Original Article

Efficacy, prognosis and safety analysis of anti-PD-1/PD-L1 inhibitor rechallenge in advanced lung cancer patients: a cohort study

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Background: The rechallenge of immune checkpoint inhibitors (ICI) is now an optional strategy for patients who discontinued ICI due to immune-related adverse events (irAEs) or disease progression. However, little data is available for the prognosis and prognostic factors of patients receiving ICI rechallenge treatment in advanced lung cancer patients. Our study aimed to explore the efficacy, prognosis and safety of patients who received anti-programmed cell death-1/programmed cell death ligand 1 (anti-PD-1/PD-L1) inhibitor rechallenge.

Methods: In our retrospective cohort study, data of advanced lung cancer patients who received anti-PD-1/PD-L1 inhibitor and discontinued due to irAEs or disease progression were collected from December 2016 to August 2021. Enrolled patients were categorized into two groups: rechallenge group (R group) and non-rechallenge group (NR group). Progression-free survival (PFS), overall survival (OS), disease control rate (DCR) and safety data were analyzed. Cox model and subgroup analysis were analyzed according to baseline characteristics, ICI type, the reason for discontinuing ICI, etc. According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1), evaluation was performed routinely every 6–8 weeks after initiating treatment with the PD-1/PD-L1 inhibitor. The last follow-up in the study was on September 20, 2021.

Results: Eighty-one patients who met our inclusion criteria were enrolled. In the whole cohort, the R group achieved better OS than the NR group [hazard ratio (HR) =0.176; 95% confidence interval (CI): 0.065–0.477; P=0.001). In the irAEs group, the survival analyses showed a trend toward improved OS in the rechallenge subgroup (HR =0.287; 95% CI: 0.081–1.025; P=0.055), and a promising DCR of 75% after an ICI rechallenge. Additionally, the exploration of safety outcomes indicated an acceptable recurrence rate (22.5%) of irAEs and an early onset of irAEs after an ICI rechallenge. In the disease progression group, the rechallenge subgroup did not improve OS (HR =0.214; 95% CI: 0.027–1.695; P=0.144), and the DCR of the rechallenge subgroup was 40% after ICI rechallenge.

Conclusions: ICI rechallenge might be an attractive option for patients who discontinue treatment due to irAEs. For patients with disease progression, further research should be conducted. The recurrence of irAEs and their early onset during the second round of ICI should be considered.

Keywords: Immune checkpoint inhibitor (ICI); immune-related adverse event (irAE); immune checkpoint inhibitor rechallenge (ICI rechallenge); disease progression

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Introduction

In recent years, immune checkpoint inhibitor (ICI) has completely changed the treatment pattern of advanced lung cancers (1). A previous study has shown that the activation of immune checkpoints, such as the programmed cell death-1/programmed cell death ligand 1 (PD-1/PD-L1) signaling pathway, can attenuate the antitumor ability of cytotoxic T cells and lead to an immunosuppressive tumor microenvironment, which contributes to tumor immune escape. Anti-PD-1/PD-L1 inhibitors can hamper the immune escape of tumor cells and enhance the body's endogenous antitumor activities (2).

Pembrolizumab (an anti-PD-1 inhibitor) was approved as a second-line treatment for advanced non-small-cell lung cancer (NSCLC) by the U.S. Food and Drug Administration in 2015; since then, several anti-PD-1/PD-L1 inhibitors have shown promising antitumor effects against lung cancers (3). Despite the considerable clinical benefits of ICIs in lung cancer patients, some patients discontinue ICIs due to disease progression, toxicity, or completion of a fixed treatment course (4,5). To achieve better clinical outcomes of ICIs in these patients, ICI rechallenge, using the same or another ICI after the initial discontinuation, has attracted much attention in clinical practice (6-8).

The efficacy of rechallenging with ICIs after ICI discontinuation has been evaluated in several solid tumors, including melanoma, renal cell carcinoma and NSCLC (9-11). For eighty metastatic patients who discontinued anti-cytotoxic T lymphocyte-associated antigen-4 (anti-CTLA-4) inhibitor and anti-PD-1 inhibitor due to immune-related adverse events (irAEs), they were rechallenged with anti-PD-1 inhibitor. In this cohort, the rate of recurrent irAEs was 14% (12). A multicenter cohort enrolled 69 patients with metastatic renal cell carcinoma, and it showed an overall response rate (ORR) of 23% and an irAEs rate of 16% during the ICI rechallenge (13). A meta-analysis included patients who retreated ICI after irAEs, and the results showed lower safety and similar efficacy outcomes compared with initial ICI treatment (5).

For advanced lung cancer patients who have benefited from initial ICI and discontinued ICI owing to irAEs, clinicians and patients tended to reuse ICIs to make full of their efficacy after irAEs were relieved. Patients who discontinued ICI owing to disease progression tend to ICI rechallenge according to philanthropic projects and the lack of new treatment strategies. However, strong concerns about the effectiveness and the recurrence of irAEs during the second round of ICI have hindered the application of rechallenge. Furthermore, there were no high-quality evidence of whether patients with disease progression would benefit from the retreatment of ICI. The efficacy-safety balance of immunotherapy rechallenge in lung cancer patients has not yet been fully clarified. Thus, we investigated the efficacy, clinical outcomes and safety outcomes of patients who discontinued anti-PD-1/PD-L1 inhibitors due to irAEs or disease progression and subsequently received additional ICI at a later date. We present the following article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-360/rc).

Methods

In this cohort study, we analyzed the overall survival (OS) in the rechallenge group (R group) as well as in the non-rechallenge group (NR group) according to the reason for discontinuing ICI. We used subgroup analyses to explore the potential risk factors for clinical outcomes and safety. We evaluated the therapeutic effect in initial and subsequent ICI according to the reason for discontinuation.

Study design and patient enrollment

The flowchart of the study design is presented in *Figure 1*. Clinical data of patients with advanced lung cancers who were hospitalized in the Department of Respiratory and Critical Care Medicine of Ruijin Hospital between December 2016 and August 2021 were collected.

Patients who met the following criteria were enrolled: (I) pathologically confirmed lung cancer; (II) previously received anti-PD-1/PD-L1 inhibitor treatment; (III)

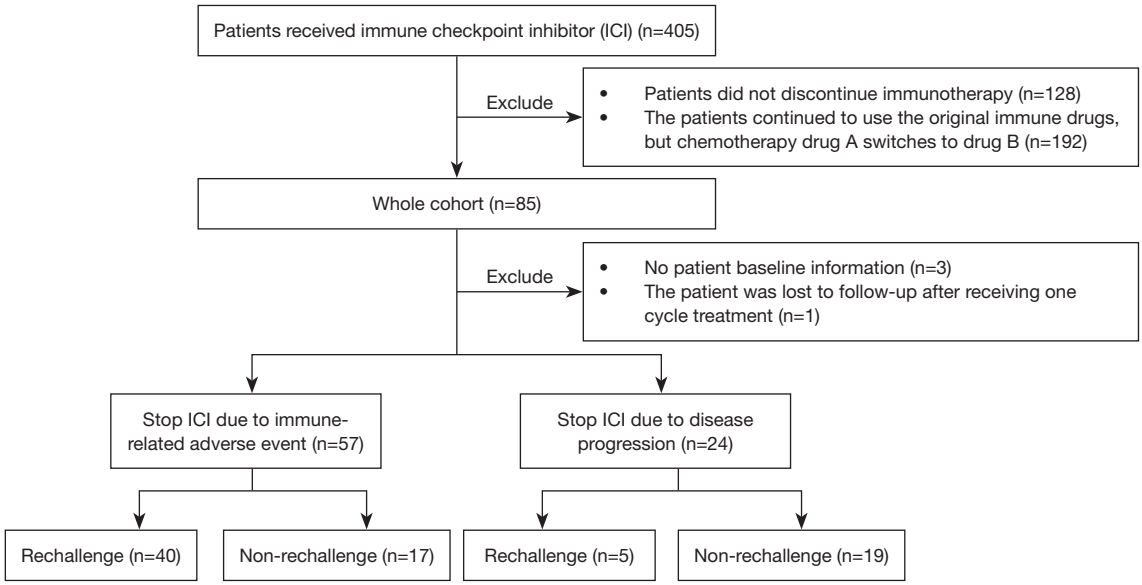

Figure 1 Flow chart of the study design. ICI, immune checkpoint inhibitor.

discontinued anti-PD-1/PD-L1 inhibitor treatment owing to disease progression or irAE; (IV) data were available for evaluation; (V) had a diagnosis of advanced-stage cancer according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system.

Enrolled patients were categorized into two groups according to the following definitions: (I) the R group (n=45): patients who discontinued anti-PD-1/PD-L1 inhibitors for more than 3 weeks and subsequently received anti-PD-1/PD-L1 inhibitors again; and (II) the NR group (n=36): patients who did not retreated with anti-PD-1/PD-L1 inhibitors. Patients were divided into two groups according to the reasons for discontinuation: the irAE group (R1 group, n=40; NR1 group, n=17) and the disease progression group (R2 group, n=5; NR2 group, n=19).

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and the protocol was reviewed and approved by the institutional review board of Ruijin Hospital (Approval No. 2019-72). Individual consent for this retrospective analysis was waived.

Data collection and evaluation

Patient data included sex, age, smoking status, Eastern Cooperative Oncology Group performance status (ECOG PS), clinical stage according to AJCC staging system (the 8th edition), PD-L1 tumor proportion score (TPS), status of metastasis, date of diagnosis, pathological type, therapeutic regimen, and reason for discontinuation.

We assessed and categorized clinical efficacy as either complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), according to the revised RECIST guidelines (version 1.1) (14). The ORR was defined as the percentage of patients with CR and PR. The disease control rate (DCR) was the percentage of patients who achieved CR, PR, or SD. As far as such information bias is concerned, the imaging evaluations of the patients are individually evaluated by two imaging investigators. In case of different imaging evaluations, an internal discussion was planned to unify the assessment.

OS was defined as the time from the first dose of an anti-PD-1/PD-L1 inhibitor to death from any cause. The last follow-up in the study was on September 20, 2021. During the follow-up, evaluation was performed routinely every 6–8 weeks after starting treatment with the PD-1/PD-L1 inhibitor. For patients not admitted to Ruijin hospital subsequently, we obtained the patient's survival status through phone calls and on-site visits.

As shown in *Figure 2*, in the R1 group, progression-free survival (PFS)1 was calculated from the 1st day of the first ICI administration to the start of the second ICI treatment, and PFS2 was calculated from the start of the second ICI treatment to tumor progression or death from any cause. In the NR1 group, PFS1 was calculated from the 1st day of the first ICI administration to the start of another therapy or the end of the initial ICI treatment. PFS2 was calculated

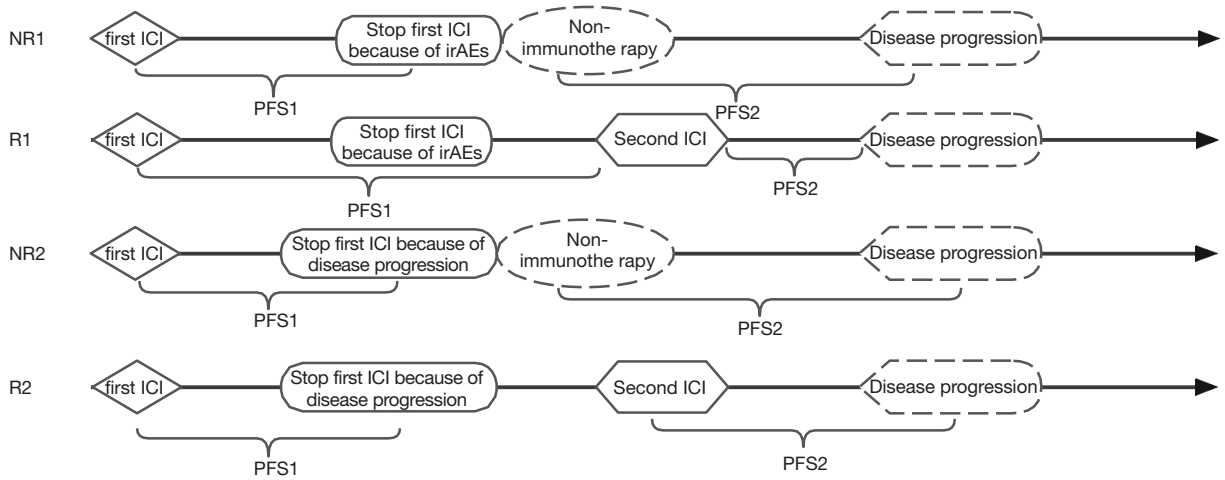

Figure 2 Definition of PFS according to the study design. NR, non-rechallenge; R, rechallenge; ICI, immune checkpoint inhibitor; PFS, progression-free survival; irAEs, immune-related adverse events.

from the end of the initial ICI treatment to tumor progression or death from any cause. In the R2 and NR2 groups, PFS1 was calculated from the start of the first ICI treatment to tumor progression, and PFS2 was calculated from the start of the second ICI treatment or another therapy to tumor progression or death from any cause. Total PFS is the cumulative value of PFS1 and PFS2.

The diagnosis of irAE was confirmed by a multidisciplinary team in Ruijin Hospital. The irAE grade was evaluated according to the fifth Common Toxicity Criteria for Adverse Events (CTCAE) classification (version 5.0).

Statistical analysis

Baseline characteristics are presented as the median and interquartile range (IQR) for continuous variables and the frequency and percentage for categorical variables. For patients with missing data, we defined them as unknown when grouping. Our missing data analysis procedures used missing completely at random (MCAR) assumptions. If the patient was lost to follow-up, we considered the last day in the hospital as the time of his death. In statistical analysis, we set the survival time of patients who were lost to follow-up as a cutoff value. PFS and OS were calculated using the Kaplan-Meier method, and differences were compared using the log-rank test. The OS rate was calculated using SPSS 24.0 (IBM, Armonk, NY, USA). Univariate and multivariate Cox regression analyses were performed to identify predictors of OS. Factors that might be associated with OS risk in the univariate analysis ($P<0.050$) were included in the multivariate Cox regression analysis. A two-tailed P value <0.050 was considered statistically significant. Graphs were drawn using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient population and clinical characteristics

Between December 2016 and August 2021, 405 patients with lung cancer receiving ICI were hospitalized in the Department of Respiratory and Critical Care Medicine of Ruijin Hospital. Of these patients, 85 patients met our inclusion criteria, but 3 patients had no baseline information and one patient was lost to follow up after receiving one cycle treatment. A total of 81 patients who met our inclusion criteria were enrolled in this study. The baseline characteristics are shown in *Table 1*. Regarding the reason for ICI discontinuation, 40 patients in the R group stopped anti-PD-1/PD-L1 inhibitors because of irAEs (R1 group), and 5 patients stopped because of disease progression (R2 group). In the NR group, 17 patients stopped treatment because of irAEs (NR1 group), and 19 stopped because of disease progression (NR2 group). An overview of the duration of the R groups is presented in *Figure 3*.

Efficacy evaluation

The median follow-up of this study was 14.5 months.

Table 1 General characteristics of the study population

Characteristics	Patients, n (%)	
	Rechallenge (n=45)	Non-rechallenge (n=36)
Median age [IQR] (years)	65 [60–71]	63 [57.25–68.50]
Sex		
Male	41 (91.1)	25 (69.4)
Female	4 (8.9)	11 (30.6)
ECOG PS		
0–1	41 (91.1)	32 (88.9)
≥2	4 (8.9)	4 (11.1)
Stage		
III	18 (40.0)	7 (19.4)
IV	27 (60.0)	29 (80.6)
Distant metastasis		
Yes	25 (55.6)	11 (30.6)
No	20 (44.4)	25 (69.4)
Pathology		
Squamous carcinoma	8 (17.8)	4 (11.1)
Adenocarcinoma	26 (57.8)	28 (77.8)
Small-cell lung cancer	8 (17.8)	4 (11.1)
Other[†]	3 (6.7)	0 (0.0)
Smoking status		
Never	13 (28.9)	17 (47.2)
Past and current	32 (71.1)	19 (52.8)
PD-L1 TPS (%)		
Negative	6 (13.3)	2 (5.6)
1–50	8 (17.8)	13 (36.1)
≥50	12 (26.7)	4 (11.1)
Unknown	19 (42.2)	17 (47.2)
Initial immunotherapy		
Anti-PD-1[‡]	37 (82.2)	34 (94.4)
Anti-PD-L1[§]	8 (17.8)	2 (5.6)
Number of ICI rounds		
1	20 (44.4)	15 (41.7)
≥2	25 (55.6)	21 (58.3)
Discontinuation reason		
Disease progression	5 (11.1)	17 (47.2)
IrAEs	40 (88.9)	19 (52.8)

[†], other, poorly differentiated carcinoma; [‡], anti-PD-1, nivolumab, pembrolizumab, camrelizumab, tislelizumab, sintilizumab, toripalimab; [§], anti-PD-L1, atezolizumab, durvalumab. IQR, interquartile range; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death ligand 1; TPS, tumor proportion score; PD-1, programmed cell death-1; ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events.

Fourteen patients in the R group and nine patients in the NR group lost to follow up. Patients in the R group had a better OS compared to those in the NR group [not reached *vs.* 14.56 months; hazard ratio (HR) =0.176; 95% confidence interval (CI): 0.065–0.477; P=0.001; *Figure 4A*]. Although statistical significance was not obtained, there was a trend toward better OS in the R1 group (not reached *vs.* 18.667 months; HR =0.287; 95% CI: 0.081–1.025; P=0.055; *Figure 4B*). No difference in OS between the R2 group and the NR2 group was observed (not reached *vs.* 12.3 months; HR =0.214; 95% CI: 0.027–1.695; P=0.144; *Figure 4C*).

According to the Cox univariate analysis of the whole cohort (*Table 2*), several clinical characteristics were associated with OS, including discontinuation due to disease progression (HR =3.923; 95% CI: 1.645–9.355; P=0.002), distant metastasis (HR =3.752; 95% CI: 1.379–10.212; P=0.010), brain metastasis (HR =3.662; 95% CI: 1.527–8.781; P=0.004), and anti-PD-1/PD-L1 inhibitor rechallenge (HR =0.176; 95% CI: 0.065–0.477; P=0.001).

After entering the above significant factors (P≤0.05) into the multivariate model, we found that receiving anti-PD-1/PD-L1 inhibitor rechallenge was an independent OS-related factor (HR =0.155; 95% CI: 0.031–0.817; P=0.022). Patients who received anti-PD-1/PD-L1 inhibitor rechallenge had an 84.5% lower risk of death. The subgroup analysis showed that the R group received more clinical benefits than the NR group. As shown in *Figure 5*, the following factors were associated with clinical benefit: R group (HR =0.176; 95% CI: 0.065–0.477), male (HR =0.221; 95% CI: 0.075–0.650), PD-L1 ≥1% (HR =0.123; 95% CI: 0.025–0.597), NSCLC (HR =0.239; 95% CI: 0.086–0.667), IV stage (HR =0.155; 95% CI: 0.045–0.533), never smoked (HR =0.080; 95% CI: 0.010–0.627), past and current smoking status (HR =0.252; 95% CI: 0.074–0.864), non-first-line ICI therapy (HR =0.122; 95% CI: 0.027–0.560); PS 0–1 (HR =0.182; 95% CI: 0.066–0.501), and combined other therapy (HR =0.203; 95% CI: 0.073–0.566).

The median PFS was not reached in the R1 group and was 15.43 (95% CI: 13.904–16.963) months in the NR1 group. The HR in the NR1 group *vs.* the R1 group was 0.484 (95% CI: 0.190–1.232; P=0.144; *Figure 6A*). Patients in the R group had a significantly better PFS2 than patients in the NR group (not reached *vs.* 11.233 months; HR =0.094; 95% CI: 0.169–1.149; P=0.085; *Figure 6B*). No difference in PFS between the R2 group and NR2 group was observed (7.1 *vs.* 10.2 months; HR =1.047; 95% CI: 0.328–3.345; P=0.938; *Figure 6C*). The median PFS2 of the R2 group was 3.2 (95% CI: 0–9.849) months. The median

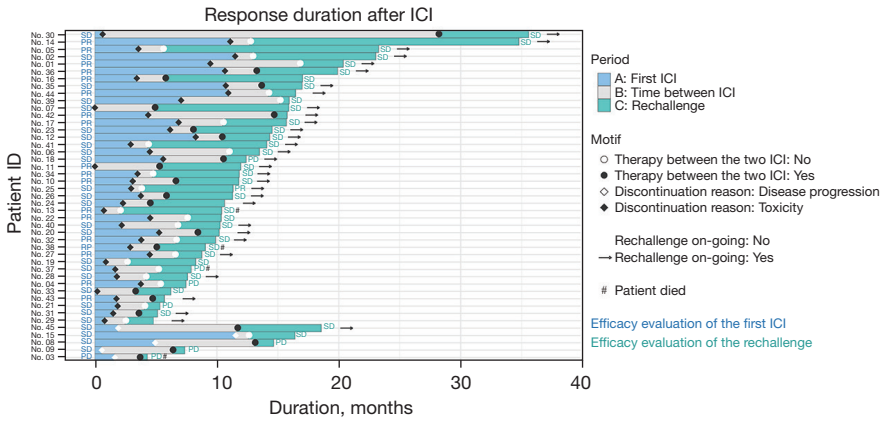

Figure 3 Overview of the duration of the R group. ICI, immune checkpoint inhibitor; SD, stable disease; PR, partial response; PD, progressive disease; R group, rechallenge group.

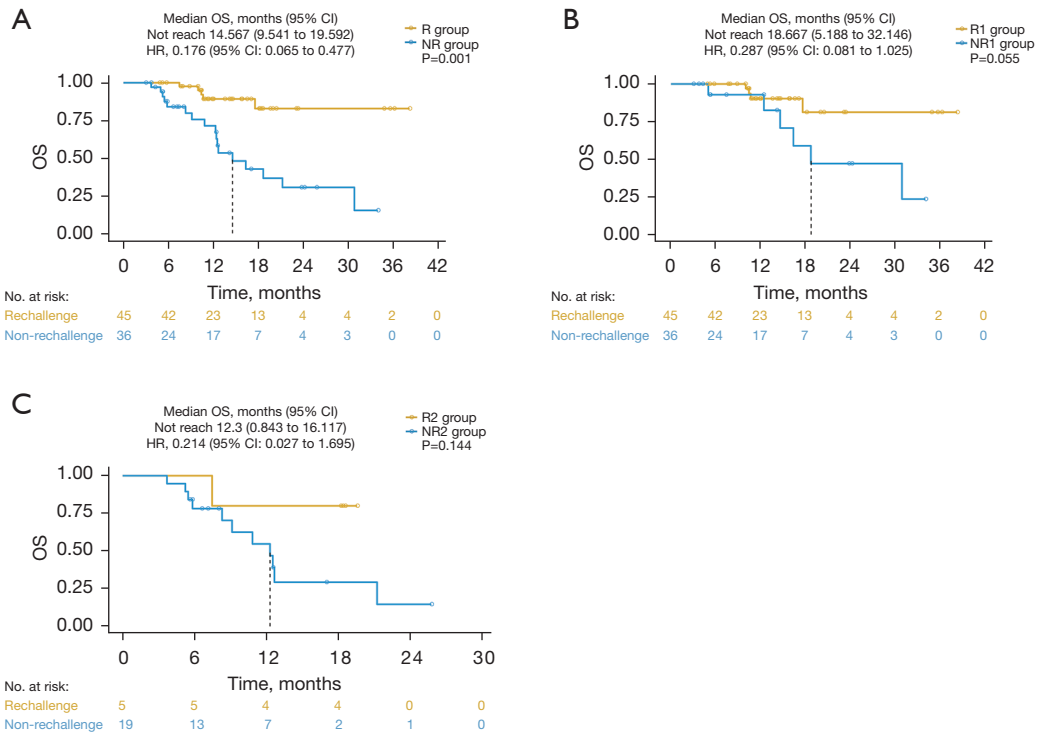

Figure 4 Kaplan-Meier curves for OS. (A) NR vs R groups (B) NR1 *vs.* R1 groups; (C) NR2 *vs.* R2 groups. R group, patients who discontinued anti-PD-1/PD-L1 inhibitor for more than 3 weeks and subsequently received anti-PD-1/PD-L1 inhibitor again; NR group, patients who did not receive rechallenge with anti-PD-1/PD-L1 inhibitor. According to the reasons for discontinuation, patients were divided into two groups: irAE group (R1 and NR1 groups) and disease progression group (R2 and NR2 groups). OS, overall survival; CI, confidence interval; HR, hazard ratio; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand 1; R group, rechallenge group; NR group, non-rechallenge group; irAEs, immune-related adverse events.

Table 2 Univariate and multivariate analysis of OS in whole group

Factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Group				
Non-rechallenge	1		1	
Rechallenge	0.176 (0.065–0.477)	0.001	0.155 (0.031–0.817)	0.022
The reason of disrupt first ICI				
IrAEs	1			
Disease progression	3.923 (1.645–9.355)	0.002		
Sex				
Male	1			
Female	1.799 (0.732–4.418)	0.200		
Age (years)				
<65	1			
≥65	1.476 (0.631–3.413)	0.374		
Smoking statue				
Never	1			
Past and current	0.503 (0.232–1.191)	0.082		
PD-L1 TPS (%)				
<1	1	0.222		
1–49	2.103 (0.427–10.365)			
≥50	2.502 (0.946–6.618)			
Unknown	0.841 (0.175–4.051)			
Clinical stage				
III	1			
IV	3.022 (0.892–10.233)	0.076		
Distant metastasis				
No	1			
Yes	3.752 (1.379–10.212)	0.010		
Pathology				
Small cell lung cancer	1			
NSCLC	0.933 (0.275–3.167)	0.912		
Brain metastasis				
No	1		1	
Yes	3.662 (1.527–8.781)	0.004	0.437 (0.026–7.460)	0.568
Line of receiving first ICIs				
1	1		1	

Table 2 *(continued)*

Table 2 *(continued)*

Factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
≥2	2.775 (0.761–10.117)	0.122	2.816 (0.271–29.216)	0.386
ICIs type				
PD-1	1			
PD-L1	1.359 (0.580–3.182)	0.819		
Combined treatment				
No	1			
Yes	0.577 (0.194–1.712)	0.321		

Anti-PD-1: nivolumab, pembrolizumab, camrelizumab, tislelizumab, sintilizumab, toripalimab; anti-PD-L1: atezolizumab, durvalumab. OS, overall survival; irAE, immune-related adverse effect; PD-L1, programmed cell death ligand 1; TPS, tumor proportion score; NSCLC, non-small-cell lung cancer; ICIs, immune checkpoint inhibitors; PD-1, programmed cell death-1; HR, hazard ratio; CI, confidence interval.

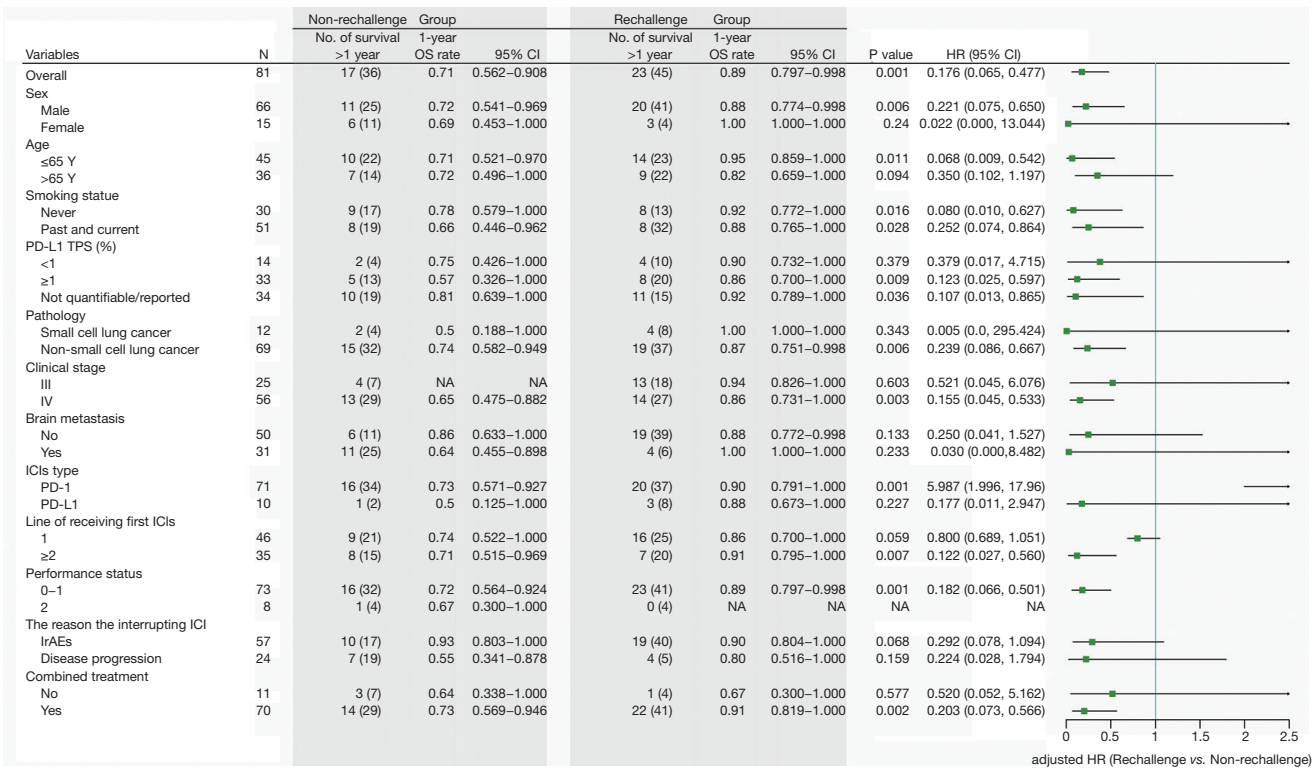

Figure 5 Multivariable analysis of OS in R and NR groups. PD-L1, programmed cell death ligand 1; TPS, tumor proportion score; ICIs, immune checkpoint inhibitors; PD-1, programmed cell death 1 inhibitor; irAEs, immune-related adverse events; OS, overall survival; NA, not available; CI, confidence interval; HR, hazard ratio; R group, rechallenge group; NR group, non-rechallenge group.

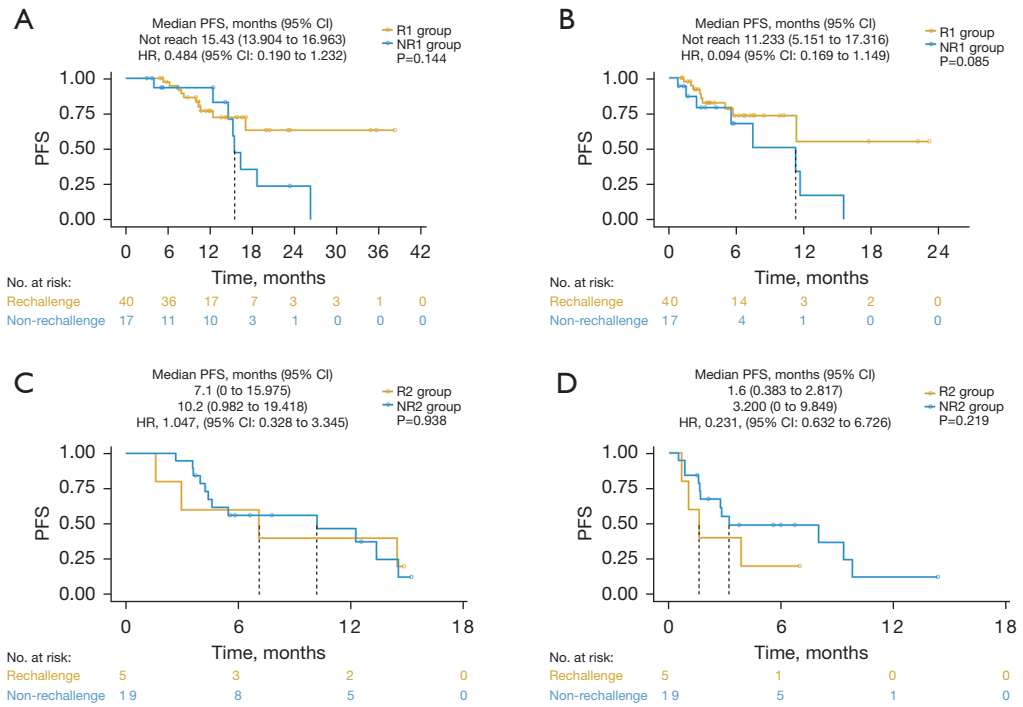

Figure 6 Kaplan-Meier curves for PFS. (A) PFS of the NR1 and R1 groups; (B) PFS2 of the NR1 and R1 groups; (C) PFS of the NR2 and R2 groups; (D) PFS2 of the NR2 and R2 groups. R group, patients who discontinued anti-PD-1/PD-L1 inhibitor for more than 3 weeks and subsequently received anti-PD-1/PD-L1 inhibitor again; NR group, patients who did not undergo rechallenge with anti-PD-1/PD-L1 inhibitor. Patients were divided into two groups according to the reason for discontinuation: the irAE group (R1 and NR1 groups) and the disease progression group (R2 and NR2 groups). PFS, progression-free survival; CI, confidence interval; HR, hazard ratio; R group, rechallenge group; NR group, non-rechallenge group; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand 1; irAEs, immune-related adverse events.

PFS2 of the rechallenge patients was 1.6 (95% CI: 0.383–2.817) months. The HR for the NR2 group *vs.* the R2 group was 0.231 (95% CI: 0.632–6.726; P=0.219; *Figure 6D*).

We also explored the anti-tumor response of rechallenge. Although the rechallenge did not present as good ORR and DCR as in the first use of anti-PD-1/PD-L1 inhibitors, a promising DCR of 75% in the R1 group was observed (*Figure 7A*). In the R2 group, no patients experienced a CR in initial and subsequent treatment. The DCR was 80% in the first ICI and 40% in the second ICI (*Figure 7B*).

Safety of retreatment with ICIs after initial irAE

Forty rechallenged patients experienced irAEs during the first ICI cycle. Specific details of the patients are given in Table S1. Among them, the most common irAE was immune-related pneumonitis (20/40). A total of 22.5% (9/40) of patients experienced irAEs during rechallenge, among which 5 patients experienced the same adverse reactions as before, while 4 patients experienced new irAEs (*Figure 8*). Among these 9 patients, only one suffered grade 3 irAEs, while the remaining 8 patients had grade 1–2 irAEs. The onset time of irAEs during the second cycle of ICI ranged from 10 to 120 days, with a median onset time of 21 days.

Discussion

The efficacy of anti-PD-1/PD-L1 inhibitors in lung cancer has been confirmed by multiple phase III clinical trials, such as Keynote-024 (15), Keynote-189 (16), and Checkmate 227 (17). Anti-PD-1/PD-L1 inhibitors have become promising options for treating advanced lung cancer patients in addition to targeted therapy, chemotherapy and radiotherapy (1). However, in clinical practice, some patients discontinue ICIs for various reasons, such as irAEs and disease progression. Previous studies have shown that

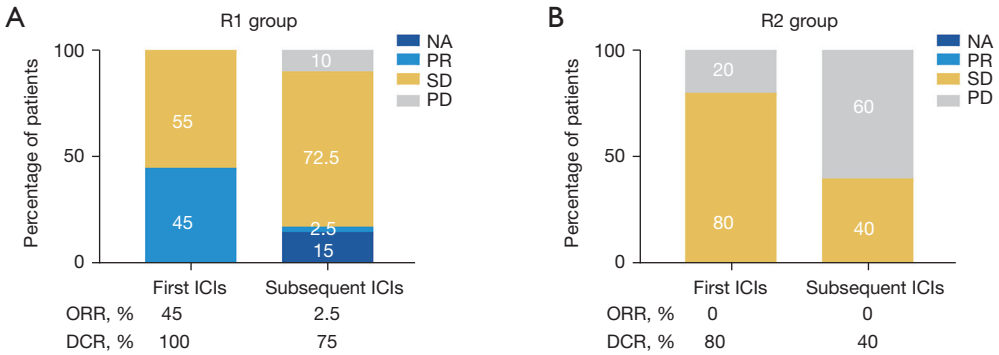

Figure 7 Clinical efficacy of the first and subsequent rounds of anti-PD-1/PD-L1 inhibitor. (A) R1 group; (B) R2 group. R group, rechallenge group; NA, not available; PR, partial response; SD, stable disease; PD, progressive disease; ICI, immune checkpoint inhibitor; ORR, objective response rate; DCR, disease control rate; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand 1.

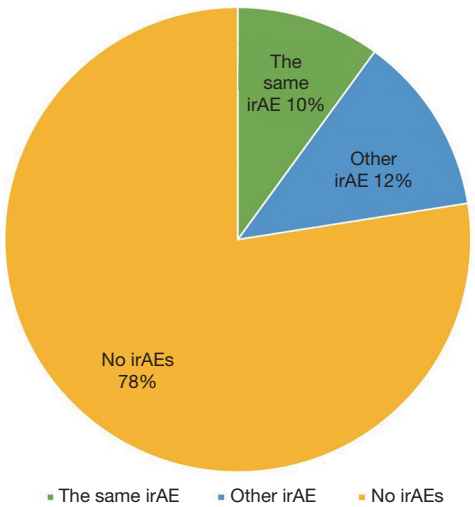

Figure 8 Recurrence rate of irAEs in irAE patients who received anti-PD-1/PD-L1 inhibitor rechallenge. IrAEs, immune-related adverse events; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand 1.

worse clinical outcomes were observed in patients who discontinued ICIs than in continuously treated patients (18-21). Considering the durable anti-tumor effect of ICI rechallenge reported in several case reports (22-24), the clinical benefit of restarting ICI has received widespread consideration.

The efficacy and safety of ICI rechallenge were first explored in melanoma (25). Pollack *et al.* enrolled 80 melanoma patients who discontinued ICIs due to severe irAEs and showed high rates of recurrent or distinct toxicities (12).

Several studies evaluated the clinical outcomes and risk assessment of irAEs in ICI-retreated patients with lung cancer. Mouri *et al.* enrolled 187 nivolumab-treated patients who ceased treatment due to a serious irAE; the results indicated that retreatment had a slightly higher efficacy without a significant increase in irAEs (21). However, another study enrolled 133 patients and showed no survival benefit in the rechallenge and non-rechallenge groups (18). In addition, several studies have looked at patients with NSCLC who stopped ICIs because of disease progression. Watanabe *et al.* enrolled 14 patients and show DCR was 21.4% during the second ICI therapy (26). A study led by Katayama explored the relationship between clinical features and the effectiveness of ICI rechallenge in patients who stopped initial ICI after disease progression, poor ECOG-PS and low body mass index (BMI) at the time of intervention with ICI rechallenge were independent prognosis factors (27).

Notably, the definition of ICI rechallenge remains unclear. A narrow definition is the resumption of ICI after irAEs improve in patients who stopped treatment due to irAEs (28). A more general definition is the resumption of ICI in patients who stopped treatment for any cause, including the adjustment of specific drugs (29,30). Research has mainly focused on the narrow definition of ICI rechallenge. However, the general definition might better match complicated real-world clinical practice. Therefore, we included patients who discontinued anti-PD-1/PD-L1 inhibitors due to irAEs or disease progression and analyzed the efficacy, clinical outcomes and safety outcomes of patients.

Our study included 81 Chinese patients who stopped initial anti-PD-1/PD-L1 inhibitors because of irAEs or

disease progression. These patients were divided into the irAEs group and the disease progression group. Each subgroup was then divided into the R and NR groups based on whether they received ICI again. The survival analysis showed that patients in R group had a better OS compared to patients in NR group (not reached *vs.* 14.56 months; HR =0.176; 95% CI: 0.065–0.477; P=0.001; *Figure 4A*). 22.5% of patients experienced irAEs during the second-time ICI. Our results indicated that improved clinical outcomes and tolerable safety could also be observed in Chinese patients treated with general ICI re-challenge.

We applied subgroup analysis to explore the potential factors associated with the clinical outcomes of rechallenge. Trends in favor of longer OS with the irAEs group were obtained in the R1 group, which was consistent with published studies (18-21). However, a similar result was not seen in the disease progression group, in which rechallenge did not improve the clinical outcomes (PFS and OS). We found heterogeneity in the clinical efficacy in patients who received anti-PD-1/PD-L1 inhibitors in the R2 group. As presented in *Figure 3*, patient 45 and patient 09 both suffered rapid progression during their first treatment. However, the difference between PFS2 was great, with 7 months for patient 45 and 1 month for patient 9. We reviewed the clinical records of these patients and found that patient 45 received anlotinib (an orally administered tyrosine kinase inhibitor that targets tumor angiogenesis) as his second-line therapy, while patient 9 received chemotherapy as her second-line therapy. Anlotinib can ameliorate the immuno-microenvironment by downregulating PD-L1 expression on vascular endothelial cells to inhibit tumor growth (31). Various therapeutic regimens might affect the antitumor efficacies of subsequent ICI. Therefore, the above exploration in the R2 group indicated that a second tumor biopsy to evaluate the tumor microenvironment might play an important role in the evaluation of ICI restart in these patients. Nevertheless, the clinical outcome of ICI rechallenge in disease progression patients remains to be explored through prospective clinical trials and multi-omics studies.

Long-term immune memory protection can be provided by ICI even in the withdrawal period, but this can also lead to some unpleasant irAEs: uncertain onset, repeat attacks, and progressive aggravation. These features increase concerns about the recurrence of irAEs among rechallenge patients. Regarding the incidence of irAEs among patients receiving ICI rechallenge, we found that the recurrence rate of irAEs was lower in our cohort than in the Santini cohort (22.5% *vs.* 52%), which might have been due to the short follow-up time in our study (32). In addition, 5 patients experienced the same adverse reactions as in their first-line ICI, while 4 patients experienced new types of irAEs. These findings highlight the necessity of exhaustive evaluation for any potential irAEs. In our cohort, the onset time of irAEs during the second round of ICI ranged from 10 to 120 days, with a median onset time of 21 days, which was much earlier than the general onset time of 1–3 months seen in previous reports. Among the 9 patients who developed irAEs during rechallenge, only one suffered grade 3 irAEs, while the remaining 8 patients had grade 1–2 irAEs, indicating the tolerable adverse effects of rechallenge.

To our knowledge, this study is the first to evaluate the efficacy and safety among Chinese patients treated with general ICI rechallenge. Our results showed that rechallenging with ICIs improved the clinical outcomes in patients treated with general ICI rechallenge. For patients who initially discontinue ICI treatment due to irAEs, ICI rechallenge may be an attractive option. However further research is needed regarding patients who discontinue ICI due to disease progression. In addition, the recurrence of irAEs and the early onset of irAEs during the second round of ICI, especially within the first 2 retreatment cycles, should be considered.

Our study has several limitations. First, this was a retrospective, single-center study. Although there is possible selection bias, our practicing clinical group can provide a degree of real-world understanding of advanced lung cancer patients who receive anti-PD-1/PD-L1 inhibitor rechallenge. Second, the follow-up time was insufficient, but some of our results are consistent with previous studies, and new insights into ICI rechallenge were obtained. Despite these limitations, our results further enrich the clinical evidence for the efficacy and safety of anti-PD-1/PD-L1 inhibitor rechallenge among patients with advanced lung cancers. Therefore, the assessment of efficacy and safety of anti-PD-1/PD-L1 inhibitor rechallenge should be explored in larger sample sizes and future prospective clinical trials.

Conclusions

Rechallenge with ICIs improved the clinical outcomes of patients treated with general ICI rechallenge. ICI rechallenge should be considered as a subsequent treatment for patients who have previously discontinued ICI due to irAEs. For patients who discontinue ICI due to disease progression, the clinical value of using ICI again may be limited and heterogeneous, and further clinical studies are

needed to explore. In addition, the recurrence of irAEs and early onset of irAEs during the second round of ICI should be considered.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-360/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-360/coif). DWD reports receiving payment for lectures, presentations, speakers bureaus, manuscript writing or educational events by Roche, BMS, MSD, Pfizer and Astra Zeneca. The other authors have no conflicts of interest to declare.

Ethics 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. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and the protocol was reviewed and approved by the institutional review board of Ruijin Hospital (Approval No. 2019-72). Individual consent for this retrospective analysis was waived.

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Supplementary

Table S1 Immune-related toxicities during first ICI round and at rechallenge

Patient (no.)	Type of immune adverse reaction	
	During first ICI round	During rechallenge
01	Pneumopathy	No
02	Skin toxicity	No
03	Hepatitis	No
04	Pneumopathy	No
05	Pneumopathy, thyroiditis	No
06	Pneumopathy	No
07	Myocarditis	No
08	Pneumopathy	No
09	Skin toxicity	No
10	Colitis	No
11	Colitis	Pneumopathy
12	Nephritis	No
13	Pneumopathy	No
14	Pneumopathy	No
15	Skin toxicity	No
16	Hepatitis	Skin toxicity
17	Myositis, thyroiditis	No
18	Pneumopathy	No
19	Pneumopathy	Pneumopathy
20	Skin toxicity	No
21	Thyroiditis	Pneumopathy
22	Pneumopathy	No
23	Pneumopathy	No
24	Pancreatitis	No
25	Pneumopathy	No
26	Skin toxicity	Skin toxicity
27	Myositis	No
28	Pneumopathy	No
29	Thyroiditis	No
30	Myositis	No
31	Pneumopathy	No
32	Pneumopathy	No
33	Pneumopathy	No
34	Pneumopathy	No
35	Pneumopathy	Pneumopathy
36	Pneumopathy	Pneumopathy
37	Thyroiditis	Pneumopathy
38	Skin toxicity	No
39	Myositis	No
40	Pneumopathy	Pneumopathy

ICI, immune checkpoint inhibitor.

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