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Safety and efficacy of rechallenge with immune checkpoint inhibitors and anlotinib in advanced non-small cell lung cancer without targetable driver mutations: a retrospective analysis

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Abstract

Objective This study assessed the safety and efficacy of rechallenging patients in advanced non-small cell lung cancer (NSCLC) without targetable driver mutations using a combination of immune checkpoint inhibitors (ICIs) and anlotinib following progression after prior immunotherapy.

Methods A retrospective analysis was performed on 14 patients who received rechallenge with ICIs combined with anlotinib at the First Affiliated Hospital of Guangzhou University of Chinese Medicine. China, between March 2020 and June 2024.

Results The study observed an objective response rate of 28.6% and a disease control rate of 92.9%. The median progression-free survival (PFS) was 11.7 months, with programmed death-ligand 1 (PD-L1)-positive patients demonstrating significantly longer PFS (13.0 months) compared with PD-L1-negative or unknown patients (10.3 months, $P=0.048$). Toxicity was manageable, with most adverse events being mild to moderate in severity. Only one case (7.1%) of grade 3 adverse events was reported, and no treatment-related fatalities occurred.

Conclusion ICIs combined with anlotinib as a rechallenge therapy exhibited promising efficacy and an acceptable safety profile in patients with advanced NSCLC without targetable driver mutations. These findings suggest a potential treatment option for patients with post-immunotherapy progression.

Keywords Non-small cell lung cancer, Immune checkpoint inhibitors, Anlotinib, Rechallenge

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Introduction

Globally, lung cancer is one of the foremost causes of cancer-related mortality, with survival rates consistently trailing behind those of other cancer types. Non-small cell lung cancer (NSCLC) represents approximately 85% of all lung cancer cases [1, 2]. Genetic diagnostic methods allow for the evaluation of driver gene mutations in NSCLC, which enables targeted therapies for patients with positive mutations. In recent years, tumor immunotherapy has emerged as a central focus in anticancer treatment research aimed to optimize therapeutic approaches. Currently, clinically approved immune checkpoint inhibitors (ICIs) primarily include those targeting programmed cell death protein-1 (PD-1), its ligand programmed death-ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4). Multiple immunotherapeutic regimens are approved for clinical use, addressing a range of pathological types and stages of lung cancer. Despite the broadening clinical use of ICIs, approximately only 30–50% of patients receiving these agents as first-line therapy experience only transient or no benefit, indicating immune resistance and subsequent disease progression [3].

NSCLC without targetable driver mutations accounts for approximately 40–50% of the total lung cancer population [4]. Current guidelines recommend first-line treatment options, such as immune monotherapy, platinum-based doublet chemotherapy, or a combination of immunotherapy and chemotherapy, for this patient population. After resistance to first-line immunotherapy, subsequent treatment options remain limited. Increasing evidence suggests that, given the dynamic nature of immune responses and the enduring benefits of ICIs, immune rechallenge could be a promising therapeutic strategy. A retrospective analysis of a Phase III trial found that patients who continued atezolizumab treatment after disease progression had a significantly longer median overall survival (OS) rate [5]. A recent meta-analysis, largely based on small retrospective cohort studies, demonstrated that ICI rechallenge provides favorable long-term efficacy in patients with NSCLC [6].

Combination therapies have attracted considerable attention in the development of therapeutic approaches for advanced NSCLC. Anlotinib, a novel multi-targeted tyrosine kinase inhibitor, has shown significant efficacy in inhibiting tumor angiogenesis and proliferation signaling pathways. Clinical studies have demonstrated that treatment with anlotinib produces substantial improvements in OS and progression-free survival (PFS) among NSCLC patients. Anlotinib is approved as a third-line treatment option for NSCLC in China [7]. The combined use of immunotherapy and angiogenesis inhibitors has significant theoretical potential for synergistic effects. This approach activates the immune system to target tumor cells via immunotherapy while using anti-angiogenic agents to improve the tumor microenvironment, enhance immune cell infiltration, and increase the efficacy of immunotherapy [8].

This study aimed to assess the safety and efficacy of rechallenging advanced NSCLC patients without targetable driver mutations with ICIs combined with anlotinib following progression on immunotherapy. Through conducting a retrospective analysis of clinical data, this research sought to provide robust evidence for clinical decision-making, address existing gaps in treatment strategies for post-immunotherapy resistance, and contribute valuable insights to improve the prognosis of patients with advanced NSCLC.

Methods

Patient eligibility

A retrospective analysis was carried out with patients with advanced NSCLC without targetable driver mutations who underwent rechallenge therapy with ICIs combined with anlotinib after progression on immunotherapy. Participants were treated at the Department of Radiation Oncology, First Affiliated Hospital of Guangzhou University of Chinese Medicine, China, from March 2020 to June 2024. Inclusion criteria were: 1) diagnosis of NSCLC confirmed by pathological examination; 2) lacking targetable driver mutations; 3) resistance to prior ICIs therapy; 4) rechallenge with a combination of ICIs and anlotinib; 5) presence of measurable target lesions as identified through imaging; 6) availability of complete clinical and pathological data, including retrievable laboratory results during treatment, such as routine blood tests, biochemical analyses, and tumor markers; and 7) regular imaging follow-ups with accessible efficacy evaluation data. This study was reviewed and approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Guangzhou University of Chinese Medicine.

Observation indicators and data collection

Clinical data were collected for each patient, including age, sex, tumor location, pathological classification, and prior treatment regimens. Treatment efficacy was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1), which categorizes outcomes as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) [9]. The objective response rate (ORR) was calculated as [CR + PR]/total cases × 100%, while the disease control rate (DCR) was calculated as [CR + PR + SD]/total cases × 100%. Patients lost to follow-up or without observed events by the end of the follow-up period were excluded. Toxicities were

evaluated according to the National Cancer Institute Common Toxicity Criteria version 5.0 (CTC5.0).

Follow-up

All the patients who were evaluated for tumor response had PFS and OS. PFS was defined as the interval from the initiation of treatment to either the confirmation of PD or death from any cause. OS was defined as the interval from the initiation of treatment to death from any cause. The follow-up period was completed on September 30, 2024.

Statistical analysis

Statistical analyses were conducted using SPSS software (version 26.0). Categorical variables were summarized as counts and percentages (n [%]). Univariate analysis of prognostic factors was performed using the Kaplan–Meier method, with between-group survival comparisons assessed by the log-rank test, PFS curves were subsequently plotted. A P value <0.05 was considered statistically significant.

Result

Patient characteristics

Participants included 14 patients with advanced NSCLC without targetable driver mutations who were treated with PD-L1 inhibitors combined with anlotinib following progression on prior immunotherapy. Of these, 71.4% ($n=10$) were male and 28.6% ($n=4$) were female. The median age was 66.1 years, with an equal distribution of patients aged ≤65 years (50.0%, $n=7$) and >65 years (50.0%, $n=7$). Histologically, adenocarcinoma was the most common subtype, accounting for 64.3% ($n=9$) of cases, followed by squamous cell carcinoma (28.6%, $n=4$) and adenosquamous carcinoma (7.2%, $n=1$). Regarding disease stage, 14.3% ($n=2$) of patients were at stage III, and 85.7% ($n=12$) were at stage IV. At the start of immune rechallenge therapy, 50.0% ($n=7$) of patients had distant metastases, including bone metastases in 28.6% ($n=4$), brain metastases in 7.1% ($n=1$), liver metastases in 14.3% ($n=2$), and adrenal metastases in 7.1% ($n=1$). In terms of smoking history, 71.4% ($n=10$) of patients were non-smokers, while 28.6% ($n=4$) had a history of smoking. Analysis of PD-L1 expression showed that 35.7% ($n=5$) of patients were PD-L1 positive, whereas 64.3% ($n=9$) were either PD-L1 negative or had unknown PD-L1 status. Further details are shown in Table 1.

Table 1 Clinicopathological features of lung cancer patients

Characteristics	Number	Percentage (%)
Gender		
Male	10	71.4
Female	4	28.6
Age(years)		
Mean	66.143	
≤ 65	7	50.0
> 65	7	50.0
ECOG PS		
0–1	10	71.4
2	1	7.2
3	3	21.4
Histologic type		
Adenocarcinoma	9	64.3
Squamous	4	28.6
Adenosquamous	1	7.2
Staging		
Stage III	2	14.3
Stage IV	12	85.7
Metastasis		
Yes	7	50.0
No	7	50.0
Metastatic sites at ICI rechallenge initiation		
Bone	4	28.6
Brain	1	7.1
Liver	2	14.3
Adrenal gland	1	7.1
Smoking		
No	10	71.4
Yes	4	28.6
PD-L1		
Positive	5	35.7
Negative or Unknown	9	64.3

Abbreviations: PD-L1 Programmed cell death 1 ligand 1

Immunotherapy regimen

During the initial immunotherapy phase, all patients received chemotherapy combined with ICIs, with the most commonly administered regimens being paclitaxel/nab-paclitaxel or pemetrexed combined with platinum. Maintenance immunotherapy was selected by 42.9% of patients ($n=6$). Of the patients undergoing initial immunotherapy, 50.0% achieved a best response of CR or PR ($n=7$). A total of 71.4% of patients achieved a PFS >6 months ($n=10$). During immune rechallenge, only 28.6% of patients ($n=4$) switched to a different ICI. Details are shown in Table 2.

Clinical effect

Among the 14 patients, the ORR was 28.6%, with 4 patients (28.6%) achieving PR. The DCR was 92.9%, including 9 patients (64.3%) with SD. One patient (7.1%) experienced PD, and a CR was not observed. The

Table 2 Initial immunotherapy patient characteristics

	Number	Percentage (%)
Initial immunotherapy regimen		
paclitaxel/nab-paclitaxel ± platinum + ICI	7	50.0
pemetrexed ± platinum + ICI	6	42.9
pemetrexed ± platinum + bevacizumab + ICI	1	7.1
Immune maintenance		
Yes	6	42.9
No	8	57.1
Rechallenge with the same ICI		
Yes	8	57.1
No	6	42.9
Best overall response to initial ICI therapy		
CR/PR	7	50.0
SD/PD	7	50.0
Initial ICI therapy PFS		
> 6 months	10	71.4
≤ 6 months	4	28.6

median PFS was 11.7 months (95% CI: 6.399–17.001; Fig. 1). By the end of follow-up, the maximum observed PFS was 14.7 months.

Univariate analysis revealed no significant associations between PFS and gender (P= 0.446), age (P= 0.434), ECOG PS (P= 0.164), histologic subtype (P= 0.166), disease stage (P= 0.82), smoking status (P= 0.939), metastasis (P= 0.475), site of metastasis (P= 0.311), immunotherapy maintenance (P= 0.962), switching ICIs (P= 0.776), the best response to initial immunotherapy (P= 0.156), or initial ICI therapy PFS (P= 0.304). Details are shown in Table 3.

The median PFS for PD-L1-positive patients was 13.0 months (95% CI: 4.86–21.140), compared with 10.3 months for PD-L1-negative or unknown patients (P= 0.048), indicating a significant PFS advantage for PD-L1-positive patients (Fig. 1).

Toxicity evaluation

Toxicity assessments were performed for all patients. Adverse events of varying severity were reported in nine patients (64.3%), predominantly including liver injury, adrenal insufficiency, hand-foot syndrome, joint pain, pruritus, rash, diarrhea, and hemoptysis. No patients discontinued treatment due to adverse events. Grade 3 adverse events were observed in 7.1% of cases, with only one instance of grade 3 hand-foot syndrome. Anlotinib was initiated at 12 mg daily in all patients, with dose reduction to 8 mg required in only one case (7.1%) due to grade 3 hand-foot syndrome. Comprehensive details of the toxicity evaluation are shown in Table 4.

Discussion

The potential of ICIs in cancer therapy has attracted significant attention in recent years, with researchers investigating new therapeutic strategies aimed at achieving enhanced treatment outcomes. However, numerous patients discontinue immunotherapy as a result of PD, immune-related adverse events (irAEs, or clinical judgment. Therapeutic options after immunotherapy failure are limited, with most patients transitioning to subsequent-line chemotherapy. Given the dynamic nature of immune responses and the sustained benefits of ICIs,

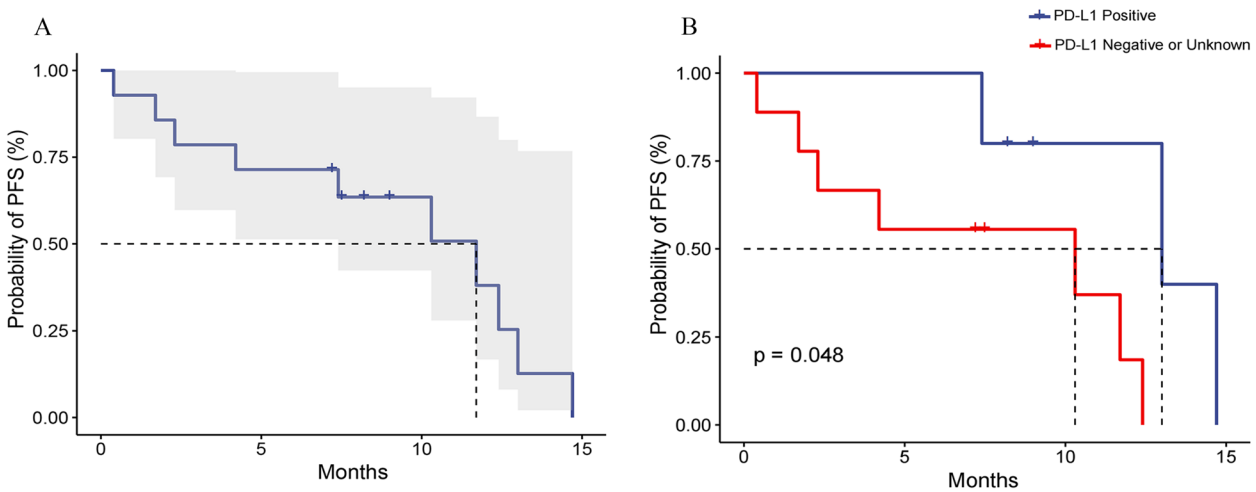

Fig. 1 Progression-free survival of patients treated with immunotherapy combined with anlotinib. **A** 14 patients received immunotherapy combined with anlotinib, 11.7 months, 95% CI: 6.399–17.001; (**B**) for patients as PD-L1 positive expression vs. as PD-L1 negative or unknown, 13.0 vs. 10.3 months (P= 0.048)

Table 3 Univariate analysis of PFS

Characteristics	PFS	95%CI	*P*-value
Gender			0.446
Male	11.70	8.245–15.155	
Female	7.4	0–17.879	
Age(years)			0.434
≤ 65	12.4	1.429–23.371	
> 65	11.7	NA	
ECOG PS			0.164
0–1	11.7	3.745–19.655	
2	14.7	NA	
3	7.4	0–18.602	
Histologic type			0.166
Adenocarcinoma	11.3	2.165–18.436	
Squamous	12.4	11.280–13.520	
Adenosquamous	4.2	NA	
Staging			0.82
Stage III	14.7	NA	
Stage IV	10.3	3.722–16.878	
Smoking			0.939
No	11.7	5.303–18.097	
Yes	10.3	2.264–18.336	
PD-L1			0.048
Positive	13.0	4.86–21.140	
Negative or Unknown	10.3	0–22.39	
Metastasis			0.475
Yes	11.7	1.489–21.911	
No	10.3	1.376–19.224	
Metastatic sites at ICI rechallenge initiation			0.311
Bone	7.4	0–15.933	
Brain	1.7	NA	
Liver	11.7	NA	
Adrenal gland	2.3	NA	
Immune maintenance			0.962
Yes	10.3	0–21.751	
No	7.4	0–17.141	
Rechallenge with the same ICI			0.776
Yes	11.7	3.414–19.986	
No	10.3	0–22.276	
Best overall response to initial ICI therapy			0.156
CR/PR	12.4	11.260–13.540	
SD/PD	7.4	0–15.612	
Initial ICI therapy PFS			0.304
> 6 months	11.7	8.822–14.578	
≤ 6 months	4.2	0–9.786	

Abbreviations: PD-L1 Programmed cell death 1 ligand 1

there is growing evidence that immune rechallenge could be a promising therapeutic strategy. The efficacy of ICIs in rechallenge following progression on frontline therapy remains a subject of debate. Multiple factors complicate treatment and affect rechallenge outcomes, for example, patients' clinical and pathological characteristics, diverse rechallenge strategies, the duration of treatment interruption, and prior therapies undertaken before

Table 4 Main toxicities of immunotherapy combined with anlotinib

Toxicity	Grades 1–2	Grades 3
Liver toxicity	2	0
Adrenocortical insufficiency	1	0
Hand-foot syndrome	1	1
Arthralgia	1	0
Pruritus	1	0
Rash	2	0
Diarrhea	2	0
Hemoptysis	1	0

rechallenge. Recent research suggests that ICI rechallenge may provide additional clinical benefits for patients with NSCLC. Fujita et al. (2018) reported an ORR, DCR, and PFS of 8.3%, 41.7%, and 3.1 months, respectively, in a retrospective analysis of advanced NSCLC patients previously treated with nivolumab [10]. Similarly, Niki et al. (2018) observed an ORR, DCR, and PFS of 27.2%, 45.5%, and 2.7 months, respectively, in 11 advanced NSCLC patients rechallenged with nivolumab or pembrolizumab [11]. Additionally, Katayama et al. (2019) documented an ORR, DCR, and PFS of 2.9%, 45.7%, and 2.7 months, respectively, in 19 NSCLC patients treated with nivolumab, pembrolizumab, or atezolizumab [12].

For patients with advanced NSCLC without targetable driver mutations, treatment options are limited after progression on ICIs and platinum-based chemotherapy [13]. Subsequent therapies typically include chemotherapy monotherapy or combinations with angiogenesis inhibitors [13]. Nevertheless, these approaches demonstrate modest efficacy in advanced NSCLC, with a median OS of only 7.3 months [14]. In this study, immune rechallenge therapy in 14 patients with advanced NSCLC without targetable driver mutations achieved an ORR of 28.6%, a DCR of 92.9%, and a median PFS of 11.7 months. These findings suggest that PFS exceeds the outcomes observed in NSCLC patients treated with salvage chemotherapy following immunotherapy failure [15–17].

PD-L1 expression is the most widely employed biomarker. PD-L1 expression significantly impacts the therapeutic efficacy of ICIs, with PD-L1 positivity representing the optimal condition for their effectiveness [18]. Of the 11 NSCLC patients who underwent rechallenge therapy as reported by Niki et al. (2018), five patients with high PD-L1 expression achieved either a PR or SD [11]. Patients in this study with PD-L1 positivity achieved a PFS of 13.0 months, compared with 10.3 months in those with negative or unknown PD-L1 expression, indicating a more favorable prognosis for patients with PD-L1 positivity. Currently, received wisdom indicates that the reliability of PD-L1 expression in predicting the outcomes of immune rechallenge remains uncertain. Moreover, both the existing literature and this study have only evaluated PD-L1 expression levels during initial ICI therapy, leaving potential changes in PD-L1 expression following initial immunotherapy unexplored. However, reassessing PD-L1 expression before rechallenge is critically important. Notably, however, retesting PD-L1 expression after immune resistance is infrequently performed in clinical practice.

Regarding safety, immune rechallenge demonstrated an acceptable safety profile, with only one reported case of grade 3 adverse events, no treatment-related fatalities, and no instances of treatment discontinuation due to adverse events. The high maintenance rate of the 12 mg anlotinib(92.9%) underscores its manageable toxicity profile in combination with ICIs. Notably, while 3 patients (21.4%) experienced grade 1–2 irAEs (including rash and hypothyroidism), these events were managed symptomatically without requiring immunotherapy dose interruption or modification. Although this study did not analyze the relationship between irAEs during initial therapy and those occurring during rechallenge, caution is warranted when rechallenging patients with a history of significant irAEs.

The most frequently employed rechallenge regimen involves ICIs combined with chemotherapy and/or anti-angiogenic therapy. Ongoing clinical studies investigating rechallenge strategies for immune resistance have found that cross-line treatments, including ICIs combined with anti-angiogenic therapy, show promising efficacy and manageable safety profiles [19]. The COSMIC-021 study found that the combination of atezolizumab and cabozantinib resulted in favorable clinical efficacy and safety in advanced non-squamous NSCLC patients who progressed following prior ICI treatment. The therapy achieved an ORR of 19%, a DCR of 80%, a median PFS of 4.5 months, and a median OS of 13.8 months. Grade ≥ 3 treatment-emergent adverse events were reported in 53% of cases. Notably, clinical benefits were observed across all treatment cohorts regardless of PD-L1 expression levels [20]. Targeting angiogenesis has long been a central focus in the treatment of NSCLC patients with disease progression after immunotherapy. Mechanistically, angiogenesis and immune suppression are deeply interconnected processes. Anlotinib, the only NMPA-approved anti-angiogenic drug for NSCLC and SCLC, modulates tumor vasculature, promotes immune cell infiltration, enhances the cytotoxicity of immune effector cells, and facilitates their targeted delivery to tumor sites, thereby amplifying the effectiveness of immunotherapy [21, 22]. Anlotinib exerts synergistic antitumor effects with

ICIs by directly inhibiting signaling pathways involved in tumor cell growth and proliferation [23]. To date, no studies have investigated the use of anlotinib as a combination therapy in rechallenge settings. Findings from this study provide meaningful insights and serve as a valuable reference for developing rechallenge treatment strategies.

This retrospective study inherently possesses certain limitations. First, the relatively small sample size may introduce bias into the findings. Although retrospective analyses often suggest that factors such as smoking history and the best response to initial immunotherapy may affect the efficacy of rechallenge treatment, the small sample size in this study limits accurate prediction of outcomes. Large-scale, multicenter prospective studies with longer follow-up periods are needed to validate these findings. Second, the study's retrospective design poses challenges in fully accounting for potential confounding factors, such as concomitant medications administered during treatment, which may affect clinical outcomes. Third, the retrospective nature of the study may lead to incomplete data collection for some patients, including inadequate testing of immune-related biomarkers, thereby constraining the analysis of predictive factors for treatment response.

Rechallenge therapy presents significant promise as a potential treatment strategy. This study provides preliminary evidence supporting the safety and efficacy of ICIs combined with anlotinib for rechallenge in advanced NSCLC without targetable driver mutations after progression on immunotherapy.

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Authors' contributions
Xinrong Chen conceived and designed the study and wrote the manuscript. Ke Wang and Yongxin Liao analysed and interpreted the data. Chuangjie Zheng contributed to data collection and interpretation. Deyu Yang and Zhichao Li participated in data interpretation. Linzhu Zhai conceived and designed the study, and revised major content of this manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analyzed during the current study can be accessed from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The publication was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine (No. K-2025–041). This study was a retrospective study, so the requirement for patient consent was waived. All patients provided written informed consent prior to treatment.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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