Immunotherapy beyond progression following first-line chemotherapy plus immunotherapy in advanced non-small cell lung cancer: A retrospective study

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Abstract. Immunotherapy has paved the way for new treatment options for advanced non-small cell lung cancer (NSCLC). However, for patients who have progressed following first-line immunotherapy combined with chemotherapy, little is known about the benefits of the continuation of immunotherapy. Thus, the current study aimed to evaluate the efficacy of immunotherapy beyond progression (IBP) in patients with advanced NSCLC. A retrospective review of patients with advanced NSCLC who experienced disease progression after receiving a combination of ICIs and chemotherapy was conducted. Kaplan-Meier survival analysis was used to estimate progression-free survival (PFS) and overall survival (OS) times, and log-rank tests were employed to compare inter-group differences. Cox regression analyses were performed to identify independent factors associated with OS and PFS. In total, 136 patients who had disease progression after prior immunotherapy were included. A comparison of patients who were treated with ICIs after disease progression (IBP group) and those who received other treatments (non-IBP group) demonstrated a higher disease control rate after second-line treatment for the IBP group (89.8 vs. 70.8%, respectively; P=0.005). Kaplan-Meier curve analysis showed statistical differences in PFS2 (interval from the second-line treatment to progression or death for any reason; P=0.012) and OS (P=0.041). Subgroup analyses indicated superior clinical outcomes for the IBP group. Multivariate analyses revealed IBP to be an independent factor associated with improved PFS2 (hazard ratio, 0.613; 95% confidence interval, 0.403-0.933; P=0.022). In conclusion, favorable clinical outcomes for IBP were observed, and IBP remains a viable choice for patients with advanced NSCLC.

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Introduction

Lung cancer is the second most commonly diagnosed cancer and the leading cause of cancer-related death. In 2020, lung cancer accounted for ~1.8 million deaths worldwide, with an estimated 2.2 million new cases diagnosed (1). Non-small cell lung cancer (NSCLC) is the most prevalent histological type, accounting for ~85% of all lung cancer cases (2). With the discovery of immune-related molecules, such as programmed cell death protein 1 (PD-1), cytotoxic T-lymphocyte protein 4 and other molecules, the precise treatment of tumors has entered the era of immunotherapy. Clinical trials have shown that the use of immune checkpoint inhibitors (ICIs) in combination with chemotherapy is more effective against NSCLC than chemotherapy alone (3-7). However, follow-up treatment options remain under investigation for patients with advanced NSCLC in whom immunotherapy has failed. Some of these patients receive a new treatment strategy, including traditional chemotherapy, anti-angiogenic drugs or radiotherapy, while others choose to continue with immunotherapy, a practice known as immunotherapy beyond progression (IBP).

Previous studies have demonstrated longer survival times or continued tumor burden reduction of IBP in patients with melanoma (8,9) and renal cell carcinoma (10,11). Limited studies have been reported for patients with NSCLC, and the clinical outcomes were variable. The KEYNOTE-010 study showed a good response for patients who received second-course pembrolizumab (12), but real-world research demonstrated no significant benefits for continued nivolumab in advanced NSCLC (13). Therefore, the merits of IBP after disease progression remain controversial.

The current study aimed to elucidate the potential benefits of continuing ICIs after first-line immunotherapy plus chemotherapy resulted in progression in patients with advanced NSCLC, and analyzed data by treatment subgroups to indicate the effects of IBP.

Patients and methods

Patient population. A total of 136 patients with advanced NSCLC who were hospitalized in Union Hospital Cancer Center (Wuhan, China) between March 2018 and July 2022, and whose response was assessed as progressive disease (PD) after receiving first-line immunotherapy plus chemotherapy, were included. The inclusion criteria were as follows: i) Pathologically confirmed NSCLC at the time of initial diagnosis; ii) stage IIIB-IV disease according to the 8th edition of the American Joint Committee on Cancer staging system (14) or recurrence after surgery; and iii) received at least two cycles of first-line ICIs in combination with chemotherapy, and disease status was defined as PD according to the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) (15). Exclusion criteria were as follows: i) Sensitized EGFR/ALK/ROS1 alteration; ii) recorded second primary malignant tumor or condition complicated with autoimmune diseases; iii) participation in clinical trials; and iv) a lack of follow-up data.

Patients who received immunotherapy beyond first-line progression were defined as the IBP group, while those who was treated with other treatments, such as chemotherapy, anti-angiogenic therapy or local radiotherapy, were defined as the non-IBP group. In the present study, further treatment after first-line progression was selected by the clinician according to the actual clinical situation, including the economic status and choice of the patient.

The following clinicopathological data were collected: Age, sex, histological type, smoking history, sites of distant metastases and Eastern Cooperative Oncology Group performance status (ECOG PS) score (16).

Efficacy evaluation. Clinical response to treatment, including complete response (CR; disappearance of all target lesions), partial response (PR; at least a 30% decrease in the sum of the diameters of the target lesions), PD (at least a 20% increase in the sum of the diameters of the target lesions and an absolute increase of the sum by at least 5 mm or the appearance of one or more new lesions) and stable disease (SD; neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD), was evaluated by RECIST 1.1 criteria. The objective response rate (ORR) was calculated as the percentage of patients with the best overall response of CR and PR (CR + PR). The disease control rate (DCR) was defined as the percentage of patients with the best overall response of CR, PR and SD (CR + PR + SD). PFS1 was the interval from the date of initially receiving first-line treatment to progression of the disease. PFS2 was the interval from the second-line treatment to progression or death for any reason. OS referred to the start of the second-line treatment until death for any cause or the final follow-up.

Statistical analysis. The χ^2 test or Fisher's exact test was used to assess the statistical difference between categorical variables. PFS time and OS time were analyzed by the Kaplan-Meier method, and the log-rank test was employed to calculate inter-group differences. Independent predictors of PFS and OS were determined by Cox regression models. Multivariate analysis was performed on variables that were statistically significant in univariate analysis, and identified independent prognostic factors associated with OS and PFS. All statistical analyses were performed using SPSS 25.0 (IBM Corp.) and R-4.2.1 (The R Foundation). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Characteristics of patients. The medical records of 136 patients with advanced NSCLC who experienced PD after first-line chemotherapy combined with ICIs were retrospectively reviewed. A total of 88 patients received IBP, while 48 patients received non-IBP treatments (Table I). Overall, the median age for all participants was 60 years (range, 25-83 years). 66.9% of patients (n=91) were aged <65 years and 83.8% were male, while 52.2% were current or former smokers. An ECOG-PS of 0-1 was recorded in 81.6% of patients (n=111). A total of 84 (61.8%) patients had adenocarcinoma and 52 (38.2%) had non-adenocarcinoma. Brain metastases were recorded in 45 (33.1%) patients, bone metastases in 56 (41.2%) patients and liver metastases in 24 (17.6%) patients. Patient characteristics, including age, sex, histological type and smoking history, were well-balanced between IBP and non-IBP groupings.

Analysis of treatment response. In order to explore the treatment responses of the two groups, DCR and ORR were analyzed and compared. The best response was judged according to RECIST 1.1 (Table II). Responses to first-line treatment were an ORR of 43.8% and a DCR of 97.9% for the non-IBP group, and an ORR of 38.6% and a DCR of 92.0% for the IBP group. Responses to second-line treatment were ORRs of 12.5% for the non-IBP group and 15.9% for the IBP group. There were no significant differences in treatment response in first-line treatment between the IBP and non-IBP groups (ORR: P=0.561; DCR: P=0.313) or for ORR after second-line treatment (P=0.592). However, the IBP group exhibited a significantly higher DCR than the non-IBP group after second-line treatment (89.8 vs. 70.8%; P=0.005) (Fig. 1).

Analysis of survival probability. The median PFS2 time was 7.7 months for the IBP group and 4.47 months for the non-IBP group. The median OS time was 26.17 months for the IBP group and 12.87 months for the non-IBP group. Kaplan-Meier plots demonstrated that IBP was significantly associated with prolonged PFS2 [hazard ratio (HR), 0.597; 95% confidence interval (CI), 0.379-0.940; P=0.012] and OS (HR, 0.584; 95% CI, 0.334-1.022; P=0.041) times (Fig. 2A and B).

Subgroup analyses were conducted, taking patient characteristics into consideration. IBP produced a higher PFS2 time (Fig. S1) in most subgroups, especially for younger patients (P=0.008), males (P=0.009), patients who had never smoked (P=0.010), those with a histological type other than adenocarcinoma (P=0.004), patients with ECOG scores 0-1 (P=0.006),

Table I. Baseline characteristics of all patients.

Characteristics	All patients, n (%)	Non-IBP, n (%)	IBP, n (%)	P-value
Age, years				0.670
≤65	91 (66.9)	31 (64.6)	60 (68.2)	
>65	45 (33.1)	17 (35.4)	28 (31.8)	
Sex				0.709
Male	114 (83.8)	41 (85.4)	73 (83.0)	
Female	22 (16.2)	7 (14.6)	15 (17.0)	
Histological type				0.385
Adenocarcinoma	84 (61.8)	32 (66.7)	52 (59.1)	
Non-Adenocarcinoma	52 (38.2)	16 (33.3)	36 (40.9)	
Smoking status				0.704
Never smoked	65 (47.8)	24 (50.0)	41 (46.6)	
Current/former smoker	71 (52.2)	24 (50.0)	47 (53.4)	
ECOG PS				0.606
0-1	111 (81.6)	39 (81.3)	72 (81.8)	
2	25 (18.4)	9 (18.8)	16 (18.2)	
Brain metastases				0.116
No	91 (66.9)	28 (58.3)	63 (71.6)	
Yes	45 (33.1)	20 (41.7)	25 (28.4)	
Bone metastases				0.932
No	80 (58.8)	28 (58.3)	52 (59.1)	
Yes	56 (41.2)	20 (41.7)	36 (40.9)	
Liver metastases				0.472
No	112 (82.4)	38 (79.2)	74 (84.1)	
Yes	24 (17.6)	10 (20.8)	14 (15.9)	

ECOG PS, Eastern Cooperative Oncology Group performance status; IBP, immunotherapy beyond progression.

and those without brain (P=0.006) or liver (P=0.002) metastases. Similarly, continuation of ICIs in second-line treatment produced more favorable OS times for younger patients (P=0.021), males (P=0.038) and those with ECOG scores 0-1 (P=0.030) (Fig. S2).

Univariate analysis showed ECOG PS 0-1 (P=0.038), good response (CR + PR) to initial immunotherapy (P=0.036) and IBP group (P=0.013) to be associated with prolonged PFS2 time (Table SI). Patients with a non-adenocarcinoma histological type (P=0.005), ECOG PS 0-1 (P<0.001) and IBP group (P=0.044) were associated with a longer OS time (Table SII). Multivariate Cox proportional hazards analyses demonstrated that IBP was an independent PFS2-related factor (HR, 0.613; 95% CI, 0.403-0.933; P=0.022; Table SI), but not an independent factor for OS (HR, 0.613; 95% CI, 0.360-1.045; P=0.072; Table SII). Moreover, ECOG PS 2 (HR, 1.953; 95% CI, 1.140-3.347; P=0.015; Table SI) and good response (CR + PR) to initial immunotherapy (HR, 0.579; 95% CI, 0.373-0.901; P=0.015; Table SI) were independent PFS2-related factors. Non-adenocarcinoma histological type (HR, 2.339; 95% CI, 1.380-3.964; P=0.002; Table SII) and ECOG PS 2 (HR, 2.897; 95% CI, 1.616-5.194; P<0.001; Table SII) were independent OS-related factors.

Analysis of IBP efficacy. A subgroup analysis of IBP efficacy was performed (Table III). Patients whose initial treatment response was CR + PR showed a prolonged PFS2 time compared with those whose treatment response was SD + PD after prior ICIs (mPFS2: 10.3 vs. 6.27 months; HR, 0.574; 95% CI, 0.346-0.952; P=0.031; Fig. 3A). Patients with a PFS1 >6 months had a higher PFS2 time than patients with a PFS1 ≤6 months (mPSF2: 10.3 vs. 4.8 months; HR, 0.555; 95% CI, 0.311-0.911; P=0.023; Fig. 4A). However, no difference in OS time was observed between the CR + PR group and the SD + PD group for first-line treatment (P=0.342; Fig. 3B) or between the PFS1 >6 months group and the PFS1 ≤6 months group (P=0.115; Fig. 4B).

Second-line immunotherapy treatment strategies were analyzed for their impact on efficacy. The patients treated with three agents [chemo (chemotherapy) + immunotherapy (IO) + anti-angiogenic therapy (anti-angio); n=28] had prolonged PFS2 times (mPSF2: 9.1 vs. 7.6 months; HR, 0.821; 95% CI, 0.466-1.445; P=0.481; Fig. S3A) compared with those treated with two agents (chemo + IO; n=40), although the difference was not statistically significant. OS times were comparable between the two groups (mOS: 27.97 vs. 26.17 months; HR, 0.917; 95% CI, 0.412-2.042; P=0.831; Fig. S3B).

Table II. Treatment responses of all patients.

Treatment response	All patients, n (%)	Non-IBP, n (%)	IBP, n (%)	P-value
First-line response				
CR	0 (0.0)	0 (0.0)	0 (0.0)	
PR	55 (40.4)	21 (43.8)	34 (38.6)	
SD	73 (53.7)	26 (54.2)	47 (53.4)	
PD	8 (5.9)	1 (2.1)	7 (8.0)	
ORR	55 (40.4)	21 (43.8)	34 (38.6)	0.561
DCR	128 (94.1)	47 (97.9)	81 (92.0)	0.313
Second-line response				
CR	0 (0.0)	0 (0.0)	0 (0.0)	
PR	20 (14.7)	6 (12.5)	14 (15.9)	
SD	93 (68.4)	28 (58.3)	65 (73.9)	
PD	23 (16.9)	14 (29.2)	9 (10.2)	
ORR	20 (14.7)	6 (12.5)	14 (15.9)	0.592
DCR	113 (83.1)	34 (70.8)	79 (89.8)	0.005

CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; ORR, objective response rate; DCR, disease control rate; IBP, immunotherapy beyond progression.

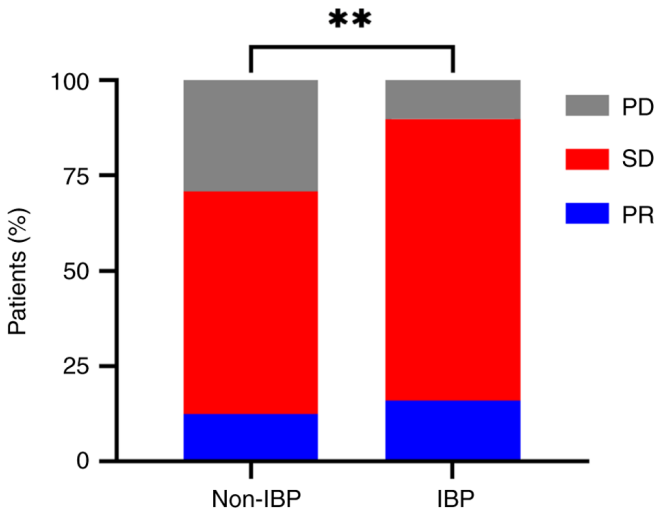

Figure 1. Disease control rate of patients following second-line treatment. PD, progressive disease; SD, stable disease; PR, partial response; IBP, immunotherapy beyond progression. **P<0.01.

Table III. Clinical characteristics of immunotherapy beyond progression group (n=88).

Clinical characteristics	Patients, n (%)
First-line response	
CR + PR	34 (38.6)
SD + PD	54 (61.4)
PFS1 time, months	
≤6	31 (35.2)
>6	57 (64.8)
Second-line treatment	
Monotherapy	13 (14.8)
Combination therapy	75 (85.2)
Immunotherapy options	
Use the same ICI	10 (11.4)
Change the ICI	78 (88.6)

CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; ICI, immune checkpoint inhibitor; PFS1, progression-free survival from first-line treatment.

Discussion

Immunotherapy is the usual treatment choice for NSCLC without driver gene mutations. ICIs relieve the inhibition of immune cells and enhance antitumor activity (17). However, patients may show individual response patterns to ICIs, including late treatment response and pseudo-progression (18), meaning that the optimal treatment duration remains uncertain. Much controversy surrounds the continuation of immunotherapy following progression after first-line immunochemotherapy and the potential patient benefits.

Previous studies have shown that IBP is effective for advanced NSCLC. Ricciuti *et al* (19) reported that discontinuation of immunotherapy at first progression was associated with shorter survival times. Another study also reported that the IBP group experienced longer OS times compared with the non-IBP group (20). Conversely, Metro *et al* (21) explored the outcomes of chemotherapy or pembrolizumab beyond first-line pembrolizumab in patients with advanced NSCLC and programmed cell death 1 ligand 1 (PD-L1) ≥50%, and found no significant difference in post-progression survival time.

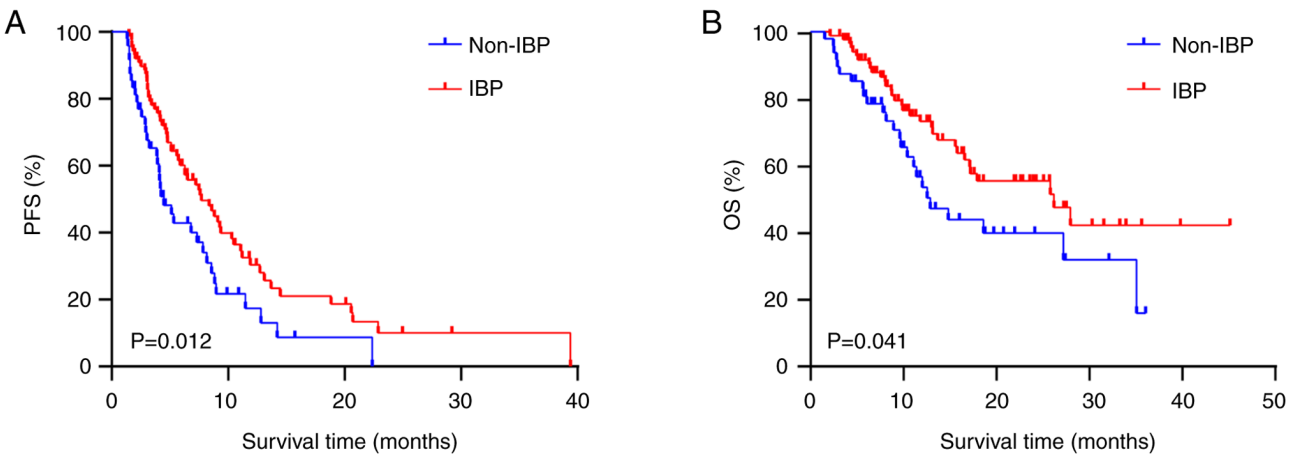

Figure 2. Kaplan-Meier curves of (A) PFS2 and (B) OS of all patients. IBP, immunotherapy beyond progression; PFS2, progression-free survival from second-line treatment; OS, overall survival.

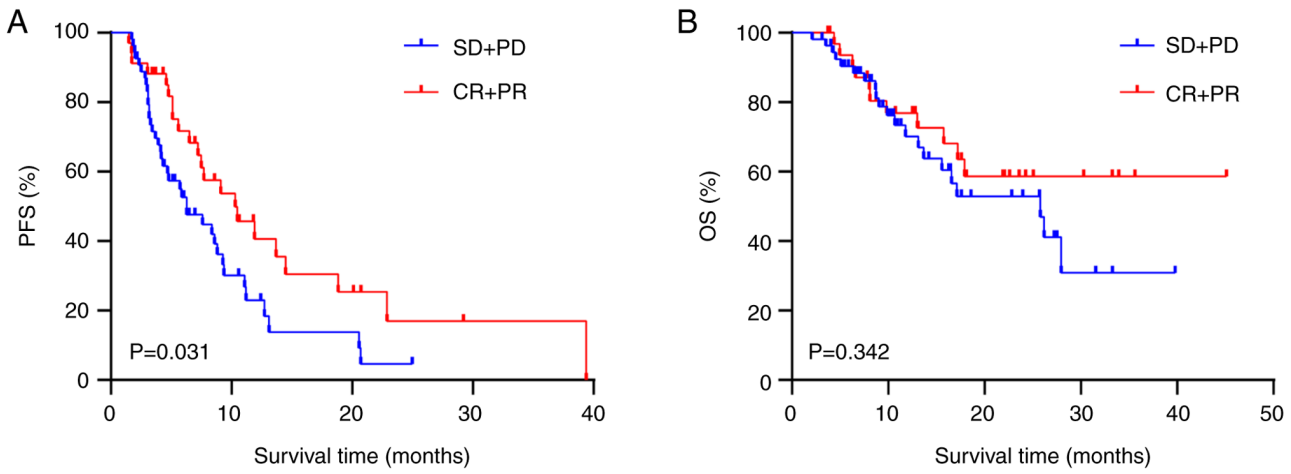

Figure 3. Kaplan-Meier curves of (A) PFS2 and (B) OS for the patients whose initial treatment response was CR + PR and for the patients whose initial treatment response was SD + PD. PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response; PFS2, progression-free survival from second-line treatment; OS, overall survival.

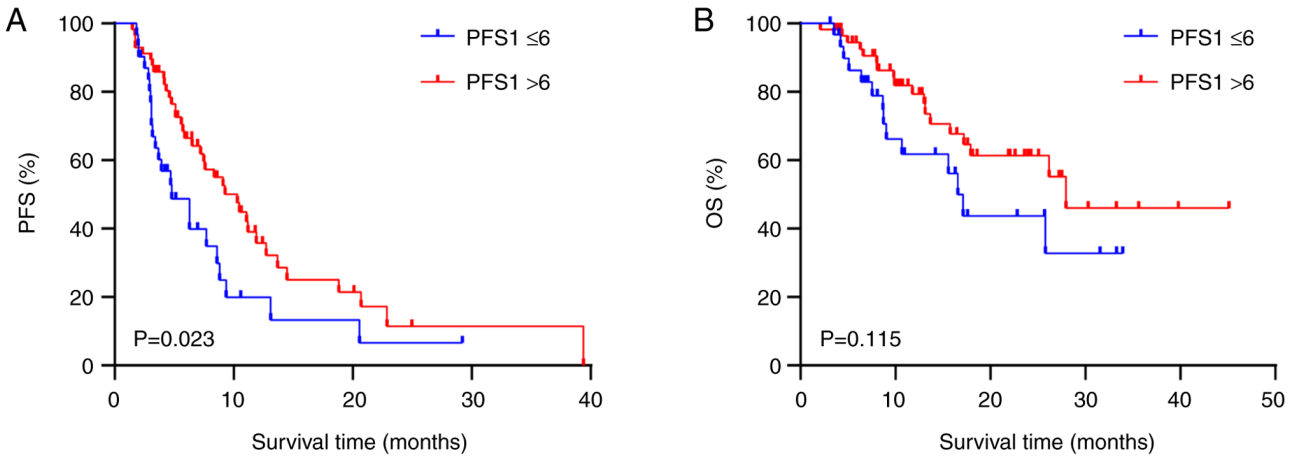

Figure 4. Kaplan-Meier curves of (A) PFS2 and (B) OS for the patients with a PFS1 time >6 months and for the patients with a PFS1 time ≤6 months. PFS1, progression-free survival from first-line treatment; PFS2, progression-free survival from second-line treatment; OS, overall survival.

IBP was initially explored in lung cancer, but these patients received first-line or multiline antitumor therapy prior to IBP or ICI monotherapy rather than immunotherapy plus chemotherapy prior to IBP (13,19,20). Few studies have

explored whether IBP in patients with NSCLC after first-line immunotherapy combined with chemotherapy is beneficial (22). In the present study, IBP achieved superior PFS2 (P=0.012) and OS (P=0.041) times after the progression of first-line immunotherapy combined with chemotherapy for the current cohort of patients, which is in line with previous studies (19,20). However, retrospective studies reported no statistical difference in PFS2 and OS times between the IBP group and the non-IBP group (13,22). The inconsistent results may be due to the small sample sizes and retrospective nature of the studies. A superior DCR was also identified (P=0.005) in the present study, similar to that found in a previous retrospective study (23). Moreover, IBP was found to be an independent prognostic factor for PFS time but not for OS time. In addition, patients with longer PFS times (PFS1 >6 months) or a favorable treatment response (CR + PR) to first-line treatment showed improved PFS2 times, which was consistent with previous findings (22,24). Therefore, for patients with a better response to prior treatment (PFS1 >6 months or CR + PR), the present results suggest a potential benefit from continued immunotherapy after first-line immunotherapy plus chemotherapy progression. The limited impact on OS time may be associated with an insufficient follow-up time and the limited sample size in the current study. Although not all patients could be followed up for a total of 40-50 months due to being included at different time periods, further follow-up along with an expanded data sample analysis is required in order to better clarify the clinical benefits of IBP.

After first-line chemoimmunotherapy, the combination of immunotherapy with anti-angiogenic drugs is a viable option. Anti-angiogenic drugs can normalize abnormal tumor vasculature and regulate the tumor immune microenvironment (25-27). Co-administration of anti-angiogenic drugs may thus improve the efficacy of immunotherapy (28). Prolonged OS times compared with those for chemotherapy or chemotherapy plus anti-angiogenic inhibitor have been shown (29). The present study analyzed triplet therapy compared with doublet therapy after the progression of first-line treatment. No significant differences were found, but the addition of anti-angiogenic therapy in second-line treatment remains a viable option. The relative merits of ICI combinations or monotherapy in second-line treatment could not be evaluated during the present work due to limited sample sizes. However, combination therapy tends to exhibit superior efficacy (24,30). Furthermore, switching the administration of anti-PD-1 and anti-PD-L1 antibodies as ICI rechallenge may be a treatment option (31), but such an analysis was outside the scope of the current study.

There are several limitations to the current study. Firstly, it was a single-center retrospective study with a small sample size and therefore selection bias could not be avoided. Secondly, given the complexity and practicality of clinical practice, RECIST were used rather than immune-related response criteria, immune RECIST (iRECIST) or immune-related RECIST (32-34). Pseudo-progression and delayed response may not be fully evaluated with RECIST, and more accurate criteria such as iRECIST are expected to be used in the future. Thirdly, no data was available regarding PD-L1 expression and tumor mutational burden before first-line and second-line treatment. PD-L1 expression may be useful to evaluate the use of IBP when there is failure of the first-line treatment. In addition, more analyses are required to evaluate PFS and OS differences based on the initial PD-L1 expression levels. Lastly, immune-related adverse events (irAEs) between the two groups were not compared, as the majority of patients lacked data regarding irAEs, although continuation of immunotherapy is not considered to significantly increase the incidence of grade3 or grade4 irAEs (19). Immunotherapy was tolerated well by most of the current patients and no discontinuation due to severe irAEs was recorded in the present study.

Overall, in the present study, the clinical benefits of continued immunotherapy after progression with first-line chemotherapy combined with immunotherapy are indicated. However, large prospective clinical studies are required to confirm these findings.

In conclusion, in the present study, patients with advanced NSCLC benefited from continuing ICI treatment after failure of prior chemotherapy plus immunotherapy. IBP should be therefore be considered for patients with advanced NSCLC.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XG, YH, KZ and LL conceived and designed this study. IDM, FG, YX participated in data collection and data curation (organising and maintaining data). XG, YH, JC and LZ analyzed the data. LL provided the administrative support. XG and YH drafted the manuscript and all authors reviewed it. KZ and LL confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Institutional Ethics Committee of the Tongji Medical College, Huazhong University of Science and Technology (approval no. S139). The requirement for informed consent for participation was waived due to the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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