Original Article

Efficacy and safety analysis of immune checkpoint inhibitor rechallenge therapy in locally advanced and advanced non-small cell lung cancer: a retrospective study

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Background: Immune checkpoint inhibitors (ICIs) have dramatically changed the first-line treatment pattern of non-small cell lung cancer (NSCLC) without driver gene alterations. However, the optimal choice for second-line treatment after initial treatment with ICIs is unclear. This study aimed to clarify the efficacy and safety of ICI rechallenge therapy in locally advanced and advanced NSCLC.

Methods: We retrospectively analyzed the histories of 224 patients with locally advanced or advanced NSCLC treated with programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors alone or in combination with chemotherapy and/or antiangiogenic therapy in first-line treatment. Progression-free survival 2 (PFS2) was the time from the first defined progress disease (PD) to the second disease progression or death. Efficacy evaluation was performed directly in accordance with RECIST v1.1 criteria. Adverse events (AEs) were graded following the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. Survival data were estimated using the Kaplan-Meier method or Cox survival regression model and compared using the log-rank test in overall cohort and other subgroups.

Results: There were no significant differences in objective response rate (ORR) and median PFS2 (mPFS2) between the ICI rechallenge group and non-rechallenge group (ORR: 10.3% *vs.* 15.3%, P=0.308; mPFS2: 5.33 *vs.* 4.40 months, P=0.715). And the ICI rechallenge group showed no new safety signals compared with non-rechallenge group. In ICI rechallenge group, patients resistant to first-line immunotherapy had a lower ORR and shorter PFS2 compared with those who responded to initial ICIs treatment (ORR: 7.0% *vs.* 17.6%, P=0.038; mPFS2: 3.68 *vs.* 5.91 months, P=0.014). No significant difference in mPFS2 was observed among different second-line treatment groups (P=0.362). Radiotherapy in second-line treatment and ICI rechallenge therapy were not the main factors affecting PFS2.

Conclusions: ICI rechallenge therapy beyond disease progression did not improve clinical outcomes in patients with NSCLC, but no new safety signals emerged. However, patients with favorable response to initial ICIs treatment still showed significant efficacy of subsequent ICI rechallenge therapy.

Keywords: Immune checkpoint inhibitors (ICIs); second-line treatment; non-small cell lung cancer (NSCLC); disease progression; ICI rechallenge therapy

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Introduction

Lung cancer is the most common cancer worldwide as well as the leading cause of cancer related death with an estimated 1.8 million deaths each year (1). Non-small cell lung cancer (NSCLC) accounts for up to 85% of all lung cancers (2). Most patients are at an unresectable locally advanced or an advanced stage at the time of initial diagnosis, with a very low 5-year survival rate (3). In recent years, immune checkpoint inhibitors (ICIs), especially programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors, has become the first-line standard of care for NSCLC patients without driver gene alterations because of the remarkable efficacy and tolerable adverse effects (4,5). Despite these advances, the majority of patients experience disease progression after initial treatment. To date, the mechanisms of resistance to first-line immunotherapy are not clear (6). The optimal choice for second-line treatment and the efficacy and safety of ICI rechallenge therapy are currently unknown.

Current treatment guidelines recommend monotherapy as second-line treatment whenever possible. Since disease progression is often associated with drug tolerance, guidelines recommend shifting to a different drug in the second-line treatment after disease progression. However, due to limited efficacy of monotherapy, clinicians are still focused on multiple combination regimens to overcome the ICIs resistance. PD-1/PD-L1 inhibitors are recommended as second-line regimen for locally advanced and advanced NSCLC, including squamous and non-squamous cancers. Several ICIs have shown significant efficacy in the second-line treatment of NSCLC without driver gene alterations (7-9). One study has shown clinically meaningful efficacy of ICI rechallenge therapy without increasing toxicity (10), which suggested that patients who respond to initial ICIs treatment are likely to respond to ICI rechallenge. Although analysis of ICIs treatment beyond progression of anti-PD-1/PD-L1 in melanoma has been reported in one study (11), there are fewer studies of NSCLC. Therefore, there are no precise conclusions as to whether ICI rechallenge therapy is effective and safe in the second-line treatment for locally advanced and advanced NSCLC patients.

Previous studies have confirmed that antiangiogenic agents have the potential to modulate the tumor microenvironment and improve cancer immunotherapy (12,13). There are many interactions between angiogenesis and immune escape (14). The Impower150 study showed that the addition of atezolizumab to bevacizumab plus chemotherapy significantly improved progression-free survival and overall survival (OS) among patients with metastatic non-squamous NSCLC (15). The results of several recent large studies have demonstrated that antiangiogenic drugs in combination with other therapeutic regimens may be able to reverse PD-1/PD-L1 inhibitors resistance with favorable efficacy and safety (16-18). This raises the question of whether antiangiogenic drugs can be used as combination regimens for second-line therapy in locally advanced and advanced NSCLC.

Highlight box

Key findings

- In clinical practice, immune checkpoint inhibitor (ICI) rechallenge therapy beyond disease progression may not improve clinical outcomes in locally advanced or advanced non-small cell lung cancer (NSCLC) patients, but patients with favorable response to initial ICIs treatment still showed significant efficacy of subsequent ICI rechallenge therapy.

What is known and what is new?

- The use of ICIs has revolutionized the treatment of NSCLC without driver gene alterations, achieved high response rates in first-line treatment. Majority of patients experience disease progression after initial treatment, the optimal choice for second-line treatment and the efficacy and safety of ICI rechallenge therapy are unclear.
- In our study, ICI rechallenge therapy beyond disease progression did not improve clinical outcomes in patients with NSCLC. There were no significant differences in objective response rate and progression-free survival (PFS) between the ICI rechallenge group and non-rechallenge group. However, patients responded to initial ICIs treatment had better PFS. In multivariate analysis, ICI rechallenge therapy and combination of radiotherapy during the second-line treatment were not independent predictors of PFS.

What is the implication, and what should change now?

- Further studies should examine efficacy and safety of different second-line treatment regimens in large randomized prospective cohorts, and determine which patient groups can easily benefit from ICI rechallenge therapy.

The management of NSCLC patients who experienced disease progression at the end of the first-line treatment remains a clinical challenge. The selection of appropriate second-line treatment strategies is critical in order to effectively manage disease progression and improve clinical outcomes. The aim of this retrospective study was to assess the efficacy and safety of ICI rechallenge therapy in locally advanced or advanced NSCLC patients. In addition, we aimed to determine which patient groups would benefit from ICI rechallenge therapy and provide a reference for clinical decision-making. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1767/rc).

Methods

Patients

We retrospectively reviewed the medical records of locally advanced or advanced NSCLC patients who received treatment at the Jiangsu Cancer Hospital between January 2019 and June 2022. The last follow-up and data collection were updated as of May 2023. The inclusion criteria were as follows: (I) patients aged 18–80 years; (II) patients who scored 0–2 on the Eastern Cooperative Oncology Group performance status (ECOG PS); (III) patients without driver gene alterations; (IV) patients histologically or cytologically diagnosed with unresectable stage III/IV NSCLC; (V) patients who had received the PD-1/PD-L1 inhibitors alone or in combination with the chemotherapy and/or antiangiogenic drugs in the first-line treatment and defined progress disease (PD) at the end of the first line; (VI) complete clinicopathological data for evaluation. All patients included in this study had at least one measurable disease. The ICIs used in the study included pembrolizumab, nivolumab, camrelizumab, toripalimab, tislelizumab and sintilimab. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Academic Ethics Committee of Jiangsu Cancer Hospital [No. (2023)082], and individual consent for this retrospective analysis was waived.

Data collection and response assessment

Medical records were collected and extracted on clinical pathologic features and treatment histories. Data and follow-up records were updated as of May 2023. The best response, defined as a complete response (CR) or partial response (PR) and stable disease (SD) achieved at least once during the process of therapy, was assessed using the RECIST v1.1 criteria. The objective response rate (ORR) was defined as the proportion of patients with the best overall response of CR or PR among all patients, and the disease control rate (DCR) was defined as the proportion of patients with the best overall response of CR or PR or SD. Progression-free survival 1 (PFS1) was defined as the time of initiation of PD-1/PD-L1 inhibitors alone or in combination with the chemotherapy and/or antiangiogenic drugs to first defined PD. Progression-free survival 2 (PFS2) was the time from the first defined PD to the second disease progression or death. The resistant group was defined as patients with PFS1 of less than six months, and the responder group was defined as patients with PFS1 of longer than six months. Adverse events (AEs) were recorded and graded by the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0.

Statistical analysis

Survival data were estimated using the Kaplan-Meier method and the log-rank test was used to assess between-group differences in progression-free survival. Hazard ratios (HRs) and associated 95% confidence interval (CI) were calculated with the use of the Cox proportional-hazards model. Chi-squared or Fisher's exact test was used to compare the differences in baseline between different groups. Statistical analyses were conducted using the SPSS version 26.0 (SPSS, Inc., Chicago, IL, USA). $P \leq 0.05$ was considered to indicate statistical significance.

Results

Patients' characteristics

In total, 224 patients were enrolled in this study. Their clinical and pathological baseline characteristics are shown in *Table 1*. The median age of the 224 patients was 65 years, and our sample included 188 males and 36 females. The majority of patients (53.1%, 119/224) was diagnosed with lung adenocarcinoma, followed by squamous cell carcinoma (43.3%). Most (75.0%) patients were clinically diagnosed with stage IV lung cancer and most patients (75.0%) did not receive combined radiotherapy during the second-line treatment. Most (85.3%) patients had an ECOG PS of 0 or 1. All patients had received PD-1/PD-L1 inhibitors alone or

Table 1 Clinical characteristics of patients and clinical activity of second-line treatment (n=224)

Characteristic	Patients, n (%)	CR	PR	SD	PD	ORR (%)	Hypothesis testing parameters of ORR	DCR (%)	Hypothesis testing parameters of DCR
Sex									
Female	36 (16.1)	0	5	20	11	13.9	0.855	69.4	0.558
Male	188 (83.9)	0	21	100	67	11.2		64.4	
Age, years									
≤60	81 (36.2)	0	9	40	32	11.1	0.862	60.5	0.268
>60	143 (63.8)	0	17	80	46	11.9		67.8	
Smoking status									
Current or former	55 (24.6)	0	5	32	18	9.1	0.502	67.3	0.707
Never	169 (75.4)	0	21	88	60	12.4		64.5	
Histology									
Adenocarcinoma	119 (53.1)	0	16	68	35	13.4	0.172	70.6	0.165
Squamous	97 (43.3)	0	8	49	40	8.2		58.8	
Other	8 (3.6)	0	2	3	3	25.0		62.5	
Stage of cancer									
Stage III	56 (25.0)	0	3	36	17	5.4	0.092	69.6	0.418
Stage IV	168 (75.0)	0	23	84	61	13.7		63.7	
Combined with radiotherapy									
Yes	56 (25.0)	0	12	32	12	21.4	0.008	78.6	0.015
No	168 (75.0)	0	14	88	66	8.3		60.7	
ECOG PS									
0	46 (20.5)	0	7	26	13	15.2	0.680	71.7	0.032
1	145 (64.7)	0	16	82	47	11.0		67.6	
2	33 (14.7)	0	3	12	18	9.1		45.5	
Second-line treatment received									
Chemotherapy alone	21 (9.4)	0	1	9	11	4.8	0.199	47.6	0.025
C + A	38 (17.0)	0	8	18	12	21.1		68.4	
ICI monotherapy	5 (2.2)	0	0	3	2	0.0		60.0	
ICIs + C	77 (34.4)	0	5	40	32	6.5		58.4	
ICIs + C + A	51 (22.8)	0	8	26	17	15.7		66.7	
ICIs + A	32 (14.3)	0	4	24	4	12.5		87.5	
Total	224	0	26	120	78	11.6		65.2	

CR, complete response; PR, partial response; SD, stable disease; PD, progress disease; ORR, objective response rate; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; C + A, chemotherapy with antiangiogenic drugs; ICI, immune checkpoint inhibitor; ICIs + C, immune checkpoint inhibitors with chemotherapy; ICIs + C + A, immune checkpoint inhibitors with chemotherapy and antiangiogenic drugs; ICIs + A, immune checkpoint inhibitors with antiangiogenic drugs.

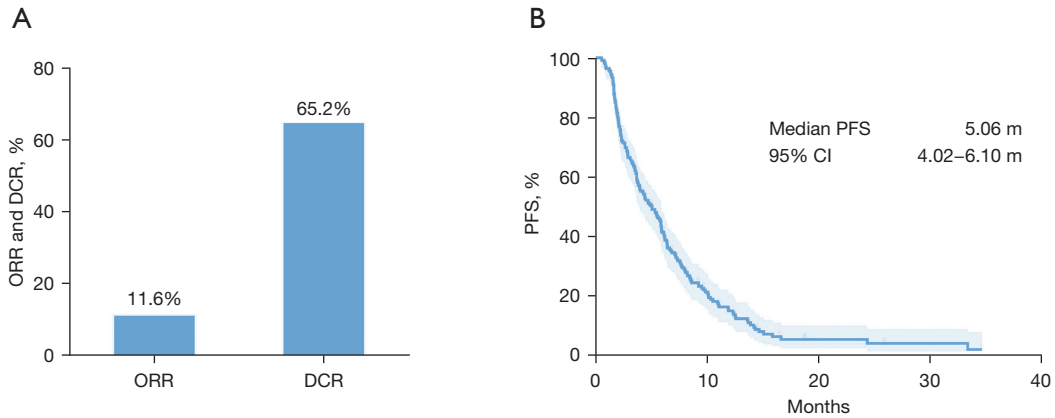

Figure 1 Overall clinical outcomes of the second-line treatment. (A) ORR and DCR of all patients. (B) PFS of all patients. n=224. ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; CI, confidence interval; m, months.

in combination with chemotherapy and/or antiangiogenic drugs during the first-line treatment and were finally evaluated as PD in first-line treatment.

Treatment characteristics

As shown in *Table 1*, 77 patients (34.4%) received ICIs combined with chemotherapy (ICIs + C) as second-line therapy, 51 patients (22.8%) received ICIs combined with chemotherapy and antiangiogenic drugs (ICIs + C + A), 38 patients (17.0%) received chemotherapy combined with antiangiogenic drugs (C + A), 32 patients (14.3%) received ICIs combined with antiangiogenic drugs (ICIs + A), 21 patients (9.4%) received chemotherapy alone and five patients (2.2%) received ICI monotherapy treatment. In addition, some (25%, 56/224) patients received radiotherapy during the second-line treatment. Among the 224 patients, 165 (73.7%) patients had an anti-PD-1 or anti-PD-L1 rechallenge in the second-line treatment. In ICI rechallenge group, 51 patients resistant to first-line immunotherapy were included in resistant group. And 114 patients responded to first-line immunotherapy were included in responder group.

Overall clinical outcomes

As shown in *Figure 1A*, the ORR was observed in 26 of 224 (11.6%) patients, and the DCR was 65.2% (146/224). No patient achieved a CR. The mPFS2 was 5.06 months with 95% CI of 4.02–6.10 months (*Figure 1B*). Twelve of the 26 patients with PR were treated with radiotherapy combined with the second-line therapy. Among those 26 patients who achieved a PR, 25 were treated with combination regimens and only one had the monotherapy, but the result showed no statistically significant difference (P=0.323).

Subgroup analyses

The ORR, DCR in radiotherapy group were significantly higher and longer than in the no radiotherapy group (ORR: 21.4% *vs.* 8.3%, P=0.008, *Figure 2A*; DCR: 78.6% *vs.* 60.7%, P=0.015, *Figure 2B*). Five patients received the PD-1/PD-L1 inhibitor monotherapy in the second-line treatment, none of them achieved complete or PR. Patients with better ECOG PS had higher DCR than those with poorer performance status (DCR: 71.7% *vs.* 67.6% *vs.* 45.5%, P=0.032, *Figure 2B*). ORR for the second-line treatment was numerically higher in the C + A group (21.1%, P=0.199) and DCR was the highest in the ICIs + A group (87.5%, P=0.025). ORR and DCR were similar between the ICI rechallenge therapy group and non-rechallenge group (ORR: 10.3% *vs.* 15.3%, P=0.308, *Figure 2C*; DCR: 66.7% *vs.* 61.0%, P=0.434, *Figure 2D*). In ICI rechallenge group, the ORR was significantly higher in the responder group than in the resistant group (ORR: 17.6% *vs.* 7.0%, P=0.038, *Figure 2E*).

In the second-line treatment, mPFS2 was 6.64 months (95% CI: 5.27–8.00) in the ICIs + A group; 6.41 months (95% CI: 3.91–8.90) in the C + A group; 5.45 months (95% CI: 3.17–7.74) in the ICIs + C group; 4.50 months (95% CI: 3.06–5.94) in the ICIs + C + A group; 3.68 months

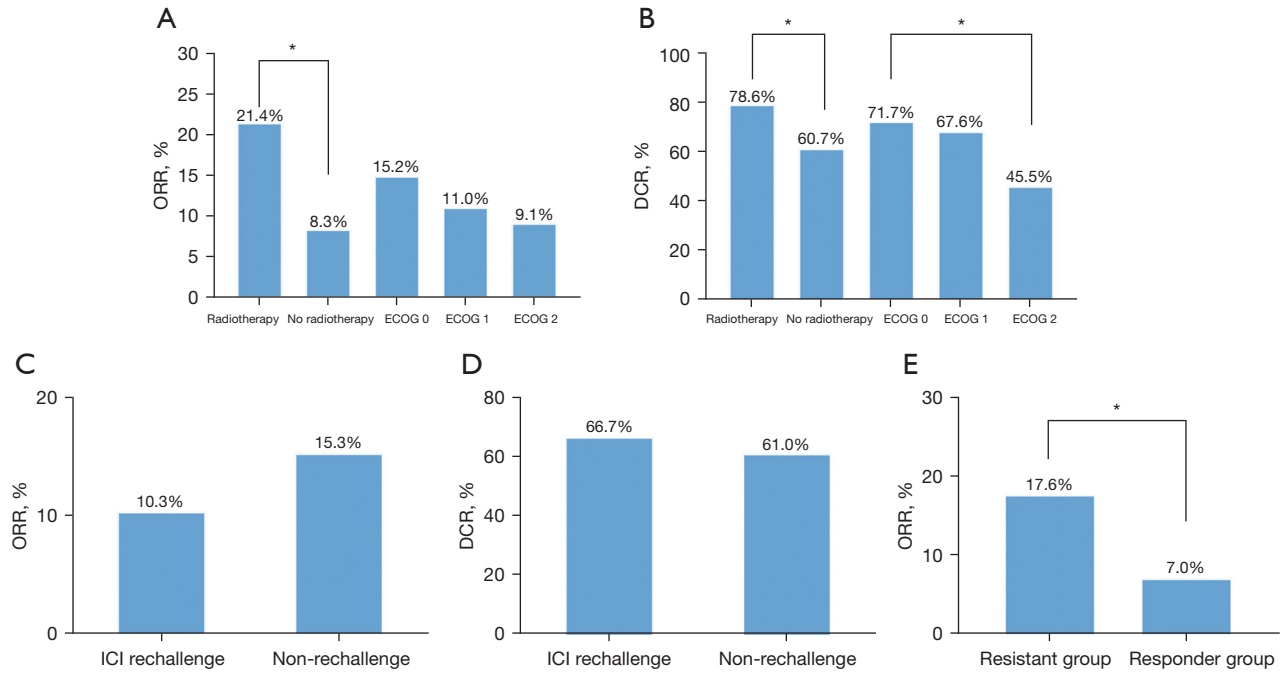

Figure 2 Clinical outcomes of the second-line treatment. (A) ORR of patients with or without radiotherapy and ORR of patients with different ECOG PS. (B) DCR of patients with or without radiotherapy and DCR of patients with different ECOG PS. (C) ORR of patients with or without ICI rechallenge. (D) DCR of patients with or without ICI rechallenge. (E) ORR of patients received ICI rechallenge treatment with different response to initial ICIs treatment. *, P<0.05. ORR, objective response rate; ECOG PS, Eastern Cooperative Oncology Group performance status; DCR, disease control rate; ICI, immune checkpoint inhibitor; resistant group, patients with PFS1 of less than 6 months; responder group, patients with PFS1 of longer than 6 months; PFS1, progression-free survival 1 (the time of initiation of PD-1/PD-L1 inhibitors alone or in combination with the chemotherapy and/or antiangiogenic drugs to first defined progress disease); PD-1, programmed death-1; PD-L1, programmed death-ligand 1.

(95% CI: 1.99–5.37) in the ICI monotherapy group and 3.22 months (95% CI: 2.28–4.16) in the chemotherapy alone group (*Figure 3A*, P=0.362). However, no statistical difference in efficacy was observed possibly because of the limited number of patients. The mPFS2 was 5.33 months (95% CI: 4.06–6.58) in ICI rechallenge therapy group and 4.40 months (95% CI: 2.67–6.14) in non-rechallenge group (HR =1.062, 95% CI: 0.77–1.47; P=0.715, *Figure 3B*). In ICI rechallenge group, PFS2 was significantly longer in the responder group than in the resistant group (mPFS2: 5.91 *vs.* 3.68 months, P=0.014, *Figure 3C*). Patients with better ECOG PS had longer PFS2 than those with poorer performance status (mPFS2: 7.98 *vs.* 4.70 *vs.* 3.68 months, P=0.015, *Figure 3D*). PFS2 in radiotherapy group was significantly longer than in the no radiotherapy group (mPFS2: 6.64 *vs.* 4.04 months, P=0.036, *Figure 3E*).

Multivariate Cox regression analysis of all patients (n=224), including sex, age, smoking status, histology, ECOG PS score, tumor, node, metastasis (TNM) stage, combination of radiotherapy and therapeutic regimen, further confirmed that ICI rechallenge therapy and combination of radiotherapy during the second-line treatment were not independent prognostic factors affecting PFS2 (*Table 2*). As shown in *Table 3*, multivariate analysis of the ICI rechallenge group (n=165) showed that response to initial ICIs treatment was associated with PFS2 (P=0.015).

Safety

As shown in *Table 4*, 65.2% (146/224) of patients experienced treatment-related AEs (TRAEs) in the second-line treatment. Several (17.0%, 38/224) patients experienced grade 3 or 4 AEs. No grade 5 TRAE was reported. The number of patients with TRAEs was 47 (61.0%), 24 (63.2%), 19 (59.4%), 35 (68.6%), 3 (60.0%) and 18 (85.7%) in the ICIs + C, C + A, ICIs + A, ICIs + C

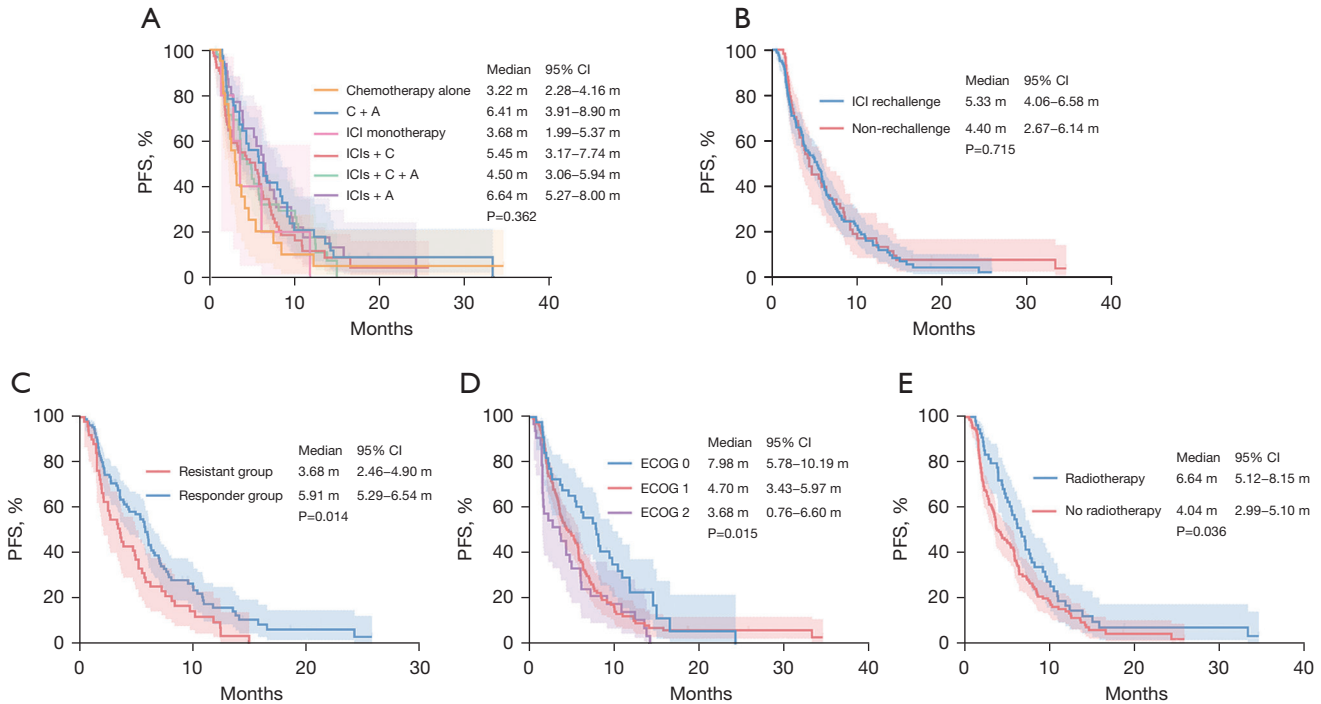

Figure 3 Kaplan-Meier curves of the second-line treatment. (A) PFS of patients with different second-line treatment options. (B) PFS of patients with or without ICI rechallenge. (C) PFS of patients received ICI rechallenge treatment with different response to initial ICIs treatment. (D) PFS of patients with different ECOG PS. (E) PFS of patients with or without radiotherapy. PFS, progression-free survival; C + A, chemotherapy with antiangiogenic drugs; ICI, immune checkpoint inhibitor; ICIs + C, immune checkpoint inhibitors with chemotherapy; ICIs + C + A, immune checkpoint inhibitors with chemotherapy and antiangiogenic drugs; ICIs + A, immune checkpoint inhibitors with antiangiogenic drugs; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; resistant group, patients with PFS1 of less than 6 months; responder group, patients with PFS1 of longer than 6 months; PFS1, progression-free survival 1 (the time of initiation of PD-1/PD-L1 inhibitors alone or in combination with the chemotherapy and/or antiangiogenic drugs to first defined progress disease); PD-1, programmed death-1; PD-L1, programmed death-ligand 1.

Table 2 Univariate analysis and multivariate analysis of factors of progression-free survival 2 in all patients (n=224)

Variable	Category	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P	HR (95% CI)	P
Sex	Male *vs.* female	0.939 (0.634–1.391)	0.754		
Age	>60 *vs.* ≤60 years	0.926 (0.687–1.249)	0.615		
Smoking status	Smoker *vs.* never smoker	0.936 (0.666–1.314)	0.701		
Histology	Non-adenocarcinoma *vs.* adenocarcinoma	1.109 (0.829–1.484)	0.485		
TNM stage	IV *vs.* III	1.323 (0.936–1.872)	0.113		
Combination of radiotherapy	Radiotherapy *vs.* no radiotherapy	0.702 (0.503–0.979)	0.037		
ECOG PS	≥1 *vs.* 0	1.595 (1.100–2.313)	0.014	1.518 (1.044–2.207)	0.029
Therapeutic regimen	Non-rechallenge *vs.* ICI rechallenge	0.941 (0.680–1.302)	0.715		

HR, hazard ratio; CI, confidence interval; TNM, tumor, node, metastasis; ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor.

Table 3 Univariate analysis and multivariate analysis of factors of progression-free survival 2 in ICI rechallenge group (n=165)

Variable	Category	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P	HR (95% CI)	P
Sex	Male *vs.* female	0.999 (0.636–1.570)	0.998		
Age	>60 vs. ≤60 years	0.997 (0.698–1.425)	0.987		
Smoking status	Smoker *vs.* never smoker	0.888 (0.605–1.304)	0.545		
Histology	Non-adenocarcinoma *vs.* adenocarcinoma	1.127 (0.801–1.587)	0.492		
TNM stage	IV *vs.* III	1.456 (0.942–2.249)	0.091		
Combination of radiotherapy	Radiotherapy *vs.* no radiotherapy	0.798 (0.541–1.179)	0.257		
ECOG PS	≥1 *vs.* 0	2.005 (1.295–3.104)	0.002	2.006 (1.295–3.108)	0.002
Response to initial ICIs treatment	Responder group *vs.* resistant group	0.640 (0.447–0.916)	0.015	0.640 (0.447–0.917)	0.015

ICI, immune checkpoint inhibitor; HR, hazard ratio; CI, confidence interval; TNM, tumor, node, metastasis; ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 4 Treatment-related adverse events of all patients

Events	Grade	ICIs + C (N=77)	ICIs + C + A (N=51)	ICIs + A (N=32)	C + A (N=38)	ICI monotherapy (N=5)	Chemotherapy alone (N=21)
Hypothyroidism	Any grade	2 (2.6)	5 (9.8)	4 (12.5)	3 (7.9)	1 (20.0)	0
	Grade 3–5	0	0	0	1 (2.6)	0	0
Neutropenia	Any grade	16 (20.8)	10 (19.6)	3 (9.4)	4 (10.5)	0	3 (14.3)
	Grade 3–5	5 (6.5)	5 (9.8)	0	3 (7.9)	0	2 (9.5)
Pneumonia	Any grade	2 (2.6)	4 (7.8)	0	1 (2.6)	1 (20.0)	0
	Grade 3–5	0	2 (3.9)	0	0	1 (20.0)	0
Anemia	Any grade	25 (32.5)	18 (35.3)	11 (34.4)	17 (44.7)	1 (20.0)	14 (66.7)
	Grade 3–5	2 (2.6)	5 (9.8)	0	2 (5.3)	0	3 (14.3)
Arrhythmia	Any grade	1 (1.3)	5 (9.8)	0	2 (5.3)	0	2 (9.5)
	Grade 3–5	0	0	0	0	0	0
Thrombocytopenia	Any grade	11 (14.3)	12 (23.5)	4 (12.5)	5 (13.2)	0	6 (28.6)
	Grade 3–5	3 (3.9)	4 (7.8)	0	2 (5.3)	0	3 (14.3)
Leukopenia	Any grade	19 (24.7)	15 (29.4)	5 (15.6)	5 (13.2)	0	5 (23.8)
	Grade 3–5	3 (3.9)	3 (5.9)	0	3 (7.9)	0	3 (14.3)
ALT/AST elevated	Any grade	8 (10.4)	8 (15.7)	2 (6.3)	4 (10.5)	1 (20.0)	4 (19.0)
	Grade 3–5	0	0	0	0	0	0
Nasal bleeding	Any grade	0	1 (2.0)	0	1 (2.6)	0	0
	Grade 3–5	0	0	0	0	0	0
Nausea	Any grade	2 (2.6)	4 (7.8)	0	0	0	1 (4.8)
	Grade 3–5	0	1 (2.0)	0	0	0	2 (9.5)

Table 4 (*continued*)

Table 4 (*continued*)

Events	Grade	ICIs + C (N=77)	ICIs + C + A (N=51)	ICIs + A (N=32)	C + A (N=38)	ICI monotherapy (N=5)	Chemotherapy alone (N=21)
Joint pain	Any grade	0	1 (2.0)	0	1 (2.6)	0	0
	Grade 3–5	0	1 (2.0)	0	0	0	0
Rash	Any grade	3 (3.9)	3 (5.9)	0	0	0	0
	Grade 3–5	0	0	0	0	0	0
Diarrhea	Any grade	0	2 (3.9)	2 (6.3)	0	0	1 (4.8)
	Grade 3–5	0	0	0	0	0	0
Hair loss	Any grade	1 (1.3)	1 (2.0)	0	0	0	0
	Grade 3–5	0	0	0	0	0	0
Poor appetite	Any grade	1 (1.3)	2 (3.9)	1 (3.1)	0	0	1 (4.8)
	Grade 3–5	0	0	0	0	0	0
Fatigue	Any grade	2 (2.6)	2 (3.9)	1 (3.1)	0	0	1 (4.8)
	Grade 3–5	1 (1.3)	0	1 (3.1)	0	0	0
Bilirubin increased	Any grade	2 (2.6)	1 (2.0)	1 (3.1)	0	0	0
	Grade 3–5	0	0	0	0	0	0
Creatinine increased	Any grade	5 (6.5)	0	4 (12.5)	2 (5.3)	1 (20.0)	2 (9.5)
	Grade 3–5	0	0	0	0	0	0
Proteinuria	Any grade	1 (1.3)	0	0	0	0	0
	Grade 3–5	0	0	0	0	0	0
Fever	Any grade	2 (2.6)	0	1 (3.1)	2 (5.3)	0	1 (4.8)
	Grade 3–5	1 (1.3)	0	1 (3.1)	1 (2.6)	0	1 (4.8)
Paresthesia	Any grade	1 (1.3)	0	0	1 (2.6)	0	0
	Grade 3–5	0	0	0	0	0	0
Hyperuricemia	Any grade	0	0	0	1 (2.6)	0	0
	Grade 3–5	0	0	0	1 (2.6)	0	0

Data are presented as n (%). ICIs + C, immune checkpoint inhibitors with chemotherapy; ICIs + C + A, immune checkpoint inhibitors with chemotherapy and antiangiogenic drugs; ICIs + A, immune checkpoint inhibitors with antiangiogenic drugs; C + A, chemotherapy with antiangiogenic drugs; ICI, immune checkpoint inhibitor; ALT, alanine aminotransferase; AST, aspartate transaminase.

+ A, ICI monotherapy and chemotherapy alone groups, respectively, while the incidence of grade 3 or 4 TRAEs in the same groups was 13.0%, 18.4%, 6.3%, 23.5%, 20.0%, and 28.6%, respectively. Similar incidences of TRAEs at any grade were observed in the different second-line treatment groups (P=0.334). Similarly, no statistically significant differences in the incidence of grade 3 and 4 AEs were observed (P=0.162).

The detailed AEs in ICI rechallenge group and non-rechallenge group are presented in *Table 5*. Similar incidences of TRAEs at any grade were observed in ICI rechallenge group and non-rechallenge group (63.0% *vs.* 71.2%, P=0.259), and no statistically significant differences in the incidence of grade 3 and 4 AEs were observed between the two groups (15.2% *vs.* 22.0%, P=0.227). Similar incidences of TRAEs at any grade were observed in the resistant group and responder group (68.6% *vs.* 60.5%, P=0.319), and no statistically significant differences in the

Table 5 Treatment-related adverse events of ICI rechallenge group and non-rechallenge group

Events	Grade	ICI rechallenge (N=165)	Non-rechallenge (N=59)
Hypothyroidism	Any grade	12 (7.3)	3 (5.1)
	Grade 3–5	0	1 (1.7)
Neutropenia	Any grade	29 (17.6)	7 (11.9)
	Grade 3–5	10 (6.1)	5 (8.5)
Pneumonia	Any grade	7 (4.2)	1 (1.7)
	Grade 3–5	3 (1.8)	0
Anemia	Any grade	55 (33.3)	31 (52.5)
	Grade 3–5	7 (4.2)	5 (8.5)
Arrhythmia	Any grade	6 (3.6)	4 (6.8)
	Grade 3–5	0	0
Thrombocytopenia	Any grade	27 (16.4)	11 (18.6)
	Grade 3–5	7 (4.2)	5 (8.5)
Leukopenia	Any grade	39 (23.6)	10 (16.9)
	Grade 3–5	6 (3.6)	6 (10.2)
ALT/AST elevated	Any grade	19 (11.5)	8 (13.6)
	Grade 3–5	0	0
Nasal bleeding	Any grade	1 (0.6)	1 (1.7)
	Grade 3–5	0	0
Nausea	Any grade	6 (3.6)	1 (1.7)
	Grade 3–5	1 (0.6)	2 (3.4)
Joint pain	Any grade	1 (0.6)	1 (1.7)
	Grade 3–5	1 (0.6)	0
Rash	Any grade	6 (3.6)	0
	Grade 3–5	0	0
Diarrhea	Any grade	4 (2.4)	1 (1.7)
	Grade 3–5	0	0
Hair loss	Any grade	2 (1.2)	0
	Grade 3–5	0	0
Poor appetite	Any grade	4 (2.4)	1 (1.7)
	Grade 3–5	0	0
Fatigue	Any grade	5 (3.0)	1 (1.7)
	Grade 3–5	2 (1.2)	0
Bilirubin increased	Any grade	4 (2.4)	0
	Grade 3–5	0	0

Table 5 (*continued*)

Table 5 (*continued*)

Events	Grade	ICI rechallenge (N=165)	Non-rechallenge (N=59)
Creatinine increased	Any grade	10 (6.1)	4 (6.8)
	Grade 3–5	0	0
Proteinuria	Any grade	1 (0.6)	0
	Grade 3–5	0	0
Fever	Any grade	3 (1.8)	3 (5.1)
	Grade 3–5	2 (1.2)	2 (3.4)
Paresthesia	Any grade	1 (0.6)	1 (1.7)
	Grade 3–5	0	0
Hyperuricemia	Any grade	0	1 (1.7)
	Grade 3–5	0	1 (1.7)

Data are presented as n (%). ICI, immune checkpoint inhibitor; ALT, alanine aminotransferase; AST, aspartate transaminase.

incidence of grade 3 and 4 AEs were observed between the two groups (17.6% *vs.* 14.0%, P=0.550) (*Table 6*).

Discussion

In this retrospective study, we explored the efficacy and safety of different second-line treatment regimens for locally advanced and advanced NSCLC. Our results suggested that ICI rechallenge therapy after disease progression did not provide clinical benefit but displaying a manageable safety profile. Response to prior immunotherapy correlated with the efficacy of second-line ICI rechallenge therapy.

Previous studies have demonstrated that there is an important relationship between the tumor immune microenvironment and tumor angiogenesis, and inhibition of neovascularization can improve the tumor immune microenvironment, which promotes the infiltration of T-lymphocytes into the tumor microenvironment and improves the efficacy of immunotherapy (12,13). The results of the IMpower150 study demonstrated that the efficacy of a combination of atezolizumab, bevacizumab, carboplatin, and paclitaxel may lead to significant improvements in PFS and OS in patients with metastatic NSCLC (15). Lung-MAP S1800A is a randomized phase II clinical study of ramucirumab in combination with pembrolizumab versus standard of care in advanced NSCLC previously treated with immunotherapy. The results of the study showed a mPFS of 4.5 months and an ORR of 22% in the pembrolizumab combined with ramucirumab treatment group (18). The study suggested that pembrolizumab in combination with ramucirumab improved survival in patients with advanced NSCLC who had received prior immunotherapy and chemotherapy. Results from the SCORPION study, a multicenter phase II study of the combination of docetaxel and ramucirumab in NSCLC patients beyond disease progression on first-line chemotherapy plus ICIs, showed an ORR of 34.4%, which was higher than our study (ORR =21.1%) (16). This discrepancy may be related to the fact that in the real-world setting, patients whose health has been declining because of the disease progression on first-line treatment, are generally less tolerant of second-line treatment. The results showed that docetaxel in combination with ramucirumab demonstrated encouraging antitumor activity and manageable safety profile in patients who failed first-line chemotherapy plus ICIs. Although the data analysis among different second-line treatment options was not statistically significant in our study, the ICIs + A group achieved the longest PFS2 of 6.64 months (95% CI: 5.27–8.00), followed by C + A group of 6.41 months (95% CI: 3.91–8.90). Therefore, the efficacy of the antiangiogenic drugs in combination with ICIs or chemotherapy may still worth exploring in second-line settings.

Meanwhile, our findings showed that the PFS2 obtained in the ICI monotherapy group was 3.68 months (95% CI: 1.99–5.37). A pooled analysis based on the five KEYNOTE series of studies showed that patients with PD showed a survival benefit in second-line pembrolizumab monotherapy after completing 35 cycles of pembrolizumab with or without chemotherapy (19). The mPFS in the ICI

Table 6 Treatment-related adverse events of resistant group and responder group during the ICI rechallenge treatment

Events	Grade	Resistant group (N=51)	Responder group (N=114)
Hypothyroidism	Any grade	3 (5.9)	9 (7.9)
	Grade 3–5	0	0
Neutropenia	Any grade	9 (17.6)	20 (17.5)
	Grade 3–5	3 (5.9)	7 (6.1)
Pneumonia	Any grade	4 (7.8)	3 (2.6)
	Grade 3–5	1 (2.0)	2 (1.8)
Anemia	Any grade	13 (25.5)	22 (19.3)
	Grade 3–5	4 (7.8)	3 (2.6)
Arrhythmia	Any grade	3 (5.9)	4 (3.5)
	Grade 3–5	0	0
Thrombocytopenia	Any grade	13 (25.5)	14 (12.3)
	Grade 3–5	5 (9.8)	2 (1.8)
Leukopenia	Any grade	14 (27.5)	24 (21.1)
	Grade 3–5	3 (5.9)	3 (2.6)
ALT/AST elevated	Any grade	8 (15.7)	12 (10.5)
	Grade 3–5	0	0
Nasal bleeding	Any grade	1 (2.0)	0
	Grade 3–5	0	0
Nausea	Any grade	3 (5.9)	3 (2.6)
	Grade 3–5	0	1 (0.9)
Rash	Any grade	1 (2.0)	4 (3.5)
	Grade 3–5	0	0
Diarrhea	Any grade	0	2 (1.8)
	Grade 3–5	0	0
Hair loss	Any grade	1 (2.0)	1 (0.9)
	Grade 3–5	0	0
Poor appetite	Any grade	1 (2.0)	3 (2.6)
	Grade 3–5	0	0
Fatigue	Any grade	5 (9.8)	4 (3.5)
	Grade 3–5	2 (3.9)	2 (1.8)
Creatinine increased	Any grade	0	10 (8.8)
	Grade 3–5	0	0
Fever	Any grade	0	3 (2.6)
	Grade 3–5	0	2 (1.8)
Paresthesia	Any grade	0	1 (0.9)
	Grade 3–5	0	0

Data are presented as n (%). ALT, alanine aminotransferase; AST, aspartate transaminase.

monotherapy of this pooled analysis was longer than in our study (10.3 *vs.* 3.68 months). We attribute this difference to the high proportion of patients with PD-L1 tumor proportion score (TPS) ≥50% in the ICI monotherapy group of this pooled analysis, of which 47/58 (81%) of patients had PD-L1 TPS of 50% or greater. However, we have not determined the efficacy difference at different PD-L1 expression levels because of the limited number of patients with known PD-L1 expression levels. Therefore, further studies are still needed to confirm whether patients with high PD-L1 expression can benefit from second-line ICI monotherapy. In our study, the chemotherapy alone group has achieved the worst PFS2 (mPFS2 =3.22 months, 95% CI: 2.28–4.16). According to European Society for Medical Oncology (ESMO) Clinical Practice Guidelines, the use of platinum-based chemotherapy after disease progression is preferred. A multicentric international study analyzed the efficacy of second-line chemotherapy regimens after disease progression, mPFS in the chemotherapy alone group was 2.9 months (95% CI: 2.4–3.3), which was very similar to our results (3.22 months) (20). Our study confirmed that the use of chemotherapy alone in the second line did not provide significant benefit to patients.

In the analysis of Cohort C of the VARGADO study (NCT02392455), nintedanib in combination with docetaxel after the first-line treatment of ICIs combination chemotherapy showed that ECOG PS >1 was associated with lower ORR, DCR and shorter PFS and OS. In our study, better physical conditions were associated with higher ORR, DCR, and relatively longer PFS2. A systematic review of the efficacy and safety of ICI rechallenge in NSCLC also suggested that patients with good ECOG PS had better outcomes (21). Radiotherapy can enhance tumor antigen presentation and induce anti-tumor T cell responses to maximize control tumor, and radiotherapy can heighten the effect of immunotherapy (22-24). Several studies have demonstrated that the combination of radiotherapy and immunotherapy prolongs PFS and OS in NSCLC patients (25,26). Given the sensitizing mechanism of radiotherapy to immunotherapy, it is also widely accepted by clinicians that all patients can benefit from second-line combination of radiotherapy after disease progression on first-line immunotherapy. A phase II prospective trial enrolled NSCLC patients treated with first-line pembrolizumab, and 21 patients received stereotactic body radiotherapy (SBRT) after disease progression. The final results showed that the addition of SBRT after progression on a PD-1 inhibitor prolonged PFS with favorable efficacy (27). Our study showed that patients who received radiotherapy during second-line treatment had significantly higher ORR and DCR and longer PFS2 than those without radiotherapy. However, multivariate analysis showed that the combination of radiotherapy during the second-line treatment was not a major factor influencing PFS2 of all patients. Similar to our study, results of a phase II study exploring treatment strategies for different oligoprogression patterns after failure of immunotherapy in metastatic NSCLC showed that only repeat oligoprogression group (diagnosis of oligoprogression with a history of oligometastatic disease) had a survival benefit from the addition of local therapy, and the benefit was not apparent in other metastatic NSCLC situations (28). The results of our study likewise confirmed this idea that local therapy during second-line treatment may benefit only a small percentage of patients. More studies of such patients are needed in the future for further clarification.

In addition, our analysis showed no significant differences in mPFS2 and ORR between the ICI rechallenge group and non-rechallenge group. Patients with locally advanced or advanced NSCLC who continued immunotherapy beyond PD after the first-line treatment showed a negative clinical benefit. Patients who received ICI rechallenge had a lower ORR compared with those who did not receive second-line immunotherapy (10.3% *vs.* 15.3%), although the difference was not statistically significant. The median PFS2 was 5.33 months (95% CI: 4.06–6.58) for patients who received ICI rechallenge and 4.40 months (95% CI: 2.67–6.14) for those who did not receive immunotherapy after failure of first-line treatment (HR =1.062, 95% CI: 0.77–1.47; P=0.715). Results from a retrospective study of the safety and efficacy of continuing ICIs in patients with disease progression after first-line ICIs plus chemotherapy, which included 59 patients, also suggested that continuing ICI rechallenge in NSCLC patients after initial disease progression did not improve clinical outcomes (29). Compared with this retrospective analysis, our study expands the sample size and reduces errors due to insufficient quantities. However, the results of the retrospective study showed that antiangiogenic drugs in combination with ICIs had the worst PFS2 (mPFS2 =1.41 months), which was completely different from our study that the ICIs + A group obtained the longest PFS2 (mPFS2 =6.64 months). We believe that this difference may be due to differences in baseline characteristics. Another retrospective study of ICI rechallenge in 40 NSCLC patients showed longer mPFS and ORR than ours (6.8 *vs.* 5.33 months; 22.5% *vs.*

10.3%) (30). There are several possible reasons for this discrepancy. Our study enrolled patients with unresectable stage III or IV NSCLC, while this study included early-stage NSCLC patients. In addition, our study enrolled patients without driver mutations and were directly rechallenged with ICI beyond PD after the first-line immunotherapy treatment. While this study included 17 patients who carried mutated genes and seven patients received chemotherapy or targeted therapy prior to ICI rechallenge treatment. Although the study suggested that ICI rechallenge may be an option for NSCLC after progress to immunotherapy, the results of all prognostic factors were nonsignificant. Further prospective studies with larger sample size are needed.

Among the 165 patients who received ICI rechallenge in the second-line treatment, the median PFS2 was 3.68 months (95% CI: 2.46–4.90) in the resistant group and 5.91 months (95% CI: 5.29–6.54) in the responder group (P=0.014). Multivariate analysis of the ICI rechallenge group (n=165) also showed that response to initial ICIs treatment was an independent factor associated with PFS2 (P=0.015). The results suggested that the efficacy of ICI rechallenge correlated with response to first-line immunotherapy. A Japanese study of PD-L1 rechallenge in 17 patients with advanced NSCLC showed that a good response of initial ICIs treatment may be one of the clinical features that predicts the efficacy of subsequent ICI rechallenge (31). Similarly, the results of a systematic review including 2,100 patients from 17 studies demonstrated the length of PFS1 was an independent prognostic factors of PFS2 (P=0.006) (32). Our study provides valuable recommendations for clinical practice that NSCLC patients who respond better to first-line immunotherapy can still benefit from ICI rechallenge.

Similar incidences of AEs at any grade were observed in the different second-line treatment groups (P=0.334), and most of them were classified as grade 1 or 2 AEs. Similarly, no statistically significant differences in the incidence of grade 3 and 4 AEs were observed (P=0.162). In the C + A group, two of 38 (5.3%) patients experienced grade 4 TRAEs. The two cases were myelosuppression and hyperuricosuria, respectively. In the ICIs + A group, three of 77 (3.9%) patients experienced grade 4 TRAEs as myelosuppression. In the ICIs + C + A group, four of 51 (7.8%) patients experienced grade 4 myelosuppression and one of them died within three months after the initiation of second-line treatment because of the severe AEs. Similar incidences of TRAEs at any grade were observed in ICI rechallenge group and non-rechallenge group (63.0% *vs.* 71.2%, P=0.259), and no statistically significant differences in the incidence of grade 3 and 4 AEs were observed between the two groups (15.2% *vs.* 22.0%, P=0.227). The ICI rechallenge group showed no new safety signals compared with patients who discontinued ICIs treatment. Similarly, second-line ICI rechallenge therapy showed acceptable toxicity profile in patients with a good response to first-line immunotherapy.

PD-L1 expression levels, tumor mutational burden (TMB), and tumor-infiltrating lymphocytes (TILs) are regarded as some of the biomarkers predicting the efficacy of ICIs treatment. PD-L1 is a surface molecule which is expressed on different types of cells. Many studies have confirmed that PD-L1 expression was a predictive biomarker for the efficacy of ICIs (33,34). In 2018, Rizvi *et al.* (35) observed a correlation between high TMB and clinical outcomes for patients with NSCLC on immunotherapy treatment, which confirmed that high TMB tended to predict the efficacy of immunotherapy. TILs play a key role in the immunogenic reaction against tumors, and several studies supported TILs as a prognostic and predictive biomarker (36,37). However, the identification and testing of robust and reliable predictive biomarkers are not sufficiently precise. Due to insufficient information on such biomarkers in patients enrolled in our study, we did not explore meaningful biomarkers in patients who responded well to initial ICIs treatment.

In spite of the fact that our study provides several significant references for the selection of second-line treatment options beyond disease progression, there are several limitations. First, stratified analysis of PD-L1 expression was not available because some patients were not tested for PD-L1 expression, which may have overlooked the impact on ICI monotherapy efficacy. Second, this was a clinical retrospective study, which may lead to selection bias. Further studies should examine efficacy and safety of different second-line treatment regimens in large randomized prospective cohorts, and determine which patient groups can easily benefit from ICI rechallenge therapy.

Conclusions

Our study suggested that ICI rechallenge therapy beyond disease progression did not improve clinical outcomes in patients with NSCLC, but no new safety signals emerged. However, some patients can benefit from immunotherapy

rechallenge. In our study, patients with favorable response to initial ICIs treatment still showed significant efficacy and acceptable toxicity profile of subsequent ICI rechallenge therapy. Considering that the optimal choice for second-line treatment after initial treatment with ICIs remains inconclusive, our study may provide important references for clinical decision-making.

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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 Academic Ethics Committee of Jiangsu Cancer Hospital [No. (2023)082] and individual consent for this retrospective analysis was waived.

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