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ORIGINAL ARTICLE

Optimal immunotherapy duration in advanced NSCLC: defining the ideal treatment window

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ABSTRACT

Objective: Immune checkpoint inhibitors (ICIs) have demonstrated substantial efficacy in patients with advanced non-small cell lung cancer (NSCLC). However, the optimal duration of ICI therapy remains unclear, and limited real-world data are available. The aim of this study was to evaluate the relationship between ICI therapy duration and overall survival (OS) in patients who achieved varying best overall response (BOR) during ICI treatment, and to compare patients treated for 6 to 18 months *vs.* at least 18 months.

Methods: This retrospective cohort study included adult patients diagnosed with advanced NSCLC who received ICI therapy at the Zhejiang Cancer Hospital between 2017 and 2022. Data collection ended on May 1, 2024, and statistical analysis was performed between May and June 2024.

Results: Using strict entry criteria, we screened 487 patients with advanced NSCLC and identified 134 eligible patients. Among these patients, the median durations of immunotherapy and follow-up were 24.57 months and 43.60 months, respectively. The objective response rate (ORR) was 58.2%, and the median progression-free survival (PFS) was 10.6 months. Median OS was not reached. At the last follow-up, 54 patients had no disease progression, and 118 patients remained alive. Patients treated with ICI therapy for ≥ 18 months had superior survival to those treated for 6 to 18 months ($P = 0.039$). Further analysis revealed that the survival benefit was associated with BOR during ICI therapy. Specifically, patients achieving complete response/partial response (CR/PR) who received ≥ 18 months of ICI therapy had a trend toward longer median OS than those treated for 6 to 18 months, but the difference did not reach statistical significance ($P = 0.177$). Patients with stable disease (SD) who received ≥ 18 months of ICI therapy had a statistically longer median OS than those treated for 6 to 18 months ($P = 0.019$). Among patients treated with ICIs for ≥ 18 months, 24 continued with ICI-based therapy and achieved a median PFS_2 of 6.67 months, an ORR of 33.3%, and a disease control rate (DCR) of 83.3%.

Conclusions: This study provides real-world evidence and novel insights into the need for continuing ICI therapy beyond 18 months in patients with advanced NSCLC who do not exhibit progressive disease. For patients achieving SD during ICI therapy, a treatment duration of at least 18 months appears appropriate. For patients achieving CR/PR, treatment decisions should be individualized according to patient-specific circumstances. However, owing to the retrospective study design, potential selection bias and confounding factors might have influenced the results. Therefore, our findings require further validation in prospective clinical studies.

KEYWORDS Immune checkpoint inhibitors; immunotherapy; non-small cell lung cancer; duration of treatment; immunotherapy rechallenge

Introduction

In patients with advanced non-small cell lung cancer (NSCLC) lacking known oncogenic driver mutations, immune checkpoint inhibitors (ICIs) targeting programmed death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1) have become an attractive and widely used treatment option, because of their durable responses and generally manageable toxicity profiles with respect to those of platinum-based doublet chemotherapy[1,2]. However, the optimal duration of ICI monotherapy remains undefined, and therapy typically extends until disease progression, intolerable adverse events, or as many as 2 years[3].

The CheckMate 153 trial prospectively evaluated the duration of ICI therapy in patients with advanced NSCLC by comparing continuous nivolumab until progression *vs.* a fixed 12-month course. Continued treatment was associated with

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superior progression-free survival (PFS) and overall survival (OS), thus suggesting that, for responsive patients, ICI therapy should extend beyond 1 year[4]. Five-year follow-up data from the Keynote-010 and Keynote-024 trials indicated that 83% and 82% of patients, respectively, who completed 2 years of pembrolizumab remained alive 3 years post-treatment, and 48% and 46%, respectively, did not show disease progression or receive subsequent therapy[5,6]. Nonetheless, clinical trial populations are highly selected and might not reflect real-world outcomes.

In a recent retrospective analysis, only approximately 20% of patients discontinued immunotherapy after 2 years, whereas 80% continued maintenance therapy. However, when analyzed at a new baseline of 2 years, the difference in OS rates between patients who discontinued *vs.* continued treatment was not statistically significant (79% *vs.* 81%, $P = 0.36$)[7]. Indefinite ICI therapy also has inherent drawbacks, such as elevated risk of medical and economic toxicity. Whereas immune-related adverse events (irAEs) typically occur within the first 3 months, their frequency increases with longer treatment durations[8]. Therefore, determining the optimal treatment duration is crucial to balance efficacy with toxicity.

Herein, we report the differential survival benefits of 6 to 18 months *vs.* more than 18 months of ICI therapy in patients with advanced NSCLC. We selected an 18-month cutoff point on the basis of existing evidence and additional validation. To justify this choice, we conducted survival analyses with alternative cutoff points, including 19–24 months, and present the results for the 24-month analysis herein. The CheckMate 153 study has supported treatment continuation beyond 1 year, and demonstrated significant improvements in PFS and a trend toward prolonged OS[4]. In contrast, retrospective studies have suggested no additional survival benefit from continuing immunotherapy beyond 2 years[7,9].

Materials and methods

Patients

This population-based retrospective cohort study included adult patients diagnosed with advanced NSCLC between 2017 and 2022 in our clinical database. Data were censored as of May 1, 2024, and analysis was conducted from May to June 2024 (**Figure 1**).

The inclusion criteria were (1) age 18 years or older; (2) diagnosis of stage IV NSCLC according to the 2019 American Joint Committee on Cancer (AJCC) TNM staging system for lung cancer; (3) receipt of single-agent or combination ICI therapy; (4) PFS exceeding 6 months; and (5) Eastern Cooperative Oncology Group performance

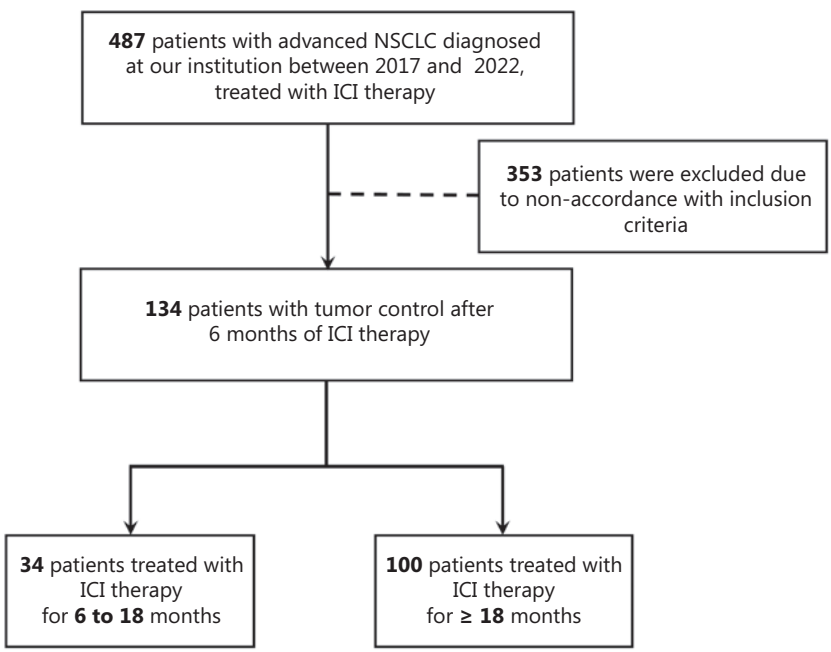


Figure 1 Flowchart of the study population.

status (ECOG-PS) score of 0–4 (with higher scores indicating greater disability).

The exclusion criteria were (1) incomplete clinical data or missing information on treatment efficacy assessment; (2) history of primary malignancies in other organs; (3) concurrent severe systemic diseases; and (4) positivity for epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and c-ros oncogene 1 (ROS-1) mutations.

The study was conducted with the informed consent of the patients and the approval of the Ethics Committee of Zhejiang Cancer Hospital, in accordance with the principles of the Declaration of Helsinki (IRB No. 2023-510).

General information collection

Patients received ICIs according to the label after Food and Drug Administration approval. The following clinicopathologic characteristics were collected for all patients: age, gender, ECOG-PS score, smoking history, histology, brain metastasis, EGFR/ALK/ROS-1 mutation status, PD-L1 immunohistochemistry status, type of ICI, treatment line of ICI, treatment for irAEs, and reasons for ICI discontinuation. All patients were evaluated radiologically for the clinical outcomes of objective response rate (ORR), PFS, and OS according to Response Evaluation Criteria in Solid Tumors (RECIST, v1.1) through computed tomography or magnetic resonance imaging. AEs were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.03).

Efficacy assessment and follow-up

The primary endpoint was OS, defined as the time from initiation of first-line therapy to death, the last follow-up, or the data cutoff (May 31, 2024). PFS was defined as the time from the start of the last ICI cycle to the date of disease progression or death. Patients without disease progression during follow-up were censored at the last contact date or data cutoff, whichever occurred first. PFS_2 was defined as the time from ICI rechallenge to subsequent progression or death.

Statistical analysis

Data collection and study population

Data collection was censored as of May 31, 2024. The study population consisted of patients diagnosed with advanced NSCLC who received ICI therapy. Patient and tumor characteristics were summarized with descriptive statistics.

Survival analyses were performed with the Kaplan-Meier method, and differences in survival curves were assessed with the log-rank test. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were estimated with the Cox proportional hazards (PH) model.

To ensure the validity of the Cox PH model, we conducted several steps to verify and handle the PH assumption:

We used the Schoenfeld residuals test to assess the PH assumption for each covariate in the Cox model. The null hypothesis of the Schoenfeld residuals test was that the hazard ratio was constant over time. A *P*-value below 0.05 indicates a violation of the PH assumption. Additionally, we visually inspected the log-minus-log (LML) plots to verify any crossing of survival curves, which can also suggest a violation of the PH assumption. For covariates that violated the PH assumption, we introduced time-dependent covariates into the Cox model. Specifically, we included interaction terms between the covariates and time. For example, for treatment duration T, we included the interaction term $X_1 \times t$ in the model.

$$\text{The modified Cox model formula is: } h(t / X) = h_0(t) \exp\left[\beta_1 X_1 + \beta_2 X_2 + \beta_3 (X_1 \times t)\right] h(t / X)$$

where X_1 represents treatment duration, X_2 represents other covariates, and β_3 represents the coefficient for the interaction term. After incorporating time-dependent covariates, we re-evaluated the PH assumption with the same methods (Schoenfeld residuals test and LML plots) to ensure that the modified model satisfied the PH assumption.

We performed univariate analysis to screen variables, then selected those with statistically significant *P*-values for inclusion in the subsequent multivariate Cox regression model.

All *P*-values were two-sided, and the threshold statistical significance was set at $P < 0.05$. Statistical analyses were performed in Statistical Package for the Social Sciences (SPSS) software (version 25; IBM Corporation, Armonk, NY).

Results

Patient characteristics

Table 1 summarizes the baseline characteristics of the patients included in the study.

Table 1 Baseline cohort characteristics

Characteristics	< 18 months (n = 34)	≥ 18 months (n = 100)	P-value
Age			0.277
< 65 years	21	51	
≥ 65 years	13	49	
Gender			0.640
Male	30	85	
Female	4	14	
ECOG PS score			0.555
0	11	38	
≥ 1	23	62	
Smoking history			0.662
Former/current	26	80	
Never	8	20	
Histologic type			0.663
ADC	16	42	
SCC	11	41	
Other	7	17	
PD-L1			0.059
0	8	13	
≥ 1	16	38	
Missing	10	49	
Brain metastasis			0.682
Yes	9	23	
No	25	77	
Liver metastasis			0.662
Yes	8	20	
No	26	80	
Lines of ICI therapy			0.607
1	18	58	
≥ 2	16	42	
ICI treatment			0.351
ICI therapy	8	32	
Combined ICI therapy	26	68	
IrAEs			0.840
Yes	17	48	
No	17	52	

ECOG PS, Eastern Cooperative Oncology Group performance status; ADC, adenocarcinoma; SCC, squamous cell carcinoma; PD-L1, programmed death-ligand 1; ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events.
P-value: chi square test for categorical variables (between < 18 months and ≥ 18 months treatment groups).

For the 34 patients treated with ICIs for 6 to 18 months, the median age was 63 years (range: 38–85 years), 88% were men, and 76.5% had a smoking history. At the start of ICI treatment, 91.2% had an ECOG PS score of 0–1. Pathologically, 47.1% had adenocarcinoma, and 32.3% had squamous cell carcinoma. A total of 26.5% of patients had brain metastases, whereas 23.5% had liver metastases. Additionally, 47.1% of patients received ICIs as a first-line treatment, and 76.5% underwent combination therapy. Among the 24 individuals in whom PD-L1 expression could be assessed, 16 showed positivity. Fifty percent of patients experienced irAEs, primarily affecting the endocrine system (41.2%), lungs (29.4%), skin (17.6%), and gastrointestinal tract (17.6%). The best overall response (BOR) was complete response (CR) or partial response (PR) in 18 patients (52.9%) and stable disease (SD) in 16 patients (47.1%). For the 100 patients treated with ICIs for 18 months or more, the median age was 65 years (range: 36–87 years), 85% were men, and 80% had a smoking history. At the start of ICI treatment, 89% had an ECOG PS score of 0–1. Pathologically, 42% of patients had adenocarcinoma, and 30.6% had squamous cell carcinoma. A total of 23% of patients had brain metastases, whereas 20% had liver metastases. Additionally, 42% of patients received ICIs as a first-line treatment, and 68% underwent combination therapy. Among 51 individuals in whom PD-L1 expression could be assessed, 38 showed positivity. Forty-eight percent of patients experienced irAEs, mainly involving the skin (29.2%), endocrine system (27.1%), lungs (22.9%), and gastrointestinal tract (12.5%). Notably, 18 patients discontinued treatment because of irAEs. No differences in baseline characteristics were observed among subgroups ($P > 0.05$) (**Table 1, Tables S1–S3**).

Overall efficacy

Among the 134 patients receiving ICI treatment, the median duration of immunotherapy and follow-up was 24.57 months and 43.60 months, respectively. The BOR was CR in 3 patients (2.24%), PR in 75 patients (55.97%), and SD in 56 patients (41.79%). The ORR was 58.2%, and the median PFS was 10.6 months. The median OS was not reached. The 2-year OS rate was 98.5%, and the 4-year OS rate was 37.3%. At the time of data analysis, 118 patients (88.06%) remained alive, whereas 70 patients (52.24%) experienced disease progression. Sites of disease progression included the lungs (42.86%), lymph nodes (27.14%), bone (12.86%), abdomen (12.86%), brain (12.86%), and pleura (10%).

Efficacy by treatment duration

In the group treated with ICIs for 6 to 18 months, 18 patients had a BOR of CR/PR, and 16 had a BOR of SD (**Tables S2 and S3**). In the group treated for 18 months or more, 60 patients had a BOR of CR/PR, and 40 had a BOR of SD (**Tables S2 and S3**). No significant differences in median PFS were observed between groups (10.50 months *vs.* 10.60 months; $P = 0.640$); however, the group treated for ≥ 18 months had a significantly longer median OS (not reached *vs.* not reached; $P = 0.039$) (**Figure 2**).

Comparison of the groups treated for 6 to < 24 months *vs.* ≥ 24 months indicated no significant difference in median PFS (10.50 months *vs.* 10.60 months; $P = 0.970$). Although the median OS was longer in the group treated for 24 months or more (not reached *vs.* not reached; $P = 0.390$), the difference was not significant (**Figure 2**).

For patients achieving CR/PR, the median OS was longer in the group treated for ≥ 18 months rather than less than 18 months (not reached *vs.* not reached; $P = 0.177$), but the difference was not statistically significant. For patients with SD, the median OS was significantly longer in the group treated for ≥ 18 months rather than less than 18 months (not reached *vs.* not reached; $P = 0.019$) (**Figure 3**).

Rechallenge with ICIs

Of the 100 patients treated for 18 months or more, 38 patients were rechallenged with ICIs after disease progression and at least 30 days without treatment: 24 received ICIs alone or in combination with chemotherapy, whereas 14 received chemotherapy or chemotherapy combined with antiangiogenic therapy. The median PFS_2 was 6.47 months. The BOR was PR in 26.3%, SD in 55.3%, and PD in 18.4% of patients. The ORR was 26.3%, and the DCR was 78.9%. Among the 24 patients receiving ICIs alone or in combination with chemotherapy (**Figure 4**), the median PFS_2 was 6.67 months; 12 patients achieved SD, 8 patients achieved PR, and 4 patients achieved PD. The ORR was 33.3%, and the DCR was 83.3%. Among the 14 patients receiving chemotherapy or chemotherapy combined with antiangiogenic therapy, the median PFS_2 was 6.12 months; 8 patients achieved SD, 2 patients achieved PR, and 4 patients achieved PD. The ORR was 14.3%, and the DCR was 71.4%. Twenty patients were alive at the data cut-off.

IrAEs

Sixty-five patients experienced irAEs, including 20 cases of endocrine reactions, 17 cases of rash, 16 cases of pneumonitis, and 3 cases of gastrointestinal reactions. Moreover, 37 patients stopped treatment because of disease progression: 18 because of irAEs, and 7 because of pandemic-related reasons.

Prognostic analysis

Univariate and multivariate analyses were conducted to assess clinical parameters affecting PFS and OS in patients with advanced NSCLC (**Tables 2 and 3**). We performed univariate analysis to screen variables, then selected those with statistically significant *P*-values ($P < 0.05$) for inclusion in the subsequent multivariate Cox regression model. Male gender correlated with poorer PFS, whereas first-line use of immunotherapy and occurrence of irAEs during immunotherapy correlated with prolonged PFS. Multivariate analysis confirmed that male [HR: 2.330 (95% CI: 1.244–4.364), $P = 0.008$], first-line use of immunotherapy [HR: 0.543 (95% CI: 0.333–0.884), $P = 0.014$], and occurrence of irAEs during immunotherapy [HR: 0.437 (95% CI: 0.295–1.028), $P = 0.038$] were independent prognostic factors for PFS. Univariate analysis also indicated that smoking history and liver metastases correlated with poorer OS, whereas achieving CR/PR during immunotherapy correlated with prolonged OS. Multivariate analysis identified liver metastases [HR: 5.421 (95% CI: 1.932–15.208), $P = 0.001$] and achieving CR/PR during immunotherapy [HR: 0.293 (95% CI: 0.104–0.823), $P = 0.020$] as independent prognostic factors for OS.

Discussion

This retrospective cohort study investigated the relationship between the duration of immunotherapy with ICIs and OS in patients with advanced NSCLC. Our findings revealed significant differences in OS between patients treated with ICIs for 6–18 months *vs.* 18 months or longer. Notably, the most significant effects on survival occurred within the 18–24 months treatment window, and limited additional benefits were achieved beyond 24 months. By introducing time-dependent covariates into the Cox PH model, we were able to capture the evolving effects of treatment on survival. Specifically, we compare the accuracy of data representation between different treatment durations. We validated the PH assumption with Schoenfeld residual tests, which revealed no significant time dependence.

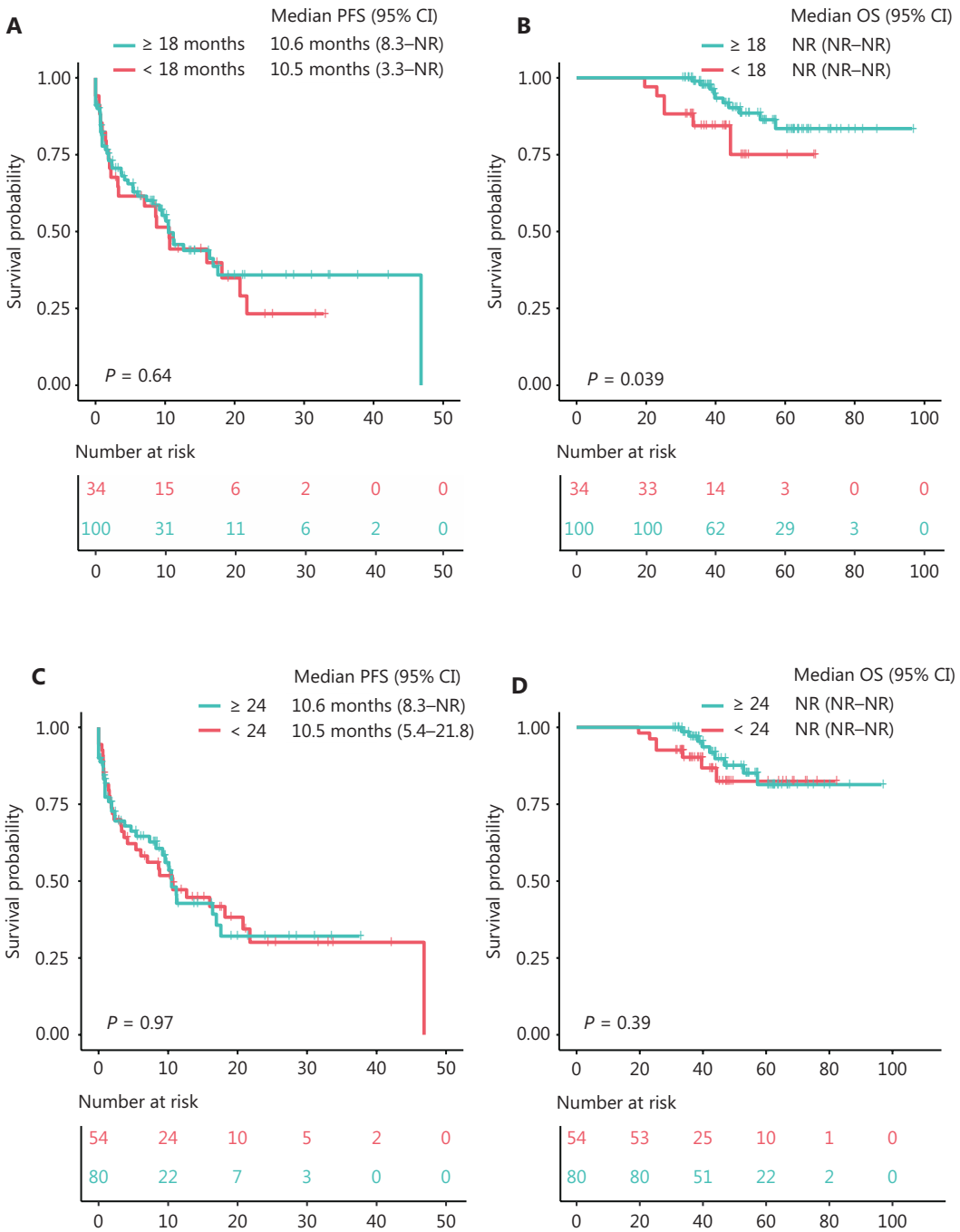


Figure 2 Kaplan-Meier curves of progression-free survival (PFS) and overall survival (OS) by treatment duration. (A) PFS in patients treated with ICI for 6 to 18 months *vs.* 18 months or more. (B) OS in patients treated with ICI for 6 to 18 months *vs.* 18 months or more. (C) PFS in patients treated with ICI for 6 to < 24 months *vs.* 24 months or more. (D) OS in patients treated with ICI for 6 to < 24 months *vs.* 24 months or more.

Although early crossover was observed, the survival curves indicated stable separation in the later phase, in agreement with the PH assumption under stable long-term risk conditions.

ICIs have been demonstrated to achieve clinically meaningful improvements in outcomes for patients with advanced NSCLC lacking driver mutations. However, determining

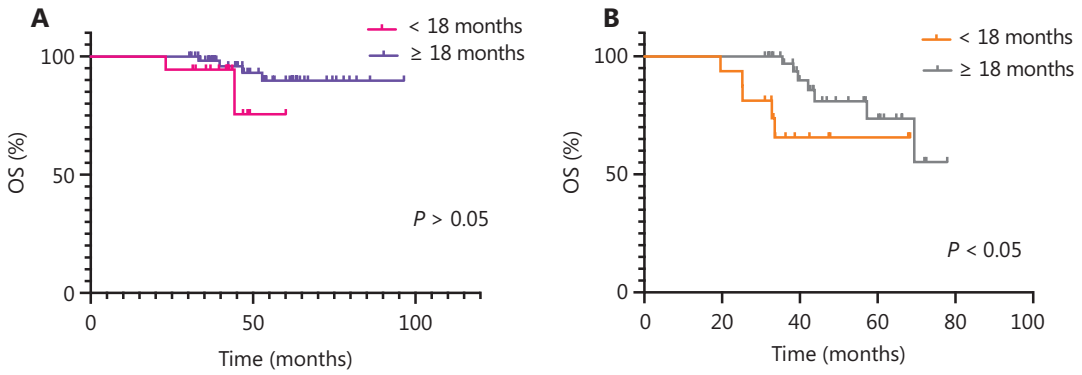


Figure 3 Kaplan-Meier curves of overall survival (OS) by treatment duration in patients achieving complete or partial response (CR/PR) and stable disease (SD). (A) Kaplan-Meier curve showing overall survival (OS) for patients achieving complete or partial response (CR/PR), stratified by treatment duration (≥ 18 months *vs.* 6 to 18 months). (B) Kaplan-Meier curve showing overall survival (OS) for patients with stable disease (SD), stratified by treatment duration (≥ 18 months *vs.* 6 to 18 months).

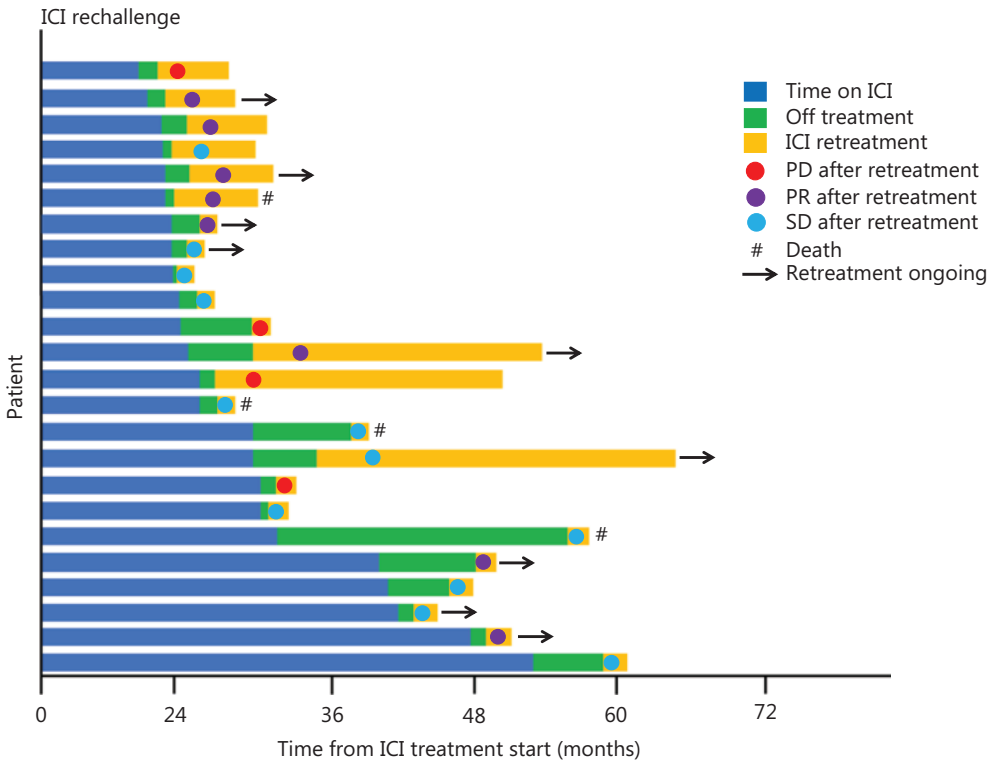


Figure 4 Treatment discontinuation over time and ICI rechallenge. Swimmer plot of patients treated with ICI for ≥ 18 months rechallenged with ICI-based therapy. ICI, immune checkpoint inhibitor; PD, progressive disease; PR, partial response; SD, stable disease.

the optimal duration of treatment remains challenging[10]. Clinically, ICI therapy is frequently continued until disease progression or unacceptable toxicity occurs, with the aim of maximizing therapeutic benefits. Nevertheless, the durable effects of ICIs and the risk of irAEs suggest that defining a specific treatment duration might be more prudent. On the one hand, from a pharmacological perspective, PD-1 receptor occupancy on circulating T cells can persist for months and promote adaptive immune responses through the formation of memory T cells[11]. On the other hand, prolonged ICI

Table 2 Univariate and multivariate analysis of progression-free survival

Parameters	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Gender (male; female)	1.949 (1.602–3.579)	0.031	2.330 (1.244–4.364)	0.008
Age (≥ 65; < 65)	1.022 (0.637–1.640)	0.928		
ECOG PS score (≥ 1; 0)	0.903 (0.612–1.355)	0.610		
Smoking history (ever/current; never)	0.740 (0.422–1.296)	0.292		
Histology type (LUAD; LUSC; other)	0.847 (0.609–1.178)	0.325		
Brain metastasis (yes; no)	0.766 (0.426–1.379)	0.374		
Liver metastasis (yes; no)	1.515 (0.864–2.657)	0.147		
Lines of ICI therapy (1; ≥ 2)	0.604 (0.376–0.972)	0.038	0.543 (0.333–0.884)	0.014
ICI treatment (ICI therapy; combined ICI therapy)	1.341 (0.823–2.185)	0.240		
IrAEs during ICI therapy (yes; no)	0.629 (0.390–1.015)	0.049	0.437 (0.295–1.028)	0.038
IrAE: pneumonitis (yes; no)	0.909 (0.434–1.904)	0.800		
IrAE: rash (yes; no)	0.904 (0.413–1.980)	0.801		
IrAE: endocrine (yes; no)	0.578 (0.286–1.166)	0.126		
Best scan response during ICI therapy (CR or PR; SD)	0.682 (0.425–1.093)	0.112		

HR, hazard ratio; CI, confidence interval, ECOG PS, Eastern Cooperative Oncology Group performance status; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; ICI, immune checkpoint inhibitor; IrAEs, immune-related adverse events; BOR, best overall response; CR, complete response; PR, partial response; SD, stable disease.

treatment may lead to overactivation of the immune system, thus increasing the risk of immune exhaustion[12]. Additionally, extended treatment durations are associated with higher rates of irAEs. For example, the CheckMate-153 trial indicated a higher incidence of irAEs with continuous nivolumab therapy than a fixed 1-year course (48% *vs.* 26%)[4]. Finally, long-term use of ICIs poses substantial economic burdens on both patients and healthcare systems. Therefore, we sought to balance the benefits and risks of treatment by determining the appropriate treatment duration, and we examined real-world cases to find answers. On the basis of existing evidence, a treatment period of 12–24 months appeared ideal. Our results further refined this timeframe, specifically demonstrating no significant difference in median PFS between the 6 to 18 months group and the ≥ 18 months group (10.67 months *vs.* 12.67 months; $P = 0.463$), but a significantly longer median OS in the ≥ 18 months group (not reached *vs.* not reached; $P = 0.039$). Comparison of the ≥ 24 months *vs.* 6 to 18 months groups indicated no significant differences in mPFS (10.67 months *vs.* 11.23 months; $P = 0.672$), although the median OS was nonsignificantly longer in the ≥ 24 months group (not reached *vs.* not reached; $P = 0.392$).

A key question is how to identify patients who can safely discontinue treatment while minimizing the risk of recurrence. Studies addressing the optimal duration of ICI treatment in advanced NSCLC, particularly considering treatment response, are limited. In NSCLC, the depth of response to ICIs might correlate with longer PFS and OS[13]. The CheckMate 153 trial has indicated that the benefit of continued nivolumab treatment is driven primarily by patients achieving CR or PR, whereas no OS or PFS benefit was observed for patients with SD or PD[4]. Our data suggest that patients achieving CR/PR during ICI treatment might benefit from continued therapy lasting 18 months (not reached *vs.* not reached; $P = 0.177$), although this finding lacked statistical significance. For patients with a best response of SD, the median OS was significantly longer in the ≥ 18 months than the < 18 months ICI treatment group (not reached *vs.* not reached; $P = 0.019$). Thus, an ICI treatment duration of 18–24 months might be a reasonable choice for patients achieving SD as their best response.

Furthermore, our findings indicated that patients receiving ICI therapy for 18 months or longer might benefit from ICI rechallenge after disease progression. Among a subset of patients who underwent ICI rechallenge, the median PFS

Table 3 Univariate and multivariate analysis of overall survival

Parameters	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Gender (male; female)	1.419 (0.404–4.986)	0.585		
Age (≥ 65; < 65)	1.040 (0.390–2.774)	0.938		
ECOG PS score (≥ 1; 0)	1.026 (0.480–2.197)	0.946		
Smoking history (ever/current; never)	1.640 (0.422–3.296)	0.042		
Histology type (LUAD; LUSC; other)	1.793 (0.909–3.537)	0.092		
Brain metastasis (yes; no)	2.170 (0.786–5.992)	0.135		
Liver metastasis (yes; no)	4.402 (1.615–11.998)	0.004	5.421 (1.932–15.208)	0.001
Lines of ICI therapy (1; ≥ 2)	0.461 (0.159–1.333)	0.153		
ICI treatment (ICI therapy; combined ICI therapy)	1.474 (0.542–4.005)	0.447		
IrAEs during ICI therapy (yes; no)	0.508 (0.184–1.402)	0.191		
IrAE: pneumonitis (yes; no)	1.158 (0.263–5.102)	0.846		
IrAE: rash (yes; no)	0.917 (0.208–4.039)	0.909		
IrAE: endocrine (yes; no)	0.743 (0.169–3.274)	0.695		
Best scan response during ICI therapy (CR or PR; SD)	0.363 (0.132–1.001)	0.050	0.293 (0.104–0.823)	0.020

HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; ICI, immune checkpoint inhibitor; IrAEs, immune-related adverse events; BOR, best overall response; CR, complete response; PR, partial response; SD, stable disease.

post-rechallenge was 6.67 months, and 20 patients were alive at the time of data cutoff. These results align with promising observations from randomized clinical trials during long-term follow-up periods regarding ICI rechallenge[14].

The occurrence of irAEs is associated with sustained responses and clinical benefit in patients with NSCLC receiving ICIs[15]. In our cohort, 65 patients experienced irAEs, including 20 cases of immune-related endocrine reactions, 17 cases of immune-related rash, 16 cases of immune-related pneumonitis, and 3 cases of immune-related gastrointestinal reactions. Further analysis confirmed that the occurrence of irAEs during immunotherapy [HR: 0.437 (95% CI: 0.295–1.028), $P = 0.038$] was an independent prognostic factor for PFS.

In summary, indefinite continuation of immunotherapy is not a strategy that consistently yields additional clinical benefits. Our results provide a rationale for an ICI treatment duration of 18–24 months for patients with advanced NSCLC whose best response to ICI treatment is SD. We acknowledge several limitations in our study. The non-randomized design and limited sample size, with only 134 of 487 initially screened patients being eligible, might have introduced confounding factors and limited the generalizability of our findings. To address these concerns, future multi-center studies with larger and more diverse patient populations are required to validate our results and enhance external validity. The retrospective nature of our study might have introduced biases such as selection bias, incomplete data, or variable adherence to treatment protocols, thereby affecting the accuracy and reliability of the findings. To mitigate these potential biases, we implemented clear inclusion and exclusion criteria, excluded cases with incomplete data, ensured consistency in treatment protocols, and conducted thorough data validation. Additionally, we used multivariate analysis to control for confounding factors. To further advance understanding, future research should explore other covariates, such as PD-L1 expression levels, and conduct long-term follow-up studies. These efforts will be essential to better understand the factors influencing survival outcomes and to provide more robust evidence of clinical practice.

Conclusions

This study elucidated the relationship between the duration of immunotherapy with ICIs and survival outcomes in patients

with advanced NSCLC. Compared with patients treated with ICIs for 6 to 18 months, those treated for ≥ 18 months had a similar median PFS but a significantly longer median OS. For patients achieving CR or PR, the median OS was longer in the group treated with ICIs for ≥ 18 rather than < 18 months, although the difference was nonsignificant. For patients with a best response of SD, the median OS was significantly longer in the group treated for ≥ 18 rather than < 18 months. Moreover, patients who received ICI therapy for 18 months or longer and experienced disease progression after stopping treatment might benefit from ICI rechallenge. The occurrence of irAEs was associated with prolonged PFS. These findings suggest that an ICI treatment duration of 18–24 months might be a reasonable choice for patients with advanced NSCLC whose best response to ICI treatment is SD. Future prospective studies are needed to validate these findings and determine the optimal duration of ICI therapy for patients with advanced NSCLC. This study has limitations arising from its non-randomized design and limited sample size. Future research should include larger and more diverse patient populations, explore additional covariates (such as PD-L1 expression), and conduct long-term follow-up studies to validate our findings and provide more robust evidence.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Kaibo Ding, Yanjun Xu.
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Contributed data or analysis tools: Kaibo Ding, Dujiang Liu.
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Data availability statement

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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