Original Article

Immune checkpoint inhibitors beyond first-line progression with prior immunotherapy in patients with advanced non-small cell lung cancer

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Background: Immunotherapy, monotherapy, and immunotherapy plus platinum-based chemotherapy are the standard treatments for advanced non-small cell lung cancer (NSCLC) patients with negative driver genes. However, the impact of similar continuing immunotherapy beyond progression (IBP) of first-line immunotherapy for advanced NSCLC has not yet been shown. This study aimed to estimate the impact of immunotherapy beyond first-line progression (IBF) and evaluate the factors associated with second-line efficacity.

Methods: Ninety-four cases of advanced NSCLC patients with progressive disease (PD) post first-line treatment with platinum-based chemotherapy plus immunotherapy and administrated prior immune checkpoint inhibitors (ICIs) between November 2017 and July 2021 were retrospectively analyzed. Survival curves were plotted using the Kaplan–Meier method. Cox proportional hazards regression analyses were applied to determine predictive factors independently associated with second-line efficacity.

Results: A total of 94 patients were incorporated in this study. Patients who continued the original ICIs after initial PD were defined as IBF (n=42), whereas those who discontinued immunotherapy were defined as non-IBF (n=52). The second-line objective response rates (ORR, ORR = CR + PR) of patients in the IBF and non-IBF groups were 13.5% *vs.* 28.6%, respectively (P=0.070). No significant survival difference was found between patients in the IBF and non-IBF groups in first-line median progression-free survival (PFS) (mPFS1, 6.2 *vs.* 5.1 months, P=0.490), second-line median PFS (mPFS2, 4.5 *vs.* 2.6 months, P=0.216), or median overall survival (OS) (mOS, 14.4 *vs.* 8.3 months, P=0.188). However, the benefits inPFS2 were observed in individuals performed PFS1 >6 months (group A) than those of PFS1 ≤6 months (group B) (median PFS2, 4.6 *vs.* 3.2 months, P=0.038). Multivariate analyses did not reveal any independent prognostic factors for efficacy.

Conclusions: The benefits of continuing prior ICIs administration beyond first-line immunotherapy progression might not be obvious in patients with advanced NSCLC, but those first line treatment showed a longer period may receive efficacy benefits.

Keywords: Non-small cell lung cancer (NSCLC); immunotherapy beyond progression (IBP); immune checkpoint inhibitors (ICIs); efficacy

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Introduction

Lung cancer is one of the most commonly diagnosed malignancies and a main cancer-related mortality worldwide (1), of which non-small cell lung cancer (NSCLC) makes up 80–85% (2). An increase in the incidence and mortality of NSCLC in China has been observed in recent years (3). Indeed, NSCLC is emerging as a global health challenge (4).

With immune escape mechanisms under investigation, gold treatment guidelines for advanced driver gene-negative NSCLC patients in China incorporated immune checkpoint inhibitor (ICI) monotherapy, including programmed cell death protein 1/programmed cell death-ligand 1 inhibitor monotherapy, and ICIs plus platinum-based doublet chemotherapy (5). In most clinical trials (6-9), such as keynote 024, checkmate 227, and so on, the survival rate of advanced NSCLC improves dramatically as a result of immunotherapy. However, continuing with ICIs with follow-up treatment regimens is still under investigation for advanced NSCLC patients on whom immunotherapy has failed.

Although immunotherapy beyond progression (IBP) among advanced NSCLC patients progressed from prior immunotherapy has been under investigation, majority of the studies included only small sample sizes. In some retrospective analyses, immunotherapy beyond initial progression has been associated with longer overall survival (OS) and progression-free survival (PFS) in patients with advanced NSCLC, which may indicate a novel therapeutic schedule. Some clinical trials have shown the opposite, however, with no statistical difference associated with continued immunotherapy. Much remains to be understood, particularly in terms of treatment beyond first-line immunotherapy.

Collectively, a retrospective research under real-world circumstances was carried out to assess the efficacity of continuing the same ICIs in advanced NSCLC patients after progression of first-line immunotherapy. The results confirm it is beneficial to certain patients in terms of clinical features. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1611/rc).

Highlight box

Key findings

- While the benefits of continuing prior immune checkpoint inhibitor administration beyond first-line immunotherapy progression might be limited for patients with advanced NSCLC, this treatment regime could be considered in patients who achieve better efficacy before first-line PD.

What is known and what is new?

- The benefits of continuing prior ICI administration beyond first-line immunotherapy progression have always been controversial.
- This is one of the earliest studies conducted on individuals who continued the original ICIs after initial PD.

What is the implication, and what should change now?

- Continuing the same ICIs may be an alternative for patients who achieve better efficacy before first-line PD.

Methods

Study design and patients

Medical records of 267 patients were reviewed; they were all with pathologically or cytologically advanced NSCLC (IIIB to IV) and recurrent NSCLC evaluated as progression disease (PD) after receiving first-line immunotherapy combined with platinum-based chemotherapy at Zhejiang Cancer Hospital (Hangzhou, China) between November 2017 and July 2021. All the patients with lung cancer were staged in accordance with the 8th TNM classification. Retrospective demographics, clinical, and radiological information were extracted from electronic medical records (EMRs).

Inclusion criteria were as follows: measurable lesions defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1; Eastern Cooperative Oncology Group (ECOG) performance status 0–1; and adequate organ and bone marrow reserved. Exclusion criteria were incomplete EMRs, prior malignancies, and enrollment in clinical trials.

Patients who were administered with the same immunotherapy scheme in second-line treatment post first PD were defined as IBF, while those who discontinued the immunotherapy for other treatments such as chemotherapy, radiotherapy, or chemoradiotherapy were defined as non-IBF. Furthermore, based on the relationship between PFS1 and 6 months, patients were separated into group A (PFS1 ≤6 months) and group B (PFS1 >6 months).

The study protocol was approved by the Ethics

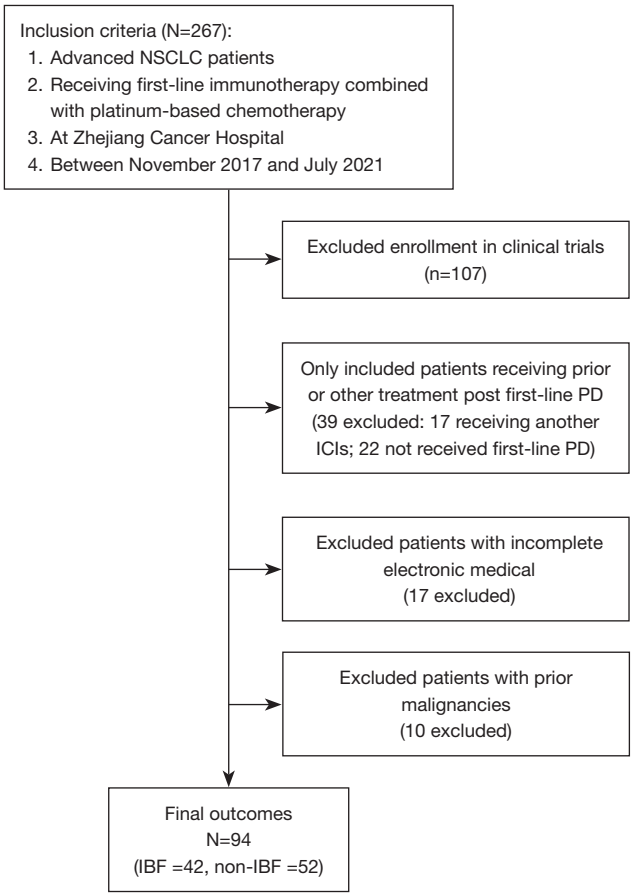

Figure 1 Flow chart of specific screening process. NSCLC, non-small cell lung cancer; PD, progressive disease; ICIs, immune checkpoint inhibitors; IBF, immunotherapy beyond first-line progression; Non-IBF, non-immunotherapy beyond first-line progression.

Committee at Zhejiang Cancer Hospital (Approval No. IRB-2022-187) and was carried out in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

Treatment and response assessments

The clinical responses, including complete response (CR), partial response (PR), stable disease (SD), and PD, were evaluated using computed tomography (CT) based on RECIST v1.1. PFS1 was defined as the time from the initiation of first-line immunotherapy to the date of confirmed PD. PFS2 was defined as the period from the first day of second-line immunotherapy to progression or all-cause mortality, whichever occurred first. OS was defined as the time from the first PD until death, loss to follow-up, or final follow-up. The objective response rate (ORR) was defined as the sum of the CR and PR, while the disease control rate (DCR) was the sum of the CR, PR, and SD. The date of the last follow-up was September 3, 2022.

Statistical analysis

Percentages (%) was presented to depict the baseline demographic statistics. Pearson's Chi-squared or Fisher's exact test was used to compare categorical variables in baseline characteristics between groups. Student's *t*-test or Mann-Whitney U test was adopted to evaluate the differences in continuous or ordinal variables. Kaplan-Meier curves were applied to calculate median PFS1, PFS2, and OS, and the log-rank test was used to evaluate differences. The multivariable Cox proportional hazard regression model was applied to determine the hazard ratio (HR) and corresponding 95% confidence interval (CI), and case characteristics with significant outcomes were regarded as independent predictive factors. P values were calculated given a two-sided hypothesis, and $P<0.05$ was considered statistically significant. Statistical analyses were performed with SPSS 22.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 8.0 (GraphPad Software Inc., San Diego, CA, USA).

Results

Patients

This retrospective study finally screened out 94 patients with advanced NSCLC who received PD post first-line treatment with platinum-based doublet chemotherapy plus immunotherapy between November 2017 and July 2021. The specific screening flow chart is shown in *Figure 1*. Baseline characteristics of patients are summarized in *Table 1*. The median age was 63 years (range, 33–76 years) old, with 33 (35.1%) patients aged above 65; 71 (75.5%) patients were male, while 23 (24.5%) were female. Thirty-one (33.0%) patients were never-smokers. The histologic subtypes present were adenocarcinoma in 45 (47.9%) patients and non-adenocarcinoma in 47 (52.1%) patients. Liver and brain metastases at diagnosis were 19 (20.2%) and 12 (12.8%), respectively. The ECOG performance status of each patient was 0 or 1. Subjects were divided into

Table 1 Baseline characteristics

Characteristics	No. of patients (%)		
	All patients (n=94)	Non-IBF (n=52)	IBF (n=42)
Age (years)			
≤65	61 (64.9)	34 (65.4)	27 (64.3)
>65	33 (35.1)	18 (34.6)	15 (35.7)
Sex			
Male	71 (75.5)	37 (71.2)	34 (81.0)
Female	23 (24.5)	15 (28.8)	8 (19.0)
ECOG performance status			
0	23 (24.5)	15 (28.8)	8 (19.0)
1	71 (75.5)	37 (71.2)	34 (81.0)
Smoking history			
Ever	63 (67.0)	33 (63.5)	30 (71.4)
Never	31 (33.0)	19 (36.5)	12 (28.6)
Histology			
Squamous	36 (38.3)	19 (36.5)	17 (40.5)
Adenocarcinoma	45 (47.9)	30 (57.8)	15 (35.7)
Adenosquamous	4 (4.3)	1 (1.9)	3 (7.1)
Unknown	9 (9.5)	2 (3.8)	7 (16.7)
PD-L1 expression			
Negative (<1%TPS)	12 (12.8)	5 (9.6)	7 (16.7)
Low (1–49%TPS)	22 (23.4)	11 (21.2)	11 (26.2)
High (≥50%TPS)	11 (11.7)	4 (7.7)	7 (16.7)
Not tested	49 (52.1)	32 (61.5)	17 (40.4)
Liver metastases			
Yes	19 (20.2)	8 (15.4)	11 (26.2)
No	75 (79.8)	44 (84.6)	31 (73.8)
Brain metastases			
Yes	12 (12.8)	10 (19.2)	2 (4.8)
No	82 (87.2)	42 (80.8)	40 (95.2)
Bone metastases			
Yes	45 (47.9)	23 (44.2)	22 (52.4)
No	49 (52.1)	29 (55.8)	20 (47.6)

IBF, immunotherapy beyond first-line progression; non-IBF, non-immunotherapy beyond first-line progression; ECOG performance status, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death-ligand 1; TPS, tumor cell proportion score.

Table 2 Data on responses of patients

Type of response	No. of patients (%)			P value
	All patients (n=94)	Non-IBF (n=52)	IBF (n=42)	
The first-line				0.842
Complete response	0 (0.0)	0 (0.0)	0 (0.0)	
Partial response	35 (37.2)	18 (34.6)	17 (40.5)	
Stable disease	45 (47.9)	26 (50.0)	19 (45.2)	
Progressive disease	14 (14.9)	8 (15.4)	6 (14.3)	
Objective response rate[a] (95% CI)	35 (37.2)	18 (34.6)	17 (40.5)	0.559
Disease control rate[b] (95% CI)	80 (85.1)	44 (84.6)	36 (85.7)	0.882
The second-line				0.121
Complete response	0 (0.0)	0 (0.0)	0 (0.0)	
Partial response	19 (20.2)	7 (13.5)	12 (28.6)	
Stable disease	39 (41.5)	21 (40.4)	18 (42.8)	
Progressive disease	29 (30.9)	18 (34.6)	11 (26.2)	
Not evaluated	7 (7.4)	6 (11.5)	1 (2.4)	
Objective response rate[a] (95% CI)	19 (20.2)	7 (13.5)	12 (28.6)	0.070
Disease control rate[b] (95% CI)	58 (61.7)	28 (53.9)	30 (71.5)	0.081

[a], complete response or partial response; [b], complete response, partial response, or stable disease. IBF, immunotherapy beyond first-line progression; non-IBF, non-immunotherapy beyond first-line progression; 95% CI, 95% confidence interval.

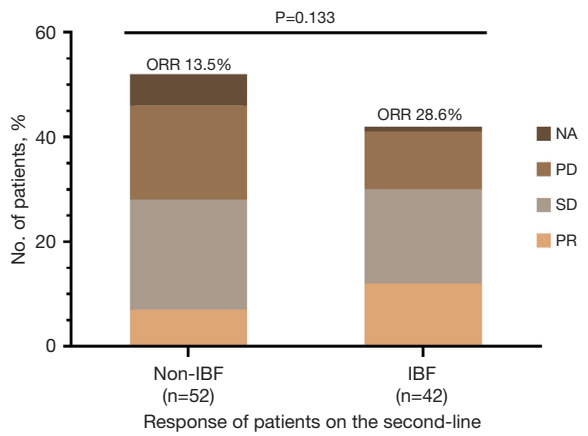

Figure 2 Response of patients to second-line treatment. Outcomes were not statistically different in ORR between non-IBF and IBF (13.5% *vs.* 28.6%, P=0.070). ORR, objective response rate; IBF, immunotherapy beyond first-line progression; non-IBF, non-immunotherapy beyond first-line progression; NA, not evaluated; PD, progressive disease; SD, stable disease; PR, partial response.

two groups as per whether the same immunotherapy was continued following PD of first-line therapy: IBF (n=42) and non-IBF (n=52). Detailed characteristics of two groups were listed in *Table 1*.

Treatment response

All the patients involved in the study exhibited RECIST v1.1 PD to first-line immunotherapy consistent with the inclusion criteria. A summary of the confirmed best overall response before and post-first progression is listed in *Table 2* and *Figure 2*. In the first-line treatments, 18 (34.6%) patients achieved PR and 26 (50.0%) had SD in the IBF subgroup, compared to 17 (40.5%) and 19 (45.2%), respectively, in the non-IBF group. A similar result was observed in second-line treatments; 7 (13.5%) PR and 21 (40.4%) SD patients were in the former compared to 12 (28.6%) PR and 18 (42.8%) in the latter. No difference was found before or post-first progression between the IBF

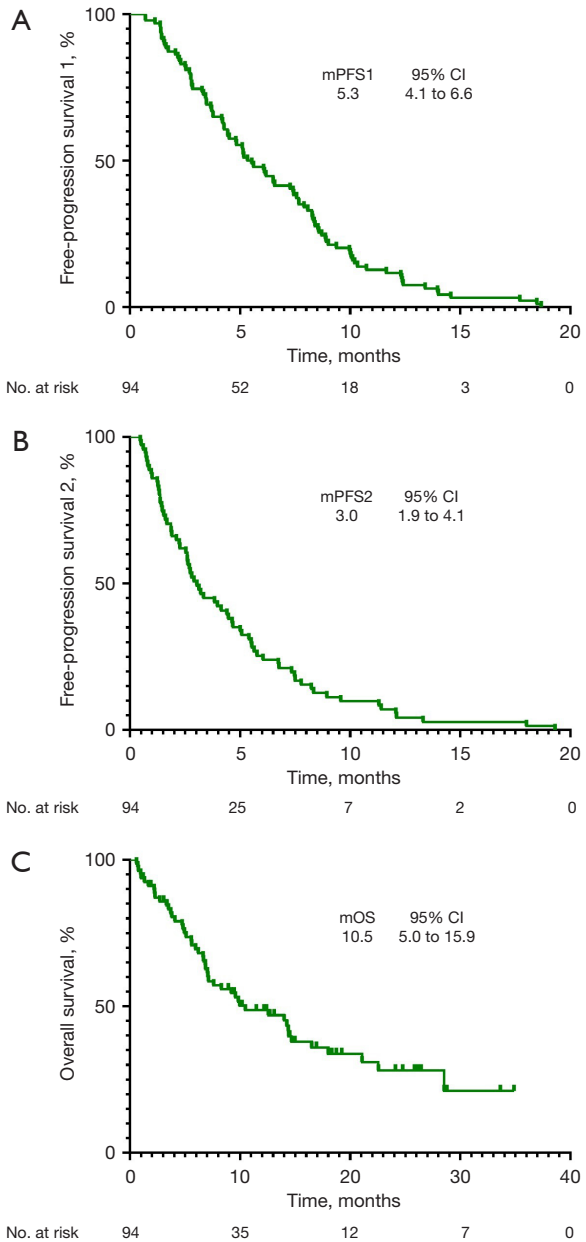

Figure 3 Kaplan-Meier curves of PFS1 (A), PFS2 (B), and OS (C) of all patients. Median PFS1, 5.3 months (95% CI: 4.1–6.6 months); median PFS2, 3.0 months (95% CI: 1.9–4.1 months); median OS, 10.5 months (95% CI: 5.0–15.9 months). PFS1, the free-progression survival of the first-line; PFS2, the free-progression survival of the second-line; OS, overall survival; 95% CI, 95% confidence interval.

and non-IBF groups in terms of ORR (first-line treatment: 34.6% *vs.* 40.5%, P=0.559; second-line treatment: 13.5% *vs.* 28.6%, P=0.070, respectively).

Efficacity analyses

A total of 15 (16.0%) individuals were lost to follow-up, including 4 (9.5%) patients in the IBF group, which did not significantly affect the study.

The overall population median PFS1 was 5.3 months (95% CI: 4.1 to 6.6 months), median PFS2 was 3.0 months (95% CI: 1.9 to 4.1 months), and median OS was 10.5 months (95% CI: 5.0 to 15.9 months) (*Figure 3*). PFS1 was statistically similar among the IBF and non-IBF groups (PFS1: 6.2 *vs.* 5.1 months, P=0.490) (*Figure 4A*), indicating the balance of primal survival. However, no significant difference was observed in PFS2 (4.5 *vs.* 2.6 months, P=0.216) (*Figure 4B*) and OS (14.4 *vs.* 8.3 months, P=0.188) (*Figure 4C*), demonstrating that continuation of immunotherapy may have no effect on survival.

Further analysis was carried on patients who achieved PFS1 ≤6 months (group A) and PFS1 >6 months (group B) during first-line therapy. Compared with group B, patients who achieved a longer PFS1 may present with a better curative outcome, with a median PFS2 of 3.2 months (95% CI: 1.2 to 5.2 months) in contrast to 4.6 months (95% CI: 1.9 to 7.3 months) in PFS1 ≤6 months patients (P=0.038) (*Figure 5A*). Although there was no statistically significant difference in OS between the two groups (P=0.221), the subgroup analysis showed that patients in group A (mOS: 10.4, 95% CI: 0.3 to 20.6 months) exhibited a favorable trend in OS compared with group B (mOS: 18.0, 95% CI: 5.4 to 30.6 months) (*Figure 5B*). Furthermore, multivariate analysis revealed that variables including sex, age, smoking history, histology, ECOG performance status, and progression patterns failed to independently impact second-line free-progression survival (*Figure 6*).

Discussion

The present study provided analysis of treatment choices in subsequent therapy after first-line failure for advanced NSCLC patients, and showed limited benefits of continuing prior ICI administration beyond first-line immunotherapy progression, except for cases with a longer maintenance period during the first-line therapy.

With immunotherapy bringing a paradigm shift in oncology treatment, treatment regimens for diverse conditions are also under development. Discoveries from initial monotherapy, combination therapy, and subsequent IBP are being kept abreast of scientific development. Some treatment patterns have shown noteworthy survival benefits,

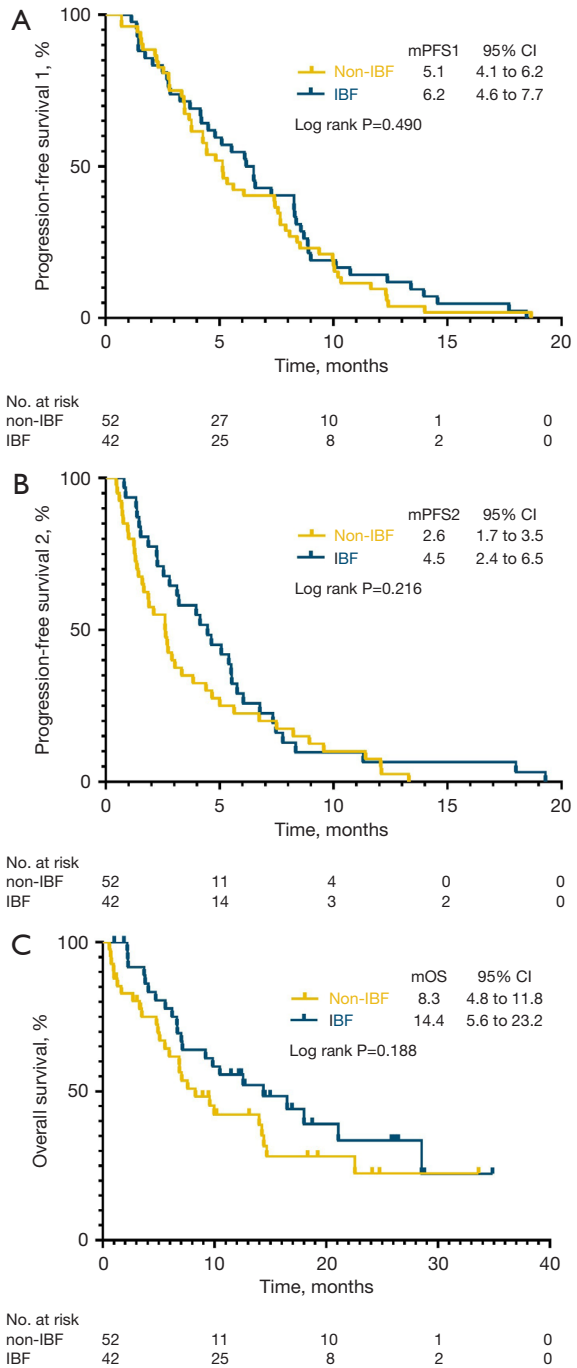

Figure 4 Kaplan-Meier curves of PFS1 (A), PFS2 (B), and OS (C) of patients in IBF and non-IBF groups. No statistically significant differences in PFS1, PFS2, and OS (median PFS1, 6.2 *vs.* 5.1 months, P=0.490; median PFS2, 4.5 *vs.* 2.6 months, P=0.216; median OS, 14.4 *vs.* 8.3 months, P=0.188). PFS1, the free-progression survival of the first-line; PFS2, the free-progression survival of the second-line; OS, overall survival; IBF, immunotherapy beyond first-line progression; non-IBF, non-immunotherapy beyond first-line progression; 95% CI, 95% confidence interval.

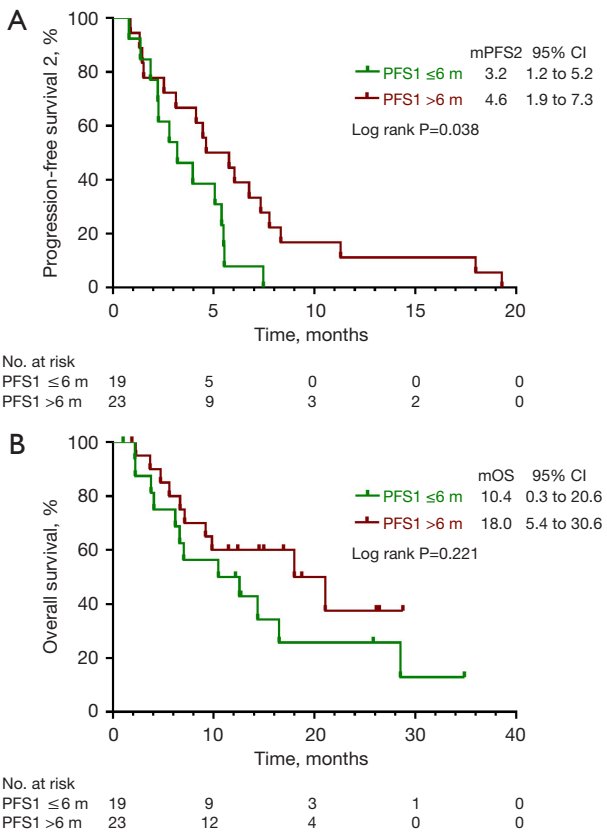

Figure 5 Kaplan-Meier curves of PFS2 (A) and OS (B) of patients in groups A (PFS1 ≤6 months) and B (PFS1 >6 months). Patients with longer survival (group B) in first-line immunotherapy had better PFS than patients with shorter survival times (group A) (median PFS2, group A *vs.* group B, 3.2 *vs.* 4.6 months, P=0.038). No significant differences in OS were observed between group A and B (median OS, 10.4 *vs.* 18.0 months, P=0.221). PFS1, the free-progression survival of the first-line; PFS2, the free-progression survival of the second-line; OS, overall survival; IBF, immunotherapy beyond first-line progression; non-IBF, non-immunotherapy beyond first-line progression.

such as the PACIFIC model (10).

A similar result has been observed in some IBP studies. A retrospective study from Ge *et al.* (11) reported IBP may enable patients with advanced NSCLC to achieve prolonged OS (median: 26.6 *vs.* 10.7 months; P=0.015) and PFS (median: 9.7 *vs.* 4.3 months; P<0.001). Regardless of the fact that there was no statistically significant difference in the ORR (15.4% *vs.* 11.6%, P=0.560), the DCR was considerably higher in the IBP group (89.7% *vs.* 61.6%, P=0.001). Similarly, according to another retrospective analysis with 60 patients, Ricciuti *et al.* (12) revealed that

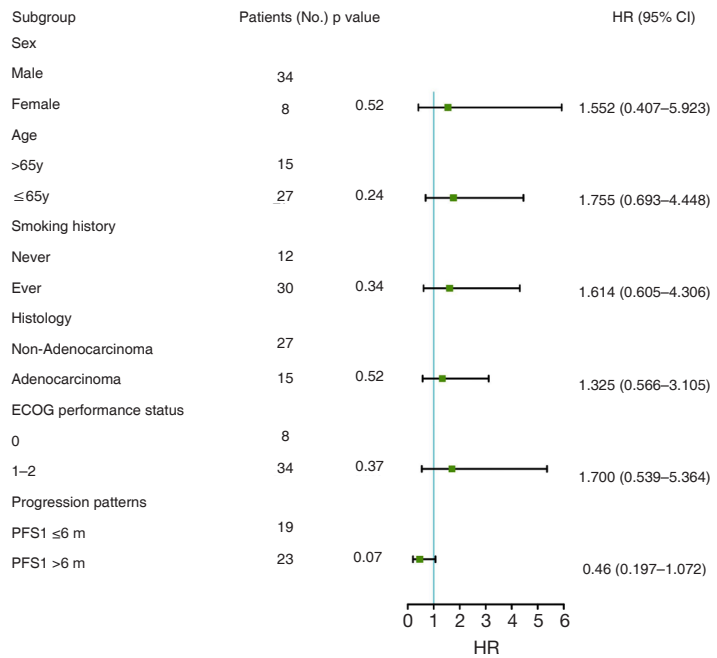

Figure 6 Forest plot of the IBF group. HR, hazard ratio; IBF, immunotherapy beyond first-line progression; ECOG, Eastern Cooperative Oncology Group; PFS1, the free-progression survival of the first-line.

Table 3 A summary of previously-published relevant studies

Reference	Regimen	IBP		Non-IBP		P value
		N	OS	N	OS	
Ge *et al.* (11)	PD-(L)1	39	26.6	86	10.7	0.015
Ricciuti *et al.* (12)	Nivolumab	60	17.8	116	3.7	<0.001
Enomoto *et al.* (14)	Nivolumab	28	15.6	46	13.4	0.40
David *et al.* (13)	Atezolizumab	168	12.7	94	8.8	NE

IBF, immunotherapy beyond first-line progression; non-IBF, non-immunotherapy beyond first-line progression; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; OS, overall survival; NE, not evaluated.

for a selected group of patients with advanced NSCLC, continuing nivolumab may provide promising clinical survival benefits, with a median OS of 17.8 months.

Nevertheless, ICI retreatment after progression remains controversial as some studies have shown opposite results. David *et al.* (13) conducted a retrospective analysis in which the median post-PD OS was 12.7 months in 168 atezolizumab-administered patients in IBP, while 8.8 months in 94 patients switching to non-protocol therapy. Enomoto *et al.* (14) showed no remarkable advantages relevant to continuation of nivolumab for advanced NSCLC patients (15.6 *vs.* 13.4 months, P=0.40). A summary of relevant studies is listed in *Table 3*. In this context, the curative effects of IBP, especially continuing the same ICI post first-line PD, remain to be determined.

Hence, this retrospective study has been designed. The study, to our knowledge, is one of the earliest studies conducted on individuals who were given an immunotherapy regime as first-line treatment, and evaluates the effect of continuing the same ICIs beyond first progression. Little survival benefits were revealed in continuing ICI administration beyond first-line immunotherapy, as shown by the statistical outcomes between PFS1, PFS2, and OS. These analyses lead us

to further explore this new therapeutic strategy. To investigate relevant clinical characteristics, this retrospective study focused on the association between first- and second-line survival for patients with advanced NSCLC. Subgroup analyses indicated that prolonged duration of first-line therapy provided a longer PFS2 and a favorable tendency for OS. The promising consequence of PFS2 may encourage us to consider this regime for those with better survival in the first-line immunotherapy. OS is influenced by many factors, which requires more prospective studies. A multivariate analysis, which showed no statistical differences, was also conducted, indicating longer first-line duration cannot predict or independently influence survival.

The present study also has some limitations. First, it is limited by its retrospective and single-center design, as well as the small sample size, which may undermine the reliability of the results by recall and selection bias. Second, the clinical response, subsequent treatment regime, and types of ICIs were only evaluated by clinicians, so we cannot adequately estimate the real impact of IBF. Third, the majority of patients lacked tumor mutation burden or PD-L1 expression, which may impact further research on predictive biomarkers. Lastly, this study did not use immune-related RECIST (irRECIST), although it has been suggested to be too complicated to be widely used in clinical practice (14). Thus, there is still much room for IBP and more prospective studies are required.

Conclusions

There were no significant benefits associated with continuation of original ICIs for advanced NSCLC patients beyond first-line immunotherapy. However, this treatment regime might be considered for patients who show better outcomes before first-line PD. Large prospective clinical trials are required to further validate these findings.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1611/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1611/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1611/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol was approved by the Ethics Committee at Zhejiang Cancer Hospital (Approval No. IRB-2022-187) and was carried out in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived.

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