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RESEARCH

Continuous immunotherapy beyond disease progression in patients with advanced non-small cell and small cell lung cancer

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Abstract

Background The benefits of continuing immunotherapy beyond disease progression in advanced non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) remain uncertain, along with the specific patient subgroups that may gain the most from this approach. This retrospective study aims to evaluate the efficacy of this approach and identify target patient populations likely to benefit.

Methods We collected data from patients with NSCLC and SCLC who experienced disease progression following initial immune checkpoint inhibitor (ICI) treatment from January 2020 to December 2023. Patients were categorized based on second-line treatment: those receiving immunotherapy beyond progression (IBP) and those receiving non-immunotherapy beyond progression (NIBP). Survival outcomes and treatment safety were compared between these two groups.

Results A total of 150 patients were included, with 111 NSCLC patients (IBP: $n=78$, NIBP: $n=33$) and 39 SCLC patients (IBP: $n=31$, NIBP: $n=8$). Significant differences in median progression-free survival (PFS) and overall survival (OS) were found in patients with driver gene-negative NSCLC (mPFS: 4.7 vs 1.3 months, HR = 0.29, $P<0.01$; mOS: 11.03 vs 2.63 months, HR = 0.13, $P<0.001$) and SCLC (mPFS: 3.9 vs 2.1 months, HR = 0.38, $P=0.02$; mOS: 9.28 vs 2.27 months, HR = 0.23, $P<0.01$). Additionally, among driver gene-negative NSCLC patients, achieving a partial response (PR) or stable disease (SD) during initial immunotherapy was associated with improved effectiveness of continued immunotherapy beyond progression.

Conclusions Continued immunotherapy as a second-line treatment may benefit patients with driver gene-negative NSCLC and SCLC who have progressed after initial immunotherapy.

Keywords Non-small cell lung cancer (NSCLC) · Small cell lung cancer (SCLC) · Immune checkpoint inhibitors (ICIs) · Immunotherapy beyond progression (IBP) · Efficacy

Introduction

Lung cancer remains the predominant cause of cancer-related mortality globally. Pathologically, lung cancer can be divided into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with NSCLC constituting around 85% of lung cancer cases and SCLC approximately 15% [1]. The advent of immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1) and its ligand (PD-L1) has notably enhanced survival rates among lung cancer patients [2–5]. Despite these advances, a majority of patients still experience disease progression following immunotherapy [6]. The efficacy of second-line immunotherapy in lung cancer patients unresponsive to initial treatment remains uncertain.

Rechallenging with immunotherapy in melanoma treatment is recommended by leading organizations, including the National Comprehensive Cancer Network, the European Society for Medical Oncology, and the Society for Immunotherapy of Cancer [7–9]. Emerging evidence suggests that continuous immunotherapy beyond progression may benefit

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lung cancer patients. For instance, a post hoc analysis of the Checkmate 153 trial indicated that some NSCLC patients continuing with second-line immunotherapy exhibited disease progression without additional adverse effects [10]. A recent meta-analysis indicated that ICI rechallenge might represent an effective approach for NSCLC, with median progression-free survival (mPFS) and median overall survival (mOS) reaching 3.0 and 13.1 months, respectively, in patients continuing second-line immunotherapy [11]. However, a European retrospective study observed no significant difference in post-progression median survival between advanced NSCLC patients with PD-L1 $\geq$ 50% who received pembrolizumab beyond progression and those receiving salvage therapy (8.1 versus 6.9 months, $P = 0.08$)[12]. The comparative efficacy of continuing versus discontinuing immunotherapy beyond progression in NSCLC patients remains uncertain.

Additionally, previous studies have reported improved clinical outcomes in SCLC patients who continue immunotherapy beyond progression [13, 14]. One retrospective study demonstrated a significant overall survival benefit, with an increase of 6.2 months in patients receiving immunotherapy rechallenge post-progression compared to those who discontinued treatment after progression [14]. Another recent retrospective study, though limited by a small sample size, suggested that ICI-based rechallenge therapy may also improve outcomes in SCLC, reporting mPFS and mOS of 5.1 and 13.6 months, respectively [13]. Despite these findings, the efficacy of ICI therapy beyond progression in SCLC remains uncertain due to limited available data.

Consequently, current evidence regarding the efficacy of continuous immunotherapy beyond progression in NSCLC and SCLC remains limited. This retrospective study assesses the outcomes of continued immunotherapy in advanced NSCLC and SCLC patients following progression after first-line treatment, utilizing post-2020 data to account for the growing adoption of ICI-based therapies. Furthermore, the study aims to identify specific patient subgroups that are most likely to benefit from this approach.

Methods

Study design and patients

This retrospective study enrolled patients with advanced NSCLC and SCLC who received first-line ICI-based therapy at Nanjing Jinling Hospital from January 2020 to December 2023. The final follow-up was completed on May 31, 2024. Patients were classified into two cohorts, namely the immunotherapy beyond progression (IBP) group and the non-immunotherapy beyond progression (NIBP) group, based on the second-line therapeutic regimens received. The inclusion criteria were as follows: (a) patients aged 18 years or older; (b) confirmed pathological diagnosis of NSCLC or SCLC; (c) advanced or surgically unresectable stage III-IV or post-operative recurrent disease; (d) Eastern Cooperative Oncology Group (ECOG) performance status of $\leq$2; (e) patients treated with immunotherapy alone or in combination with chemotherapy and/or other drugs as first-line treatment, with progressive disease (PD) confirmed at the end of the first-line treatment; (f) PD verified by the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1); (g) IBP group patients undergoing at least two cycles of second-line immunotherapy. Patients participating in clinical trials, with other primary tumors, or with incomplete medical records were excluded. The study was conducted in compliance with the Declaration of Helsinki, with individual consent waived for this retrospective analysis.

Data collection and efficacy evaluation

Clinical data, including demographic information (sex, age), histological subtype, gene alteration status, smoking history, ECOG performance status at first-line treatment, surgical history, treatment regimen, adverse events, time to disease progression, time to death, and follow-up details, were obtained from hospital medical records. Based on RECIST v1.1 criteria, the best response was categorized as complete response (CR), partial response (PR), stable disease (SD), or PD at least once during therapy. The objective response rate (ORR) was calculated as the percentage of patients achieving CR or PR, while the disease control rate (DCR) was defined as the percentage with SD, CR, or PR as their best response. Progression-free survival (PFS) was defined as the period from the initiation of second-line treatment beyond disease progression, encompassing immunotherapy, chemotherapy, or other therapies, until second disease progression or death from any cause. Overall survival (OS) was calculated from the beginning of second-line treatment until death. Treatment-related adverse events (TRAEs) were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Statistical analysis

Chi-squared tests or Fisher's exact tests were used to compare baseline differences between groups. PFS and OS were estimated using the Kaplan–Meier method, with intergroup differences assessed via the log-rank test. The Cox proportional hazards model was applied to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) to identify factors influencing clinical outcomes. Restricted Mean Survival Time (RMST) was employed to compare survival between groups in cases of significant time-dependent changes or

crossover in survival curves. Multivariate analysis was conducted on factors with statistical significance in univariate analysis and those clinically associated with prognosis. Statistical significance was defined as $P \leq 0.05$. Meta-analyses were conducted using a random-effects model. All statistical analyses were performed using R software (version 4.2.3).

Results

Clinicopathological characteristics

From January 2020 to December 2023, 167 patients were enrolled at Jinling Hospital, including 126 with NSCLC and 41 with SCLC, all of whom had experienced disease progression following initial treatment with immunotherapy, chemotherapy, or anti-angiogenic agents. Screening excluded one patient with a secondary primary tumor, one who had participated in clinical trials, seven who had not shown progression beyond first-line therapy, and eight with incomplete medical records. This resulted in a final cohort of 150 patients, comprising 111 with NSCLC and 39 with SCLC, eligible for analysis (Fig. 1). The initial treatment regimen primarily involved immunotherapy combined with chemotherapy for both NSCLC and SCLC patients. In the NSCLC cohort, 84 received this combination, 25 received it with anti-angiogenic drugs, one received immunotherapy with anti-angiogenic therapy, and one received single-agent immunotherapy. In the cohort of patients with stage III NSCLC, the majority received systemic first-line ICI-based therapy. Only 1 patient in the NIBP group received concurrent chemoradiation followed by immunotherapy at the first line, with progression occurring after completing both concurrent chemoradiotherapy and consolidation immunotherapy. In the SCLC cohort, 31 received the combination therapy, while 9 received it with anti-angiogenic drugs. The immunotherapy agents administered in this study included sintilimab, camrelizumab, tislelizumab, pembrolizumab, penpulimab, sugemalimab, atezolizumab, and durvalumab.

The clinical characteristics of patients undergoing second-round treatment are summarized in Table 1. The IBP group accounted for 70.3% ($n = 78$) of NSCLC patients and

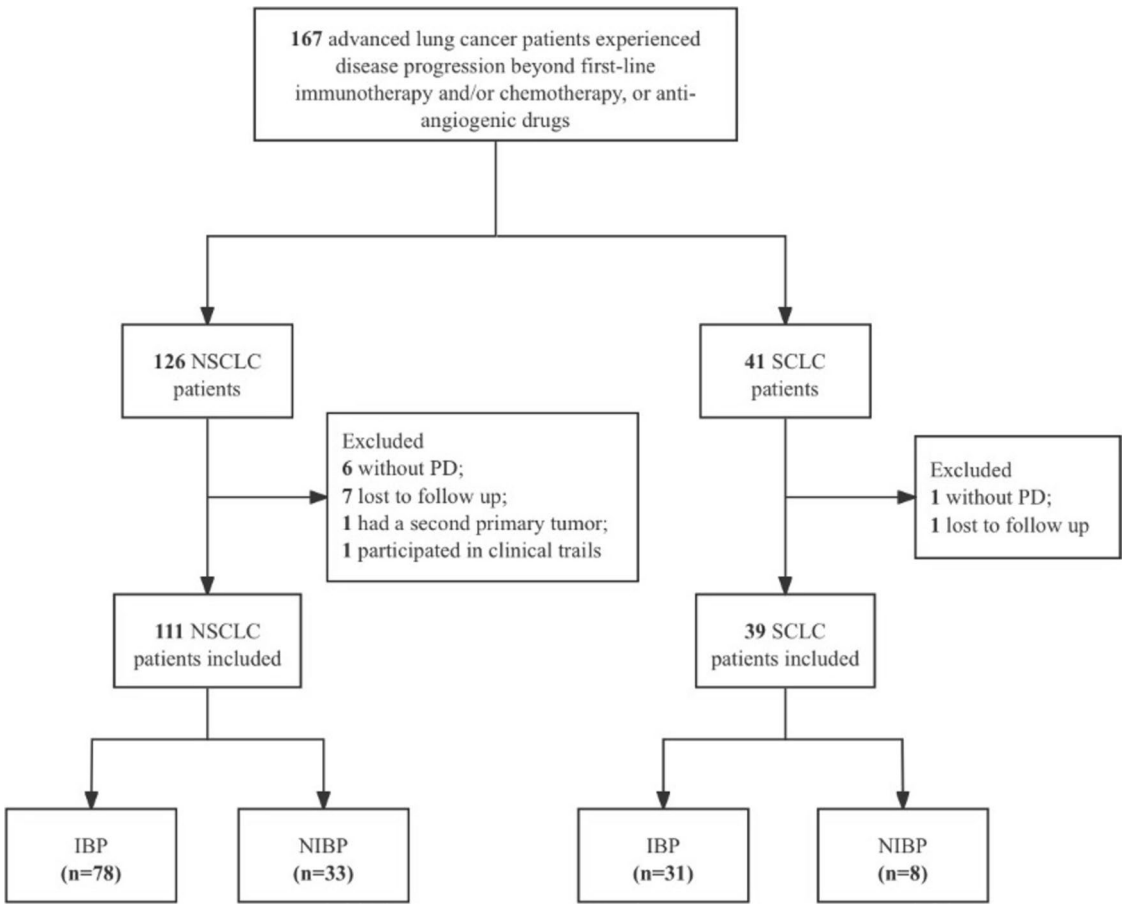

Fig. 1 The flowchart of the study NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; PD, progression disease; IBP, immunotherapy beyond progression; NIBP, non-immunotherapy beyond progression

Table 1 The clinical characteristics of patients with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC)

Characteristics	Number of NSCLC patients (%)		P value	Number of SCLC patients (%)		*P* value
	IBP ($n=78$)	NIBP ($n=33$)		IBP ($n=31$)	NIBP ($n=8$)	
Sex						
Male	64	22	0.21	28	7	1
Female	14	11		3	1	
Age (years)						
<65	36	15	1.0	16	4	0.85
≥ 65	42	18		15	4	
ECOG PS						
0	25	12	1.0	14	1	0.40
1 or 2	53	21		17	7	
Smoking history						
Ever	50	16	0.31	20	7	0.56
Never	28	17		11	1	
Underlying disease						
Yes	48	23	0.72	19	6	0.84
No	30	10		12	2	
Histology						
Adenocarcinoma	39	19	0.23	/	/	/
Squamous	39	12		/	/	
Other	0	2				
Stage of cancer						
Stage III	26	10	0.95	/	/	/
Stage IV	52	23		/	/	
Gene alteration status						
Positive	15	14	0.08	/	/	/
Negative	63	19		/	/	
Surgery						
Yes	12	5	1.0	0	0	
No	67	27		31	8	
Best response to first-line immunotherapy						
SD/PR	69	30	0.96	23	6	1.0
PD	9	3		8	2	
Immunotherapy						
PD-1	74	28	0.11	16	4	1.0
PD-L1	5	4		15	4	
Second-line radiotherapy						
Yes	32	10	0.57	8	4	0.22
No	46	23		23	4	
Second-line therapy regimen						
IO + ChT	37	/		12	/	
IO + ChT + A	27	/		9	/	
IO + A	11	/		8	/	
IO	3	/		2	/	
ChT + A	/	19		/	/	
ChT	/	10		/	3	
A	/	4		/	5	

IO, immunotherapy; ChT, chemotherapy; A, anti-angiogenic therapy

79.5% ($n=31$) of SCLC patients. The majority of patients with NSCLC ($n=64$) and SCLC ($n=21$) in the NIBP received immunotherapy combined with chemotherapy (or plus anti-angiogenic therapy) at the second-line ([Supplementary Information(SI)] Table S7 and S8). Baseline characteristics were comparable between the IBP and NIBP groups, with no statistically significant differences observed ($P>0.05$).

Clinical outcomes in the total NSCLC patient cohort

For NSCLC patients, the median progression-free survival (mPFS) was 4 months (95% CI 3.3–5.8), and the median overall survival (mOS) was 9.8 months (95% CI 5.4–13.2), with a data cutoff of December 1, 2023. The median follow-up period after second-line treatment was 8.27 months (range, 6.5–10.7 months), and the median number of second-line immunotherapy cycles administered was 4 (range, 2–23).

Kaplan–Meier analysis revealed no significant difference in PFS and OS among NSCLC patients (mPFS: 4.4 vs. 3.1 months, HR = 0.71, $P=0.18$; mOS: 10.3 vs. 5.0 months, HR = 1.34, $P=0.56$) (Fig. 2a and b). However, restricted mean survival time (RMST) analysis indicated an mPFS of 5.53 months in the IBP group and 3.87 months in the NIBP group within a 10-month window of second-line treatment. The difference of 1.66 months (95% CI 0.07–3.26, $P=0.04$, [Supplementary Information (SI)] Fig. 6a) suggested a significantly longer mPFS in the IBP group. Additionally, as shown in Table 2, the IBP group exhibited an objective response rate (ORR) of 35.9% compared to 30.3% in the NIBP group ($P=0.57$) and a disease control rate (DCR) of 71.8% compared to 54.5% in the NIBP group ($P=0.078$).

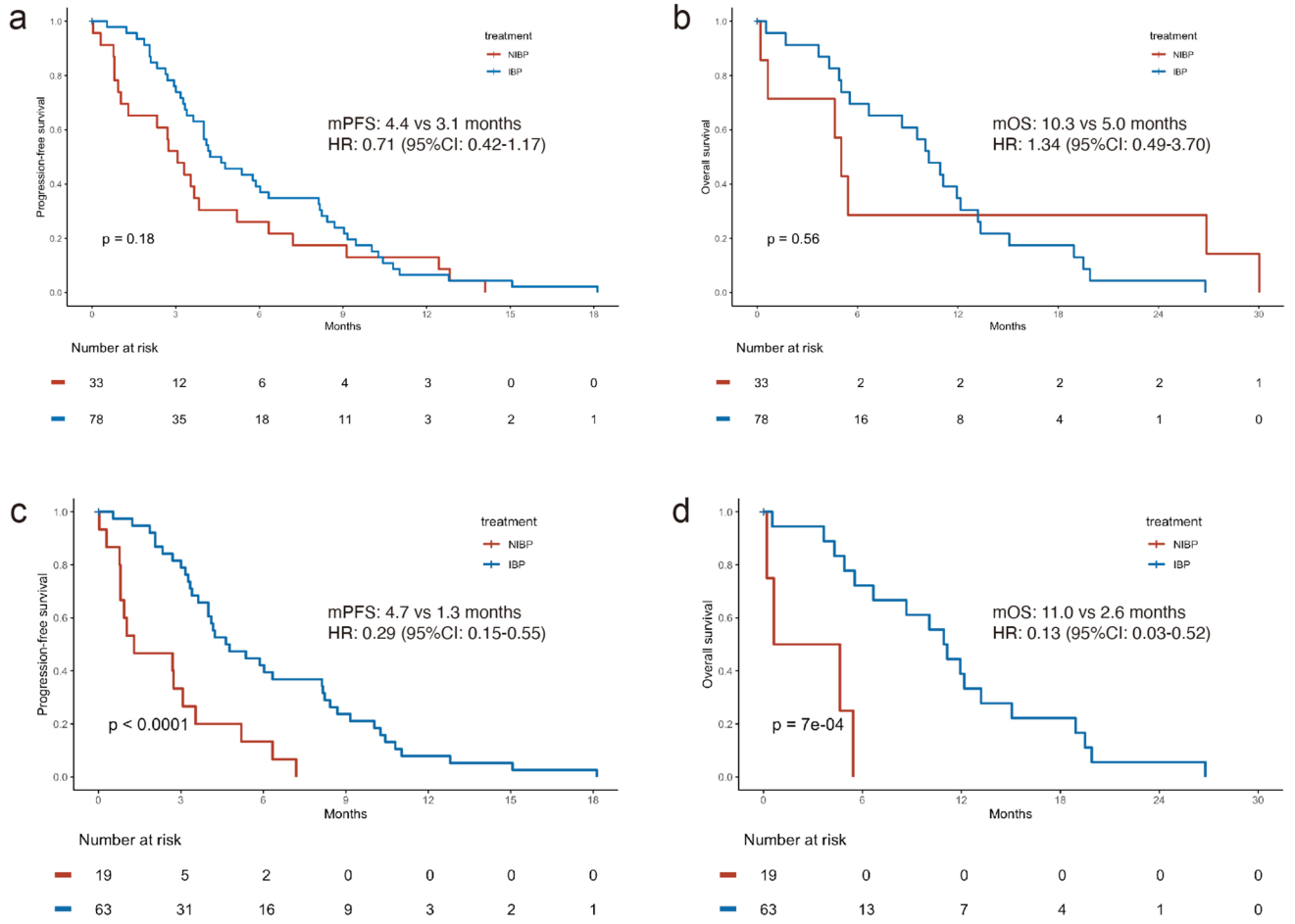

Fig. 2 Kaplan–Meier curves of PFS and OS in the total patients with NSCLC (**a**, **b**) and patients with driver gene-negative NSCLC (**c**, **d**) IBP, immunotherapy beyond progression; NIBP, non-immunotherapy beyond progression; mPFS, median progression-free survival; mOS, median overall survival; HR, hazard ratio; CI, confidence interval

Table 2 Tumor response in patients with advanced NSCLC and SCLC

Best response in second-line treatment, *n* (%)	Patients with NSCLC		P value	Patients with SCLC		*P* value
	IBP (*n* = 78)	NIBP (*n* = 33)		IBP (*n* = 31)	NIBP (*n* = 8)	
CR	0 (0)	0 (0)		0 (0)	0 (0)	
PR	28 (35.9)	10 (30.3)		12 (38.7)	1 (12.5)	
SD	28 (35.9)	8 (24.2)		13 (41.9)	4 (50)	
PD	22 (28.2)	15 (45.5)		6 (19.4)	3 (37.5)	
ORR	28 (35.9)	10 (30.3)	0.57	12 (38.7)	1 (12.5)	0.16
DCR	56 (71.8)	18 (54.5)	0.08	25 (80.6)	5 (62.5)	0.28

Clinical outcomes in patients with driver gene-positive and negative NSCLC

Further analysis was performed to assess the efficacy of continuous immunotherapy beyond progression in NSCLC patients with either driver gene-positive or negative status. No statistically significant differences in PFS or OS were observed between the IBP and NIBP groups among patients with driver gene-positive NSCLC ([Supplementary Information (SI)] Fig. 7). However, in driver gene-negative NSCLC patients, the IBP group demonstrated significantly higher median progression-free survival (mPFS) compared to the NIBP group (4.7 vs. 1.3 months, HR = 0.29, $P < 0.01$). This effect was particularly pronounced among males, patients with squamous histology, those aged ≥ 65 years, smokers, patients with stage IV disease, those with no prior surgery, and those receiving immunotherapy combined with chemotherapy as first-line treatment. ([Supplementary Information (SI)] Fig. 8) The IBP group also demonstrated significantly higher mOS than the NIBP group (11.03 vs. 2.63 months, HR = 0.13, $P < 0.001$) (Fig. 2d). While no significant difference in ORR was found between the IBP and NIBP groups in driver gene-negative NSCLC patients (34.9% vs. 26.3%, $P = 0.48$), the DCR was significantly higher in the IBP group compared to the NIBP group (71.4% vs. 31.6%, $P < 0.01$) ([Supplementary Information (SI)] Table S1).

Multivariate COX regression analysis of patients with driver gene-negative NSCLC ($n = 82$), including factors such as age, sex, ECOG PS score, histology, underlying conditions, smoking status, surgical history, metastasis (TNM) stage, initial response, and combination of radiotherapy with continuous immunotherapy beyond progression, further confirmed that rechallenge with ICI treatment was not an independent prognostic factor affecting PFS and OS (Table 3).

Subgroup analysis by the CR/PR/SD response to initial immunotherapy in NSCLC

Patients who achieved CR, PR, or SD after initial immunotherapy were categorized as the benefit subgroup, while those with PD were categorized as the non-benefit subgroup. We conducted a benefit subgroup analysis to evaluate the efficacy of IBP based on the best response to initial immunotherapy. In the overall NSCLC benefit subgroup, no statistically significant differences in PFS or OS were observed between the IBP and NIBP groups (mPFS: 4.70 vs. 3.42 months, HR: 0.84, 95% CI 0.49–1.47, $p = 0.55$; mOS: 10.93 vs. 5.03 months, HR: 0.48, 95% CI 0.13–1.70, $P = 0.25$) (Fig. 3a and b). However, in the benefit subgroup of driver gene-negative NSCLC patients, both PFS and OS were significantly longer in the IBP group compared to the NIBP group (mPFS: 4.77 vs. 1.17 months, HR: 0.31, 95% CI 0.15–0.64, $P < 0.001$; mOS: 11.93 vs. 2.63 months, HR: 0.10, 95% CI 0.01–0.74, $P < 0.01$). Kaplan–Meier curves for the benefit subgroup (CR/PR/SD response to initial immunotherapy) are shown in Fig. 3c and d. In addition, we observed a statistically significant difference in PFS between the IBP and NIBP groups of NSCLC patients with driver gene-negative status who achieved SD as the best response to initial immunotherapy ([Supplementary Information](SI) Fig. 9).

Clinical outcomes in patients with SCLC

The mPFS in the overall SCLC cohort was 3.47 months (95% CI 2.83–5.5), and the mOS was 6.22 months (95% CI 4.43–11.8). The median number of second-line immunotherapy cycles administered was 3 (range, 2–19). Patients with SCLC in the IBP group had significantly longer PFS and OS compared to those in the NIBP group (mPFS: 3.9 vs. 2.1 months, HR: 0.38, 95% CI 0.16–0.87, $P = 0.02$; mOS: 9.28 vs. 2.27 months, HR: 0.23, 95% CI 0.08–1.77, $P < 0.01$) (Fig. 4). However, ORR and DCR were similar between the IBP and NIBP groups, with no statistically significant differences observed, although the IBP group showed a trend toward longer mPFS and mOS than the NIBP group (ORR: 38.7% vs. 12.5%, $P = 0.161$; DCR: 80.6% vs. 62.5%, $P = 0.277$, Table 2).

Safety

As shown in [Supplementary Information (SI)] Table S2, 85.3% (128/150) of patients with advanced NSCLC and

Table 3 Univariate and multivariate analysis of continuous immunotherapy beyond disease progression in patients with driver gene-negative NSCLC

Risk factors	Univariable analysis				Multivariable analysis			
	PFS		OS		PFS		OS	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Age (≥65 vs. <65)	1.60 (0.90–2.80)	0.11	0.97 (0.40–2.30)	0.95	1.25 (0.60–2.60)	0.57	3.79 (0.64–22.58)	0.14
Sex (male vs. female)	0.53 (0.27–1.00)	0.06	1.70 (0.52–5.30)	0.40	0.48 (0.17–1.33)	0.16	0.94 (0.09–9.61)	0.96
ECOG score (≥1 vs. 0)	0.82 (0.45–1.50)	0.50	0.69 (0.24–2.00)	0.50	0.44 (0.18–1.05)	0.07	0.21 (0.02–2.45)	0.22
Histology (squamous vs. non-squamous)	0.64 (0.36–1.10)	0.13	0.34 (0.13–0.88)	0.03*	1.37 (0.65–2.88)	0.41	0.20 (0.04–1.10)	0.06
Underlying disease (yes vs. no)	0.50 (0.27–0.91)	0.02*	1.10 (0.44–2.80)	0.85	0.50 (0.25–1.00)	0.05	0.16 (0.02–1.17)	0.07
Best response to prior immunotherapy (SD/CR/PR vs. PD)	1.40 (0.80–2.50)	0.23	0.94 (0.39–2.30)	0.90	1.38 (0.69–2.74)	0.36	1.22 (0.26–5.64)	0.80
Smoking status (yes vs. no)	0.61 (0.35–1.10)	0.08	1.70 (0.66–4.40)	0.27	0.72 (0.33–1.57)	0.41	17.7 (2.45–127.52)	0.004**
Surgery (yes vs. no)	1.10 (0.48–2.40)	0.85	2.30 (0.77–6.90)	0.14	0.88 (0.34–2.31)	0.80	14.83 (2.18–00.95)	0.006**
Stage (IV vs. III)	0.67 (0.37–1.20)	0.18	0.78 (0.31–2.00)	0.59	0.72(0.34–1.52)	0.39	0.71 (0.19–2.61)	0.61
Second-line radiotherapy (yes vs. no)	1.20 (0.69–2.10)	0.51	1.30 (0.50–3.40)	0.59	1.45 (0.69–0.70)	0.32	2.40 (0.61–9.41)	0.21
Continuous immunotherapy beyond PD (yes vs. no)	0.29 (0.15–0.55)	<0.001***	0.13 (0.03–0.52)	0.004**	0.22 (0.09–0.50)	<0.001***	0.09 (0.01–0.96)	0.046*

*$P<0.05$; **$P<0.01$; ***$P<0.001$

SCLC experienced TRAEs during second-line treatment. Among NSCLC patients, 81 experienced grade 1 or 2 adverse events (AEs), and 13 experienced grade 3 or 4 AEs. In the SCLC cohort, 28 patients had grade 1 or 2 AEs, and 6 patients had grade 3 or 4 AEs. No grade 5 TRAEs were reported in any patients. The most common adverse events included anemia, hypothyroidism, and abnormal liver function ([Supplementary Information (SI)] Table S3). No statistically significant differences were observed in the incidence of grade 3 and 4 AEs between the IBP and NIBP groups (NSCLC: 9.0% vs. 18.2%, $P=0.17$; SCLC: 9.7% vs. 37.5%, $P=0.05$). Similarly, the incidence of grade 1 and 2 TRAEs was comparable between the two groups (NSCLC: 71.8% vs. 75.8%, $P=0.67$; SCLC: 77.4% vs. 50.0%, $P=0.12$).

Meta-analysis of continuous immunotherapy beyond progression

We conducted meta-analyses to evaluate the efficacy of continuous immunotherapy beyond progression in lung cancer ([Supplementary Information (SI)] Table S4–S6; Fig. 11–12). A total of 14 studies were included in the meta-analyses, comprising 11 on NSCLC and 3 on SCLC, including our own [15–27]. The meta-analysis results showed that patients with driver gene-negative NSCLC who received continuous immunotherapy beyond progression had significantly longer PFS and OS compared to those who did not continue immunotherapy (PFS: HR 0.59, 95% CI 0.45–0.78; OS: HR 0.60, 95% CI 0.51–0.71) (Fig. 5). Additionally, statistically significant differences in PFS and OS were observed between the continuous and non-continuous immunotherapy groups among patients with SCLC, further supporting the benefit of continuous immunotherapy in this subgroup (PFS: HR 0.40, 95% CI 0.22–0.72; OS: HR 0.24, 95% CI 0.11–0.53) ([Supplementary Information (SI)] Fig. 10).

Discussion

ICIs-based therapy has demonstrated efficacy in treating most patients with advanced lung cancer. However, some patients eventually develop immune resistance or experience disease progression. A phase III study demonstrated that individuals with advanced NSCLC who initially responded to ICIs may develop resistance within four years [28]. Studies have suggested that continuing immunotherapy beyond progression may be more beneficial than traditional treatments, such as chemotherapy or radiation therapy [29]. However, it remains unclear which specific subgroups of lung cancer patients would derive the most benefit from this approach. Therefore, in our retrospective study, we evaluated

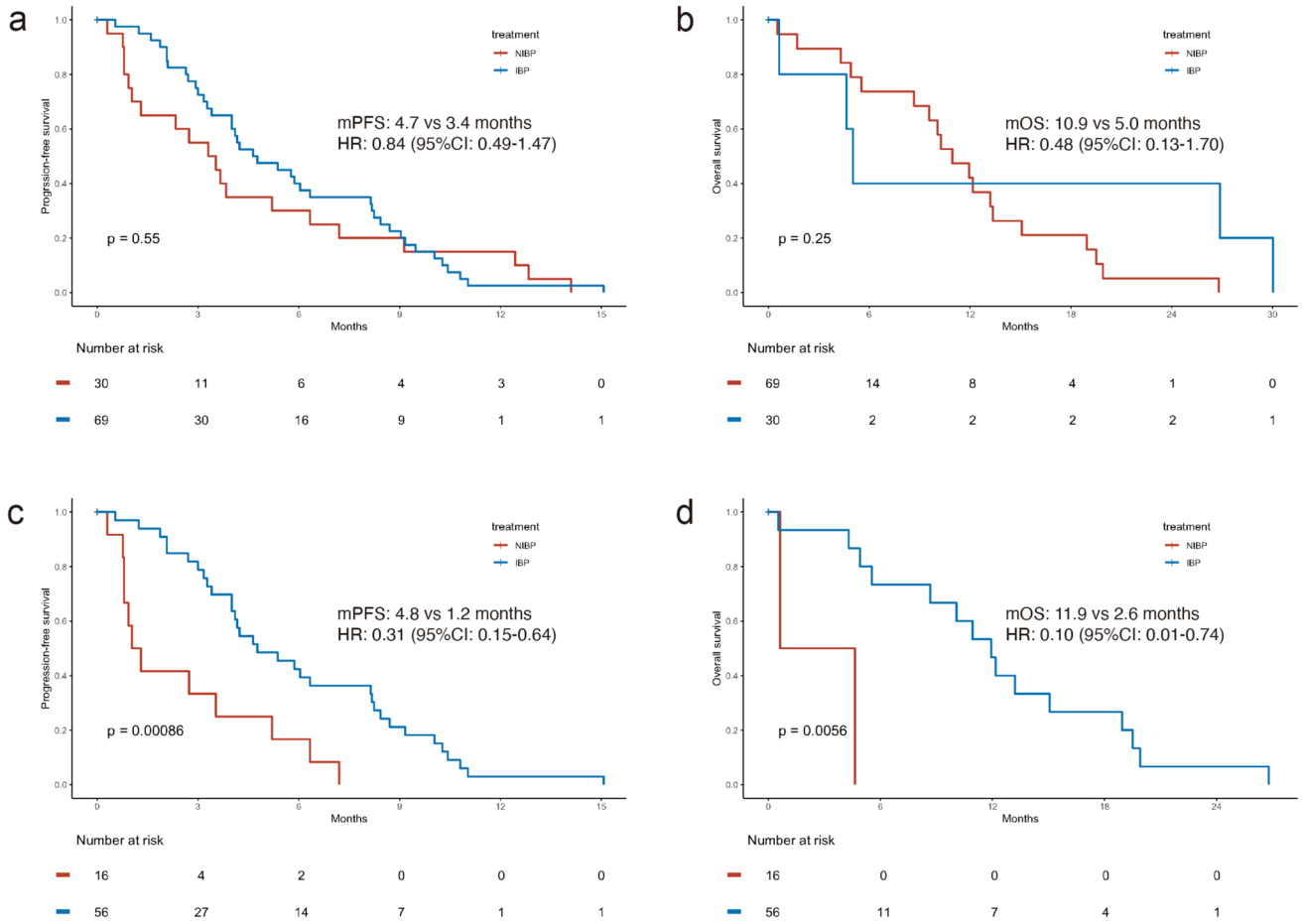

Fig. 3 Kaplan–Meier curves of PFS and OS in the benefit subgroup (the CR/PR/SD response to initial immunotherapy subgroup) of total patients with NSCLC (**a**, **b**) and patients with driver gene-negative NSCLC (**c**, **d**). IBP, immunotherapy beyond progression; NIBP, non-immunotherapy beyond progression; mPFS, median progression-free survival; mOS, median overall survival; HR, hazard ratio; CI, confidence interval

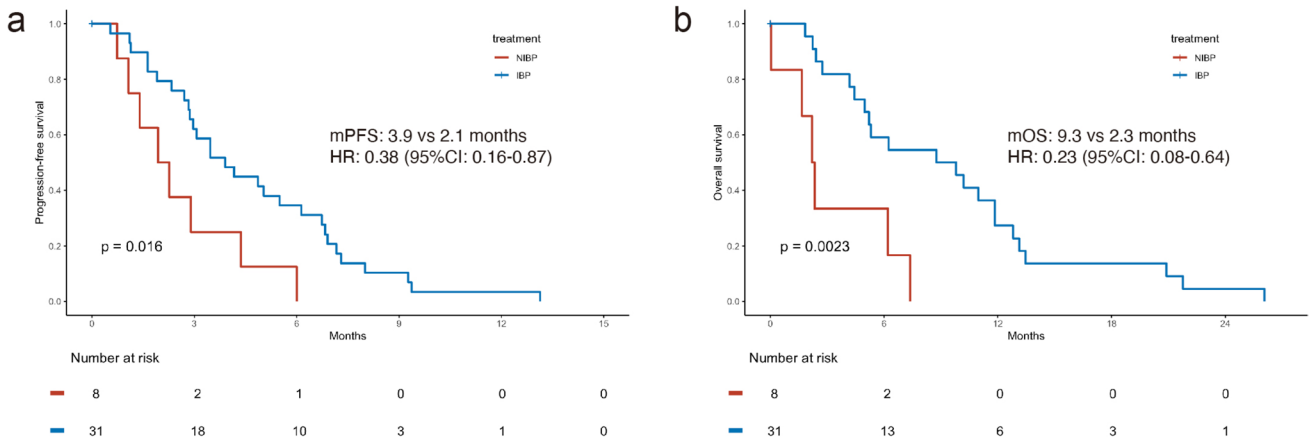

Fig. 4 Kaplan–Meier curves of PFS and OS in patients with SCLC (**a**, **b**) IBP, immunotherapy beyond progression; NIBP, non-immunotherapy beyond progression; mPFS, median progression-free survival; mOS, median overall survival; HR, hazard ratio; CI, confidence interval

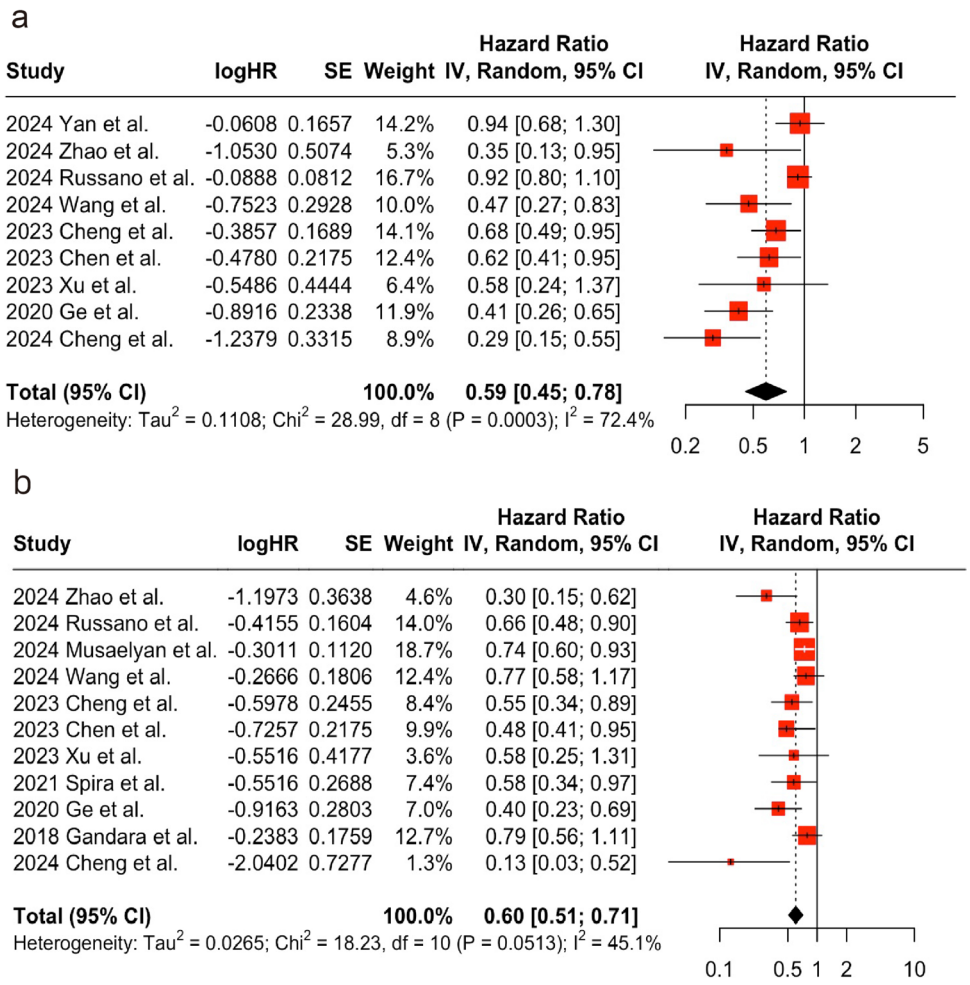

Fig. 5 Forest plots of the hazard ratios for PFS (**a**) and OS (**b**) in the IBP group versus the NIBP group in patients with driver gene-negative NSCLC

the effectiveness and safety of continuous immunotherapy following disease progression in patients with NSCLC and SCLC. We observed significant clinical benefits in advanced NSCLC patients without specific genetic mutations and in patients with SCLC. Additionally, we found a PR or SD response to initial immunotherapy may be associated with the effectiveness of continued immunotherapy in second-line treatment.

In our study, the mPFS in the overall NSCLC population who received IBP was 4.43 months (95% CI 4.0–8.13). A significant difference in PFS was observed within a 10-month window of second-line treatment between the IBP and NIBP groups (RMST: 5.53 vs. 3.87 months, $P=0.04$), suggesting a potential benefit of continuing immunotherapy after progression in NSCLC patients. To further identify which NSCLC patients would benefit most, we categorized patients into driver gene-positive and driver gene-negative groups. No significant differences in PFS and OS were found between IBP and NIBP groups among driver gene-positive patients, whose most common mutations included EGFR, KRAS, and HER2. NSCLC patients harboring different driver gene mutations may exhibit varying responses to immunotherapy. Previous studies have suggested that immunotherapy tends to be less effective in NSCLC patients with driver gene alterations such as EGFR, ALK, ROS1, and HER2, likely due to an unfavorable tumor microenvironment [30–33]. However, patients with KRAS G12C and TP53 mutations may potentially experience better responses to immune checkpoint inhibitor (ICI) monotherapy [34, 35]. These findings suggest that distinguishing between different driver gene mutations may help identify the optimal patient population for immunotherapy in driver gene-positive NSCLC.

Our results showed that continuous immunotherapy beyond progression significantly improved clinical outcomes, including PFS and OS, in driver gene-negative NSCLC patients. Additionally, the DCR in the IBP group was statistically significantly higher than in the NIBP group (71.4% vs. 31.6%). Consistent with our findings, a previous study with 204 NSCLC patients who received continuous immunotherapy found that the absence of targetable gene alterations was independently associated with improved PFS and OS [33]. However, another smaller retrospective study reported that clinical outcomes

of continuous immunotherapy beyond progression were similar to those of other second-line therapies [26]. Our meta-analysis suggested that continuous immunotherapy beyond progression for NSCLC patients with driver gene negative may be superior to other therapies in second-line treatment. Additional studies are warranted to verify the benefit of continuous immunotherapy in driver gene-negative NSCLC patients. Furthermore, our multivariate analysis in driver gene-negative NSCLC patients showed that a history of smoking and surgery were independent factors influencing PFS in second-line treatment. PFS was significantly longer in non-smokers and those without prior surgery, likely due to the adverse impact of smoking and surgery on NSCLC progression [36, 37]. Future studies are needed to further explore these findings.

Several studies recommend that patients achieving a CR or PR with initial immunotherapy should continue with immunotherapy as second-line treatment due to the associated survival benefits [15, 25, 26, 33]. However, controversy exists over whether patients with SD or PD after first-line treatment should continue immunotherapy in subsequent lines. A study of 796 patients treated with ipilimumab and nivolumab reported long-term survival benefits in patients whose best initial response was SD [38]. Our study observed that continued immunotherapy as a second-line treatment improved survival in driver gene-negative NSCLC patients who achieved CR, PR, or SD as their best response to initial immunotherapy (Fig. 3c, d, and [Supplementary Information (SI)] Fig. 9). Although these findings suggest that patients with driver gene-negative NSCLC who achieve CR, PR, or SD after initial immunotherapy may benefit from continued treatment, they remain debatable due to the limited available evidence. Building on prior findings, a prospective study investigating the efficacy of continuing immunotherapy beyond progression in patients with advanced lung cancer is currently in progress. Further prospective studies are needed to validate this finding.

Immunotherapy has shown potential in SCLC, as supported by several studies [39–41]. However, the efficacy of second-line immunotherapy following initial treatment remains uncertain in SCLC patients. A retrospective study found that rechallenge with immunotherapy after progression extended OS by 6.2 months (mOS: 11.6 vs. 5.4 months, HR: 0.39, 95% CI 0.16–0.92) compared to discontinuing immunotherapy [14]. In the ASTRUM-005 study, 27.8% of patients in the treatment group received subsequent immunotherapy after progression, compared to only 9.7% in the control group, indicating a higher proportion than in previous studies [42]. Similarly, our study included 39 SCLC patients and showed that mPFS and mOS in the IBP group (3.9 months and 9.28 months, respectively) were significantly longer than in the NIBP group.

Our study had certain limitations. First, due to the limitations of retrospective and single-center design, as well as the small sample size, the reliability of the results may be compromised by recall and selection biases. Second, due to the lack of PD-L1 expression data in some patients, a stratified analysis based on PD-L1 expression could not be performed. This limitation may have hindered the evaluation of the potential impact of PD-L1 expression on the efficacy of immunotherapy. In addition, different types of PD-1/PD-L1 monoclonal antibodies may have varying efficacy, which introduces potential confounding factors. Therefore, more prospective studies are needed to fully assess the effectiveness and safety of continued immunotherapy beyond progression and to better identify patients who may benefit from this approach.

Conclusion

Continuous immunotherapy as a second-line treatment following disease progression during initial immunotherapy may improve clinical outcomes in patients with driver gene-negative NSCLC and SCLC. In advanced NSCLC patients with driver gene-negative status who have achieved a favorable response (CR, PR, or SD) to prior treatment, continuation of immunotherapy beyond progression may be associated with improved survival. Larger prospective clinical trials are necessary to further validate these findings.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval 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. Research involving human participants and their data was approved by Ethics Committee of Jinling Hospital, and individual consent for this retrospective analysis was waived.

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