-4.45)	0.228
TNM stage	IV vs. III	1.49 (0.87-2.57)	0.146	1.65 (0.93-2.93)	0.089
Histology	Squamous vs. non-squamous	1.00 (0.70-1.43)	0.993	0.85 (0.58-1.24)	0.391
Treatment line	2 vs. ≥3	0.96 (0.63-1.48)	0.865	0.99 (0.62-1.59)	0.963
Therapeutic regimen	ICI combination therapy vs. ICI monotherapy	0.37 (0.26-0.53)	<0.001	0.35 (0.24-0.51)	<0.001

PFS, progression-free survival; ICI, immune checkpoint inhibitor; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group performance status.

Table S2 Univariate and multivariate Cox regression analyses of clinical parameters on OS between ICI combination therapy and ICI monotherapy

Variable	Category	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P	HR (95% CI)	P
Sex	Male vs. female	1.18 (0.71-1.96)	0.519	1.33 (0.49-3.65)	0.578
Age (years)	≥65 vs. <65	0.88 (0.56-1.37)	0.562	0.86 (0.54-1.35)	0.503
ECOG PS	2 vs. <2	1.72 (0.80-3.73)	0.168	1.92 (0.86-4.28)	0.109
Smoking histology	Smoker vs. never smoker	1.18 (0.74-1.88)	0.491	1.06 (0.41-2.73)	0.899
TNM stage	IV vs. III	1.61 (0.85-3.02)	0.141	1.46 (0.76-2.81)	0.261
Histology	Squamous vs. non-squamous	0.94 (0.63-1.42)	0.777	0.79 (0.52-1.22)	0.289
Treatment line	2 vs. ≥3	0.70 (0.44-1.12)	0.136	0.71 (0.43-1.17)	0.179
Therapeutic regimen	ICI combination therapy vs. ICI monotherapy	0.41 (0.27-0.62)	<0.001	0.39 (0.26-0.60)	<0.001

OS, overall survival; ICI, immune checkpoint inhibitor; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group performance status.

Table S3 Univariate and multivariate Cox regression analyses of clinical parameters on PFS between ICI + C and ICI monotherapy

Variable	Category	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P	HR (95% CI)	P
Sex	Male vs. female	1.07 (0.66-1.73)	0.781	0.71 (0.21-2.41)	0.586
Age (years)	≥65 vs. <65	0.77 (0.50-1.17)	0.217	0.65 (0.42-1.01)	0.054
ECOG PS	2 vs. <2	1.31 (0.61-2.83)	0.488	1.44 (0.66-3.16)	0.363
Smoking histology	Smoker vs. never smoker	1.19 (0.75-1.88)	0.453	1.71 (0.53-5.54)	0.369
TNM stage	IV vs. III	1.66 (0.91-3.03)	0.102	1.89 (0.98-3.65)	0.057
Histology	Squamous vs. non-squamous	0.87 (0.59-1.28)	0.481	0.81 (0.54-1.23)	0.329
Treatment line	2 vs. ≥3	1.05 (0.64-1.73)	0.854	1.12 (0.65-1.94)	0.681
Therapeutic regimen	ICI + C vs. ICI monotherapy	0.42 (0.29-0.63)	<0.001	0.38 (0.25-0.57)	<0.001

PFS, progression-free survival; ICI, immune checkpoint inhibitor; ICI + C, ICI plus chemotherapy; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group performance status.

Table S4 Univariate and multivariate Cox regression analyses of clinical parameters on OS between ICI + C and ICI monotherapy

Variable	Category	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P	HR (95% CI)	P
Sex	Male vs. female	1.33 (0.75-2.37)	0.336	1.94 (0.54-7.01)	0.313
Age (years)	≥65 vs. <65	0.92 (0.57-1.48)	0.721	0.86 (0.52-1.41)	0.550
ECOG PS	2 vs. <2	1.61 (0.70-3.71)	0.264	1.95 (0.82-4.65)	0.131
Smoking histology	Smoker vs. never smoker	1.25 (0.73-2.14)	0.413	0.86 (0.26-2.86)	0.804
TNM stage	IV vs. III	1.87 (0.90-3.89)	0.094	1.80 (0.84-3.86)	0.133
Histology	Squamous vs. non-squamous	0.87 (0.56-1.36)	0.550	0.74 (0.46-1.19)	0.221
Treatment line	2 vs. ≥3	0.76 (0.44-1.30)	0.314	0.79 (0.44-1.41)	0.429
Therapeutic regimen	ICI + C vs. ICI monotherapy	0.40 (0.25-0.64)	<0.001	0.38 (0.24-0.62)	<0.001

OS, overall survival; ICI, immune checkpoint inhibitor; ICI + C, ICI plus chemotherapy; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group performance status.

Table S5 Univariate and multivariate Cox regression analyses of clinical parameters on PFS between ICI + A and ICI monotherapy

Variable	Category	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P	HR (95% CI)	P
Sex	Male vs. female	0.97 (0.56-1.68)	0.904	0.51 (0.15-1.75)	0.283
Age (years)	≥65 vs. <65	0.69 (0.42-1.12)	0.132	0.59 (0.36-0.99)	0.047
ECOG PS	2 vs. <2	1.68 (0.67-4.21)	0.265	1.51 (0.60-3.84)	0.382
Smoking histology	Smoker vs. never smoker	1.32 (0.78-2.21)	0.302	2.24 (0.67-7.43)	0.189
TNM stage	IV vs. III	1.51 (0.77-2.94)	0.230	1.82 (0.88-3.79)	0.109
Histology	Squamous vs. non-squamous	1.02 (0.65-1.60)	0.936	0.79 (0.49-1.30)	0.359
Treatment line	2 vs. ≥3	1.08 (0.65-1.82)	0.759	0.97(0.53-1.80)	0.933
Therapeutic regimen	ICI + A vs. ICI monotherapy	0.30 (0.17-0.53)	<0.001	0.30 (0.17-0.53)	<0.001

PFS, progression-free survival; ICI, immune checkpoint inhibitor; ICI + A, ICI plus anti-angiogenic therapy; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group performance status.

Table S6 Univariate and multivariate Cox regression analyses of clinical parameters on OS between ICI + A and ICI monotherapy

Variable	Category	Univariate Analysis		Multivariate Analysis	
		HR (95% CI)	P	HR (95% CI)	P
Sex	Male vs. female	1.09 (0.61-1.98)	0.766	0.92 (0.26-3.29)	0.891
Age (years)	≥65 vs. <65	0.84 (0.50-1.44)	0.534	0.81 (0.47-1.4)	0.456
ECOG PS	2 vs. <2	2.03 (0.81-5.12)	0.133	2.10 (0.81-5.43)	0.125
Smoking histology	Smoker vs. never smoker	1.24 (0.71-2.15)	0.450	1.48 (0.44-5.00)	0.529
TNM stage	IV vs. III	1.86 (0.85-4.09)	0.122	1.75 (0.77-3.97)	0.180
Histology	Squamous vs. non-squamous	0.95 (0.59-1.54)	0.842	0.78 (0.47-1.30)	0.343
Treatment line	2 vs. ≥3	0.83 (0.48-1.43)	0.501	0.75 (0.41-1.36)	0.338
Therapeutic regimen	ICI + A vs. ICI monotherapy	0.44 (0.24-0.80)	0.007	0.43 (0.23-0.80)	0.008

OS, overall survival; ICI, immune checkpoint inhibitor; ICI + A, ICI plus anti-angiogenic therapy; HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group performance status.