Original Article

The prognostic factors of clinical outcomes in non-small cell lung cancer patients receiving subsequent treatments after progression on initial immunotherapy

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Background: The standard of care for non-small cell lung cancer (NSCLC) patients who encounter progression on initial immune checkpoint inhibitor (ICI) based treatment is uncertain. In the real world, there are various subsequent treatment options, but how to find the most suitable treatment for different patients is still unknown. The present study aimed to explore prognostic factors of subsequent treatment after progression (STAP) (defined as the next treatment after progression from the initial immunotherapy) of initial immunotherapy.

Methods: In this retrospective cohort study, NSCLC patients received regimens after progression of initial immunotherapy at Beijing Chest Hospital, Capital Medical University, between March 2016 and May 2023 were retrieved. The major efficacy endpoint was progression-free survival 2 (PFS2), defined as the time from the initiation of next treatment after initial immunotherapy failure to disease progression or death from any cause. Subgroup analyses were conducted according to baseline characteristics, some subsequent regimens beyond progression, etc. for prognostic factors exploration. The Cox proportional hazards model was used for multivariate analysis.

Results: There were 176 patients enrolled. Median age was 64 years. There were 36 (20.5%) females, and 123 (69.9%) were smokers. Adenocarcinoma (99, 56.2%) was the major histological subtype. There were 95 (54.0%) patients with negative expression for programmed cell death ligand 1 (PD-L1). After progressive disease, 92 (52.3%) patients reused ICI-based treatment after progressive disease. Median PFS2 was 3.6 months [95% confidence interval (CI): 2.8–4.4]. Longer PFS2 was observed in patients with PD-L1 positive expression [hazard ratio (HR) =0.672, 95% CI: 0.477–0.947, P=0.023] or PFS ≥6 months in initial immunotherapy (HR =0.543, 95% CI: 0.358–0.824, P=0.004). Besides, patients switching to new ICI-based treatments without radiotherapy gained better PFS2 compared with patients receiving prior regimens (P=0.019).

Conclusions: PD-L1 positive expression, and longer PFS in initial immunotherapy would be good prognostic factors for NSCLC patients undergoing STAP on first immunotherapy. Besides, compared with original regimen, changing ICI would prolong PFS2 for NSCLC patients reusing ICI.

Keywords: Non-small cell lung cancer (NSCLC); immune checkpoint inhibitor (ICI); retreatment

Submitted Jan 09, 2024. Accepted for publication Aug 06, 2024. Published online Sep 26, 2024.
doi: 10.21037/jtd-24-57
View this article at: https://dx.doi.org/10.21037/jtd-24-57

Introduction

With a series of in-depth research on tumor immunity, the evolving immunotherapy has become a landmark in the history of tumor medicine. Over the past few years, immune checkpoint inhibitors (ICIs) based therapy has shown an excellent efficacy for patients diagnosed as advanced or metastatic non-small cell lung cancer (NSCLC) patients without targetable driver gene (1-4), and ICI monotherapy or combined with chemotherapy with or without anti-angiogenic agents has mainly constituted the treatment for NSCLC in daily clinical practice (5). However, disease progression which is usually inevitable would occur in the vast majority of patients (6). Since there is no universally accepted subsequent treatment after progression (STAP) (defined as the next treatment after progression from the initial immunotherapy), traditional platinum-based chemotherapy dominates treatment options for patients suffering initial ICI treatment failure, with median overall survival (OS) ranging from 4.4 to 6.8 months, median progression-free survival (PFS) ranging from 2.4 to 4.1 months and objective response rate (ORR) ranging from 20.0% to 22.8% (7,8). As the limited efficacy of salvage chemotherapy, novel treatments are worth being explored.

ICI retreatment has emerged in recent years, gradually becoming another option available after disease progression on initial immunotherapy treatment. Several clinical trials have demonstrated the potential validity of treatment beyond progression with ICI in other carcinoma (9,10). Regarding NSCLC, ICI retreatment has also been proven to be feasible (11,12). A phase 2 trial showed that patients receiving pembrolizumab plus next-line chemotherapy gained better PFS compared with others receiving single-agent chemotherapy alone, when progression of the disease was observed on initial immunotherapy (13). In addition, some retrospective research has proved that patients receiving ICI retreatment achieve better clinical outcomes than those not receiving any anticancer therapy, in real-world situations (14-16). For ICI retreatment, most studies have focused on the effectiveness of the same ICI as the initial option (12,17). OAK study, a randomized phase III study, showed that patients can still derive survival benefit again without extra increased safety risk for receiving atezolizumab beyond progression on initial atezolizumab therapy (12). Although the data of retreatment with another ICI are limited, they show an inspiring result (18). A retrospective study showed that patients who had progressed on nivolumab can still benefit from new ICI—pembrolizumab with the median PFS of 3.1 months, but notably, those responding to pembrolizumab had very high (≥80%) expression of programmed cell death ligand 1 (PD-L1) (18).

PD-L1 expression in tumors is regarded as a productive predictive biomarker for efficacy of ICI therapy (19) which is widely applied in clinical practice, while standard predictors to predict the efficacy of STAP remain to be explored.

Therefore, we performed the retrospective study aiming to explore influencing factors of efficacy of STAP for NSCLC patients who had received initial ICI-based treatment and experienced disease progression, and to discover an appropriate regimen for them. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-57/rc).

Highlight box

Key findings

- Non-small cell lung cancer (NSCLC) patients who achieved partial response in subsequent regimens, progression-free survival (PFS) ≥6 months in initial immunotherapy or had positive expression of programmed cell death ligand 1 would have a longer PFS in subsequent treatment after progression of initial immunotherapy.
- Compared with original regimens, using new immune checkpoint inhibitor would provide longer PFS in subsequent treatment for NSCLC patients who reuse immunotherapy after progression of initial immunotherapy.

What is known and what is new?

- Several studies have already showed the survival benefit of immunotherapy retreatment as a subsequent therapy for NSCLC patients who have progressed on their initial immunotherapy.
- According to our results, there was no difference in PFS for NSCLC patients between subsequently receiving immunotherapy retreatment or chemotherapy-based therapy after progression of initial immunotherapy. Moreover, we showed some prognostic factors of treatment beyond progression of initial immunotherapy.

What is the implication, and what should change now?

- In this retrospective study, our results can provide physicians with a new vision to help them screen candidates who would achieve a better survival benefit from receiving subsequent therapy after failure to initial immunotherapy. More related research is needed to further demonstrate our results.

Methods

Study design and patients

In this retrospective cohort study, advanced or metastatic NSCLC patients receiving subsequent treatment with or

without ICI after progression on initial immunotherapy at Beijing Chest Hospital, Capital Medical University, between March 2016 and May 2023 were included for analysis. The follow-up data were obtained by phone calls, clinic medical records and hospital discharge records. The data were censored if the patient had not experienced progression at the last follow-up. All the patients were followed up until 31 May 2023. Patients older than 18 years, diagnosed with primary NSCLC and at least one target lesion, receiving STAP because of progression of initial ICI-based treatment were eligible. Patients whose initial ICI-based treatment was interrupted by immune-related adverse events and those receiving targeted therapy as STAP were excluded. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Beijing Chest Hospital, Capital Medical University [(2020) - Scientific Research - Provisional Review No. (09)] and individual consent for this retrospective analysis was waived.

Study assessment

Demographic and baseline characteristics and survival outcomes were retrieved from the medical information system, including age, gender, smoking status, Eastern Cooperative Oncology Group performance status (ECOG PS), histological subtype, tumor clinical stage, driver gene mutation status, PD-L1 expression status, treatment line, regimens of initial immunotherapy and STAP, etc. PD-L1 expression [tumor proportion score (TPS)] was evaluated by the Dako PD-L1 IHC 22C3 pharmDx assay (PD-L1 positive expression: TPS ≥1%; PD-L1 negative expression: TPS <1%). Disease progression and the response evaluation was confirmed according to Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) by two senior tumor physicians.

The primary efficacy endpoint was PFS2, defined as the time from the initiation of next treatment after initial immunotherapy failure to disease progression or death from any cause. Secondary endpoints were ORR2 (ORR of STAP), and disease control rate 2 (DCR2) (DCR of STAP). ORR was defined as the proportion of patients with complete response (CR) and partial response (PR). DCR was defined as the proportion of patients with CR, PR and stable disease (SD).

Statistical analysis

The continuous and categorical variables were presented as medians [interquartile range (IQR)] and numbers (percentages), individually. PFS and 95% confidence intervals (CIs) were calculated by the Kaplan-Meier method, and differences were compared by log-rank test.

Subgroup analyses for efficacy predictors were performed based on age (<65 *vs.* ≥65 years), gender (female *vs.* male), smoking status (current/previous *vs.* never), ECOG PS (≥2 *vs.* 0–1), histological subtypes at initial ICI-based treatment (squamous cell carcinoma *vs.* adenocarcinoma), PD-L1 expression at initial ICI-based treatment (TPS; negative <1% *vs.* positive ≥1%), treatment lines (2nd *vs.* ≥3rd), best overall response [BOR; PR *vs.* SD/progressive disease (PD)], PFS1 defined as PFS of initial ICI-based treatment (PFS1 <3 *vs.* PFS1 ≥3 months; PFS1 <6 *vs.* PFS1 ≥6 months), and regimens of STAP hazard ratios (HRs) and 95% CI were evaluated with Cox proportional-hazards model in multivariable analyses. P value <0.05 was considered statistically significant, and all statistical tests were two-sided. All statistical analyses were performed using SPSS 26.0 and GraphPad Prism 8.0.

Results

Demographic information

There were 176 patients who received follow-up treatments after acquiring resistance residence between March 2016 and April 2023 included, and the process of patient inclusion and exclusion is shown in *Figure 1*. Among them, 140 (79.5%) patients were male, and 123 (69.9%) had been smokers. The median age of patients was 64 years (IQR, 58–68 years). Most patients (157/176, 89.2%) had ECOG PS of 1. The predominant histological subtype was adenocarcinoma. Moreover, in view of the complex conditions in the real world, two (1.1%) adenosquamous carcinoma and two (1.1%) NSCLC which were unable to define the exact subtype in pathology were also included. Before receiving initial immunotherapy, driver genes were tested in 143 patients, of which 63 (35.8%) were positive, including 25 (14.2%) patients who were EGFR-mutated, and 133 (75.6%) patients who were confirmed to be at stage IV. PD-L1 expression data were available for all patients, which were measured when they prepared to receive initial immunotherapy, of whom 95 (54%) patients were PD-L1 positive. Treatment lines of STAP were second in 98 (55.7%) patients, and third or beyond in 78 (44.3%) patients, respectively. Detailed demographic information of patients included is presented in *Table 1*.

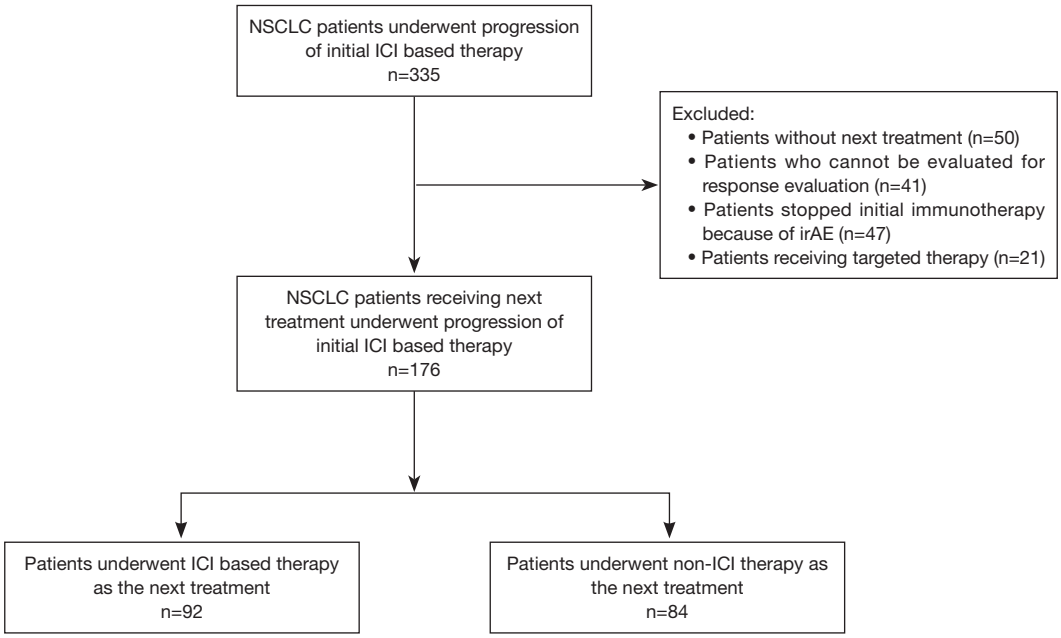

Figure 1 Flowchart of patient inclusion and exclusion. NSCLC, non-small cell lung cancer; ICI immune checkpoint inhibitor; irAE, immune-related adverse event.

Characteristics of initial ICI-based treatment

In reference to the initial ICI-based treatment, most patients (110/176, 62.5%) had received ICI combined with chemotherapy. Median PFS1 was 4.9 months; 57 (32.4%), 79 (44.9%), and 40 (22.7%) patients had achieved PR, SD, and PD, respectively, with an ORR1 (ORR of initial ICI-based treatment) of 32.4% and a DCR1 (DCR of initial ICI-based treatment) of 77.3% (*Table 2*).

Risk factors associated with PFS2

The last follow-up was on May 31, 2023. The median follow-up was 26.0 months (IQR, 17.2–35.4 months). During follow-up, 156 (88.6%) cases of progression occurred and median PFS2 was 3.6 months (95% CI: 2.8–4.4). While most patients (82/176, 46.6%) achieved SD, PR was observed in 16 cases (9.1%). ORR2 was 9.1% and DCR2 was 55.7% (*Table 3*). For univariate analysis, tendencies for longer PFS2 were related to patients with longer PFS1 [PFS1 ≥3 months (P=0.0013), PFS1 ≥6 months (P<0.0001)], BOR1 (BOR of initial ICI-based treatment) of PR (P=0.024), or whose PD-L1 expression were positive (P=0.0036). However, age, gender, smoking status, histological, and treatment lines did not affect PFS (*Figure 2*). Multivariate analysis was used to adjust for the confounders of these factors, which indicated that patients with PD-L1 positive expression (positive *vs.* negative, HR =0.672, 95% CI: 0.477–0.947; P=0.023) or PFS1 ≥6 months (PFS1 ≥6 *vs.* <6 months, HR =0.543, 95% CI: 0.358–0.824; P=0.004) were associated with longer PFS2 (*Figure 3*).

Different options of STAP

After progression to the first immunotherapy, depending on a distinct condition of individual, some patients (84/176, 47.7%) switched to receive other treatments including chemotherapy, radiotherapy or anti-angiogenesis therapy, while others [92 (52.3%)] received ICI-based treatments again, and 20 (11.4%) of them switched to new ICI. Half of the 72 (40.9%) patients who used the original ICI received the same treatment regimen as the initial immunotherapy regimen, which was the most common regimen for patients still using ICI, and most of the remaining patients underwent ICI combined chemotherapy with or without anti-angiogenic agents (*Table 4*). For patients without ICI treatment in subsequent therapy, they separately received

Table 1 Demographic and baseline characteristics (n=176)

Patients' clinical information	N (%)
Age (years)	
Median [range]	64 [35–84]
<65	95 (54.0)
≥65	81 (46.0)
Gender	
Female	36 (20.5)
Male	140 (79.5)
Smoking status	
Current/previous	123 (69.9)
Never	53 (30.1)
ECOG PS	
0	13 (7.4)
1	157 (89.2)
2	6 (3.4)
Histological subtypes	
Adenocarcinoma	99 (56.3)
Squamous cell carcinoma	73 (41.5)
Adenosquamous carcinoma	2 (1.1)
NSCLC	2 (1.1)
Clinical stage before initial immunotherapy	
I	2 (1.1)
II	2 (1.1)
III	39 (22.2)
IV	133 (75.6)
Driver genes before initial immunotherapy	
Wild type	80 (45.5)
EGFR-mutated	25 (14.2)
KRAS-mutated	23 (13.1)
Others-mutated	15 (8.5)
Unknown	33 (18.8)
PD-L1 TPS before initial immunotherapy	
<1%	95 (54.0)
1–49%	37 (21.0)
≥50%	44 (25.0)
Treatment lines	
2nd	98 (55.7)
≥3rd	78 (44.3)
PFS1 <3 months	44 (25.0)
PFS1 ≥3 months	132 (75.0)
PFS1 <6 months	101 (57.4)
PFS1 ≥6 months	75 (42.6)

The percentages might not equal 100% on account of rounding. ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; KRAS, Kirsten rats sarcoma viral oncogene; PD-L1, programmed cell death ligand 1; TPS, tumor proportion score; PFS1, progression-free survival of initial immunotherapy treatment.

local radiotherapy, chemotherapy, anti-angiogenic therapy or a combination of those regimens (*Table 4*).

Subgroup analysis of PFS2 according to subsequent regimens

To explore the optimal regimen for patients after progression, we conducted a subgroup analysis of the subsequent regimens in relation to their PFS2 (*Figure 4*). Because of the differences between local radiotherapy and other systemic therapies, we excluded patients whose next treatment after initial immunotherapy progression included radiotherapy. After excluding the interference of radiotherapy, 81 (46.0%) patients received immunotherapy or its combination therapy, and 55 (31.3%) patients received non-immunotherapy. According to our results, immunotherapy had no effect on the PFS2 (P=0.60) (*Figure 4A*).

In this study, a subset of patients (36/176, 20.5%) continued receiving the original regimen after progressing on initial immunotherapy. No statistically significant difference was observed in PFS2 between patients (45/176, 25.6%) receiving immunotherapy after exclusion patients treated with original regimen, and those (55/176, 31.3%) receiving non-immunotherapy, according to our results (P=0.10) (*Figure 4B*), probably because of the small sample size. After excluding the interference of initial regimens, of the patients who continued to receive immunotherapy,

Table 2 Regimens and best overall response to initial immunotherapy (n=176)

Regimens and best overall response	N (%)
Initial immunotherapy regimens	
ICI monotherapy	35 (19.9)
ICI + chemo	110 (62.5)
ICI + chemo + A	25 (14.2)
ICI + A	6 (3.4)
Best overall response of initial immunotherapy	
CR	0
PR	57 (32.4)
SD	79 (44.9)
PD	40 (22.7)
ORR	57 (32.4)
DCR	136 (77.3)

ICI, immune checkpoint inhibitor; chemo, chemotherapy; A, anti-angiogenic therapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate (ORR = CR + PR); DCR, disease control rate (DCR = CR + PR + SD).

Table 3 Response evaluation of the treatment after initial ICI progression (n=176)

Best overall response	N (%)
CR	0
PR	16 (9.1)
SD	82 (46.6)
PD	78 (44.3)
ORR2	16 (9.1)
DCR2	98 (55.7)

ICI, immune checkpoint inhibitor; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR2, objective response rate of STAP on initial ICI-based treatment (ORR2 = CR + PR); DCR2, DCR2, disease control rate of STAP on initial ICI-based treatment (DCR = CR + PR + SD); STAP, subsequent treatment after progression.

26 (14.8%) still used the initial ICI, while others (19/176, 10.8%) switched to new ICI. We analyzed the PFS2 of both, and found that changing ICI is not a risk factor for PFS2 (P=0.39) (*Figure 4E*).

By contrast, PFS2 was significantly shorter in patients (36/176, 20.5%) who did not change their regimens than in patients (19/179, 10.8%) who were treated with a new ICI (P=0.019) (*Figure 4G*). Besides, there was no significant difference in PFS2 (P=0.23) (*Figure 4C*) between patients (36/176, 20.5%) receiving the original regimens compared to those (53/176, 30.1%) receiving non-immunotherapy, and there was a significantly shorter PFS2 (P=0.0082) (*Figure 4F*) when they (36/176, 20.5%) compared to patients (45/176, 25.6%) receiving ICI and changing regimens.

In addition, according to our results, there was a tendency for a longer PFS2 in patients (26/176, 14.8%) who received the same ICI but new regimens compared to patients (36/176, 20.5%) who used original regimens, although the tendency is not statistically significant (P=0.055) (*Figure 4D*).

Finally, considering that anti-angiogenic therapy is a common therapy as a combination with immunotherapy and chemotherapy in practice, we analyzed the PFS2 difference between patients (19/176, 10.8%) who received immunotherapy with chemotherapy and those (17/176, 9.7%) who received immunology with chemotherapy and anti-angiogenic agent, and found anti-angiogenic agent did not affect PFS2 (P=0.06) (*Figure 4H*).

Discussion

With the growing knowledge of immune checkpoints, especially the discovery of programmed cell death protein 1 (PD-1)/PD-L1 (20-23), a new era of immunotherapy for tumor treatment has begun. The application of immunotherapy represented by anti-PD-L1 and PD-1 antibodies, either alone or in combination, has dramatically improved the survival of NSCLC patients without druggable genomic alteration (1-4), innovating the regimens of NSCLC therapy. However, progression will occur inevitably in a majority of patients, even if they have achieved good outcomes from initial ICI-based treatment. There is no standard regimen for patients to choose after progression of initial ICI-based treatment, in real-world settings, some patients undergo ICI retreatment, while others return to other treatments, such as chemotherapy, radiotherapy, anti-angiogenic drugs or combination of them. Rebiopsy after progression is also an option to find potential druggable molecular alterations, as the heterogeneity of NSCLC, however, most patients would miss this chance because of its invasive nature. A phase 2 clinical trial reported patients derived more survival benefits when they received ICI combined with chemotherapy

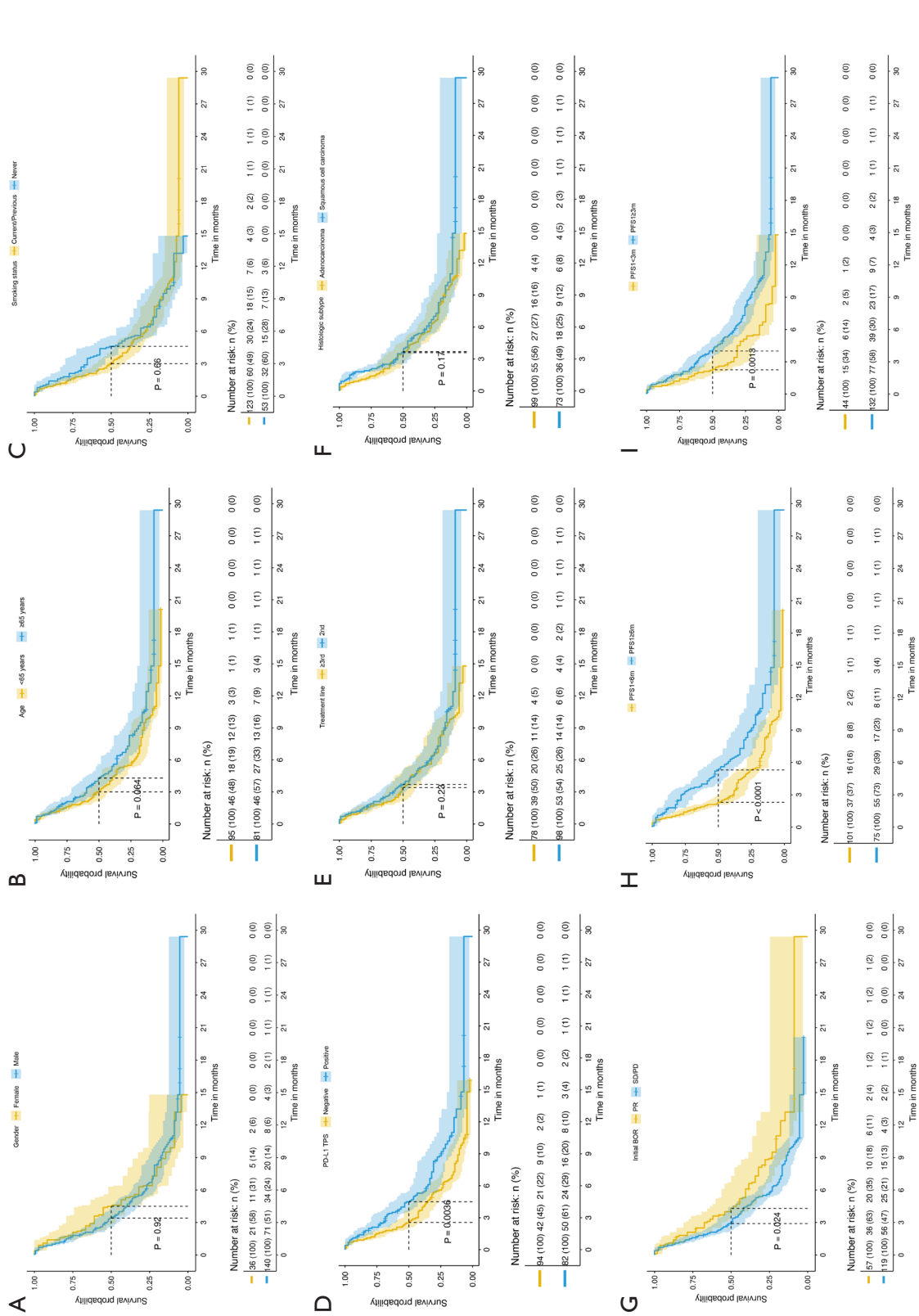

Figure 2 Kaplan-Meier curves of PFS2 in patients with different baseline characteristics. (A) gender; (B) age [patients were divided into ≥65 years group (n=81) and <65 years group (n=95)]; (C) smoking status; (D) PD-L1 TPS (negative means PD-L1 expression <1%, positive means PD-L1 expression ≥1%), PD-L1 positive expression predicts a better PFS2 (P=0.0036); (E) treatment line; (F) histologic subtype (we only analysis the patients whose histologic subtype is adenocarcinoma or squamous cell carcinoma); (G) patients achieved PR of initial BOR have a longer PFS2 (P=0.024); (H) PFS1 <6 months predicts a worse PFS2 (P<0.0001); (I) PFS1 <3 months predicts a worse PFS2 (P=0.0013). PD-L1, programmed cell death ligand 1; TPS, tumor proportion score; ICI, immune checkpoint inhibitor; PFS1, progression-free survival of initial immunotherapy; m, months; BOR, best overall response; PR, partial response; SD, stable disease; PD, progressive disease.

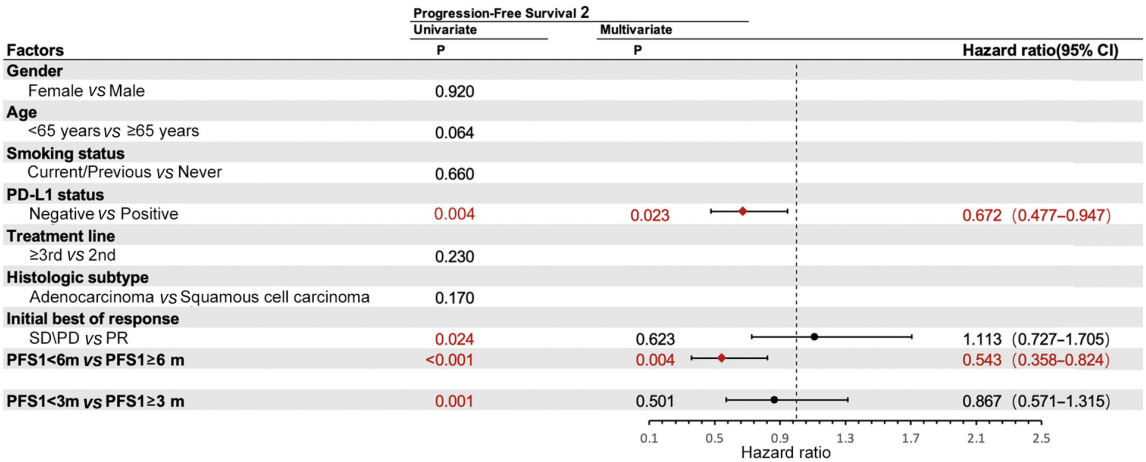

Figure 3 Univariate and multivariate analysis of progression-free survival 2. CI, confidence interval; PD-L1, programmed cell death ligand 1; PR, partial response; SD, stable disease; PD, progressive disease; PFS1, progression-free survival of initial immunotherapy; m, months.

Table 4 Next regimens after progression on initial immunotherapy (n=176)

Regimens	N (%)
With ICIs	92 (52.3)
New ICIs	20 (11.4)
Anti-PD-1	11 (6.3)
Anti-PD-L1	6 (3.4)
Anti-PD-L1 + anti-TGF-β	3 (1.7)
Original ICIs	72 (40.9)
Anti-PD-1	71 (40.3)
Anti-PD-L1	1 (0.6)
Same with initial regimens	36 (20.5)
Anti-PD-1 monotherapy	15 (8.5)
Anti-PD-1 + chemo	16 (9.1)
Anti-PD-1 + chemo + A	4 (2.3)
Anti-PD-1 + A	1 (0.6)
ICI + chemo	19 (10.8)
Anti-PD-1 + chemo	18 (10.2)
Anti-PD-L1 + chemo	1 (0.6)
ICI + A	4 (2.3)
Anti-PD-1 + A	3 (1.7)
Anti-PD-L1 + A	1 (0.6)
ICI + chemo + A	17 (9.7)
Anti-PD-1	15 (8.5)
Anti-PD-L1	2 (1.1)
ICI + chemo + R	4 (2.3)
Anti-PD-1	3 (1.7)
Anti-PD-L1	1 (0.6)
ICI + R	6 (3.4)
Anti-PD-1	5 (2.8)
Anti-PD-L1	1 (0.6)
ICI monotherapy	2 (1.1)
Anti-PD-1	1 (0.6)
Anti-PD-L1	1 (0.6)
Anti-PD-1 + chemo + A + R	1 (0.6)
Bispecific antibodies (anti-PD-L1 + anti-TGF-β)	3 (1.7)
Without ICIs	84 (47.7)
A	12 (6.8)
Chemo	21 (11.9)
Chemo + A	22 (12.5)
Chemo + R	4 (2.3)
Chemo + A + R	1 (0.6)
R	24 (13.6)

The percentages might not equal 100% on account of rounding. ICI, immune checkpoint inhibitor; A, anti-angiogenic therapy; chemo, chemotherapy; R, radiotherapy; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; TGF-β, transforming growth factor-β.

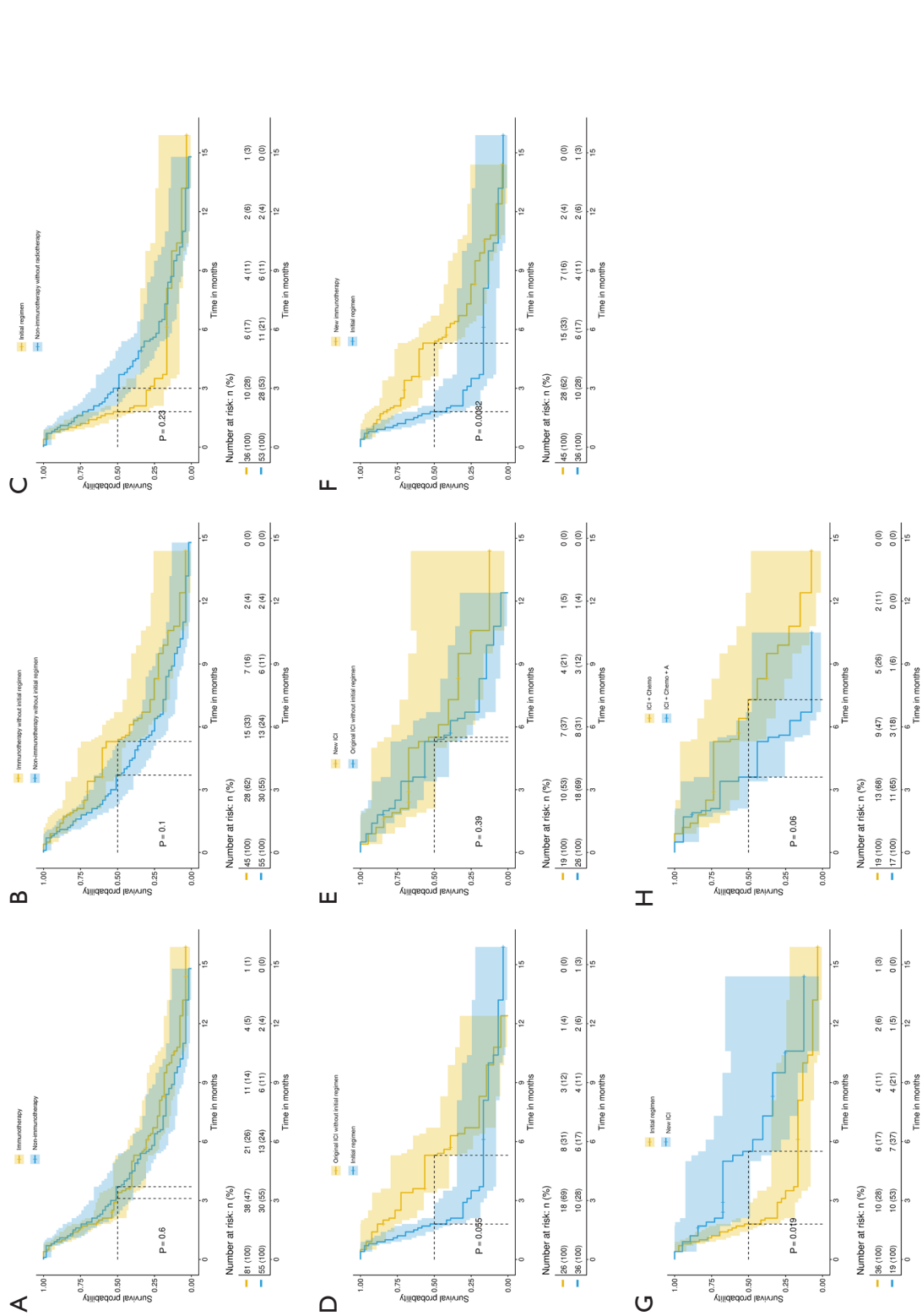

Figure 4 Kaplan–Meier curves of progression-free survival 2 in patients with different systemic regimens after initial immunotherapy progression. (A) Survival curves for patients with and without ICI-based treatment; (B) survival curves for patients with and without ICI-based treatment, excluding patients receiving initial regimen; (C) survival curves for patients with initial regimen and non-immunotherapy; (D) survival curves for patients with initial regimen and patients receiving new regimen but still using original ICI; (E) survival curves for patients with new ICI and patients receiving new regimen but still using original ICI; (F) survival curves for patients with initial regimen and new ICI-based treatment; (G) survival curves for patients with new ICI-based treatment and initial regimen; (H) survival curves for patients receiving ICI with chemotherapy and patients receiving ICI with chemotherapy plus anti-angiogenic therapy. ICI, immune checkpoint inhibitor; chemo, chemotherapy; A, anti-angiogenic therapy.

after failure in previous immunotherapy, compared with receiving chemotherapy alone (13). In this study, 92 (52.3%) of 176 patients received ICI retreatment while the rest received non-immunotherapy as STAP of initial ICI-based treatment. We analyzed the difference in PFS2 between them, however, we did not find a survival advantage of ICI retreatment in patients (*Figure 4A*, P=0.60; *Figure 4B*, P=0.10). The explanation for our result may be due to the fact that most of the patients who received non-immunotherapy were treated with combinations of drugs, such as chemotherapy plus anti-angiogenic agents, and the synergistic effect (24-26) among the antitumor drugs, allowed them to have a decent efficacy as well. Jain reported that intra-tumoral vascular disruption and "leakage" can be resulted from elevated levels of vascular endothelial growth factor; such effects increase interstitial pressure, which decreases the delivery of chemotherapy to the tumor (27). Besides, a clinical trial conducted by Willett and colleagues demonstrated that bevacizumab may enhance the delivery of medications and increase endothelial sensitivity to chemotherapy (28).

Some patients may be re-exposed to ICI despite the initial progression, however, the need to change the original ICI is inconclusive. Several retrospective studies have demonstrated STAP with the same regimen as initial immunotherapy can provide longer survival for NSCLC patients, compared with non-STAP (12,14,15). However, we have not found to find the advantage of original regimen compared with new ICI-based treatment (*Figure 4F*, P=0.0082). Meanwhile, we found new ICI excluding radiotherapy led to longer PFS than original regimen (*Figure 4G*, P=0.019). After excluding radiotherapy and original regimen, there was no difference of PFS2 between new ICI and prior ICI (*Figure 4E*, P=0.39), which is consistent with a previous study (29).

A considerable number of patients receiving STAP will also unavoidably re-progress, which emphasizes the need to screen a beneficial candidate group for STAP. A retrospective study showed that advanced NSCLC patients who achieved CR/PR with initial immunotherapy had a longer PFS of ICI retreatment than those with SD/PD (30). Another retrospective study reported that patients with ECOG PS ≥2 or body mass index <20 had poorer PFS of ICI rechallenge after progression of initial immunotherapy (31). In this study, we found PFS1 ≥6 months, positive PD-L1 expression was associated with better PFS2. According to our results, the length of PFS of initial ICI-based treatment is cue to the PFS of STAP; patients with PFS1 ≥6 months obtained a better survival benefit in STAP of initial ICI-based treatment. Other researchers also observed this phenomenon (32) which may be perhaps explained by the effect of immune memory cells patients produced in prior immunotherapy. PD-L1 expression measured before receiving initial ICI-based treatment plays a key role in prediction of clinical benefits of initial immunotherapy (19). PD-L1 status (positive *vs.* negative, HR =0.672, 95% CI: 0.477–0.947; P=0.023) showed a significant relation of PFS in STAP with prior immunotherapy in this study, and patients with PD-L1 positive expression would have a longer PFS2. Our results further stress the essential role of evaluating PD-L1 expression in immunotherapy. All above-mentioned results provide new insights into the risk factors associated with PFS of STAP after initial immunotherapy of NSCLC, but more prospective research is needed.

There are several limitations in this study. Firstly, the small size of the sample and the nature of retrospective study precluded additional analysis. Secondly, various STAPs of initial immunotherapy were mainly determined by the patient's supervising physician, which led to selection bias.

Conclusions

The present study showed that NSCLC patients with PD-L1 positive expression, or PFS1 ≥6 months tend to have a longer PFS2. For NSCLC patients continuing ICI-based treatment after progression of initial immunotherapy, new ICI would provide a longer PFS2 compared with initial regimen. More related research is needed to further demonstrate our findings.

Acknowledgments

The authors appreciate all the people who helped us during the research and writing stage for their lots of useful advice. *Funding:* None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-57/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-57/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-57/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-57/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 was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Beijing Chest Hospital, Capital Medical University [(2020) - Scientific Research - Provisional Review No. (09)] and individual consent for this retrospective analysis was waived.

References

1. Mazieres J, Rittmeyer A, Gadgeel S, et al. Atezolizumab Versus Docetaxel in Pretreated Patients With NSCLC: Final Results From the Randomized Phase 2 POPLAR and Phase 3 OAK Clinical Trials. J Thorac Oncol 2021;16:140-50.
2. Novello S, Kowalski DM, Luft A, et al. Pembrolizumab Plus Chemotherapy in Squamous Non-Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study. J Clin Oncol 2023;41:1999-2006.
3. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50. J Clin Oncol 2021;39:2339-49.
4. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med 2018;378:2288-301.
5. Ettinger DS, Wood DE, Aisner DL, et al. NCCN Guidelines® Insights: Non-Small Cell Lung Cancer, Version 2.2023. J Natl Compr Canc Netw 2023;21:340-50.
6. Schoenfeld AJ, Hellmann MD. Acquired Resistance to Immune Checkpoint Inhibitors. Cancer Cell 2020;37:443-55.
7. Bersanelli M, Buti S, Giannarelli D, et al. Chemotherapy in non-small cell lung cancer patients after prior immunotherapy: The multicenter retrospective CLARITY study. Lung Cancer 2020;150:123-31.
8. Diker O, Olgun P. Salvage chemotherapy in patients with nonsmall cell lung cancer after prior immunotherapy: a retrospective, real-life experience study. Anticancer Drugs 2022;33:752-7.
9. Beaver JA, Hazarika M, Mulkey F, et al. Patients with melanoma treated with an anti-PD-1 antibody beyond RECIST progression: a US Food and Drug Administration pooled analysis. Lancet Oncol 2018;19:229-39.
10. Escudier B, Motzer RJ, Sharma P, et al. Treatment Beyond Progression in Patients with Advanced Renal Cell Carcinoma Treated with Nivolumab in CheckMate 025. Eur Urol 2017;72:368-76.
11. Herbst RS, Garon EB, Kim DW, et al. Long-Term Outcomes and Retreatment Among Patients With Previously Treated, Programmed Death-Ligand 1-Positive, Advanced Non-Small-Cell Lung Cancer in the KEYNOTE-010 Study. J Clin Oncol 2020;38:1580-90.
12. Gandara DR, von Pawel J, Mazieres J, et al. Atezolizumab Treatment Beyond Progression in Advanced NSCLC: Results From the Randomized, Phase III OAK Study. J Thorac Oncol 2018;13:1906-18.
13. Salous T, Shukla NA, Althouse SK, et al. A phase 2 trial of chemotherapy plus pembrolizumab in patients with advanced non-small cell lung cancer previously treated with a PD-1 or PD-L1 inhibitor: Big Ten Cancer Research Consortium BTCRC-LUN15-029. Cancer 2023;129:264-71.
14. Guven DC, Yekeduz E, Erul E, et al. The benefit of treatment beyond progression with immune checkpoint inhibitors: a multi-center retrospective cohort study. J Cancer Res Clin Oncol 2023;149:3599-606.
15. Chen C, Xiong X, Cheng Y, et al. Expanding the applications of immune checkpoint inhibitors in advanced lung cancer beyond disease progression. Front Immunol 2023;14:1266992.
16. Stinchcombe TE, Miksad RA, Gossai A, et al. Real-World Outcomes for Advanced Non-Small Cell Lung Cancer Patients Treated With a PD-L1 Inhibitor Beyond Progression. Clin Lung Cancer 2020;21:389-394.e3.
17. Ricciuti B, Genova C, Bassanelli M, et al. Safety and Efficacy of Nivolumab in Patients With Advanced Non-

small-cell Lung Cancer Treated Beyond Progression. Clin Lung Cancer 2019;20:178-185.e2.
18. Fujita K, Uchida N, Kanai O, et al. Retreatment with pembrolizumab in advanced non-small cell lung cancer patients previously treated with nivolumab: emerging reports of 12 cases. Cancer Chemother Pharmacol 2018;81:1105-9.
19. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33.
20. Dong H, Zhu G, Tamada K, et al. B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. Nat Med 1999;5:1365-9.
21. Freeman GJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 2000;192:1027-34.
22. Ishida Y, Agata Y, Shibahara K, et al. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. EMBO J 1992;11:3887-95.
23. Nishimura H, Nose M, Hiai H, et al. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. Immunity 1999;11:141-51.
24. Xing P, Mu Y, Wang Y, et al. Real world study of regimen containing bevacizumab as first-line therapy in Chinese patients with advanced non-small cell lung cancer. Thorac Cancer 2018;9:805-13.
25. Zhou CC, Bai CX, Guan ZZ, et al. Safety and efficacy of first-line bevacizumab combination therapy in Chinese population with advanced non-squamous NSCLC: data of subgroup analyses from MO19390 (SAiL) study. Clin Transl Oncol 2014;16:463-8.
26. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542-50.
27. Jain RK. Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. Nat Med 2001;7:987-9.
28. Willett CG, Boucher Y, di Tomaso E, et al. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. Nat Med 2004;10:145-7.
29. Xu Z, Hao X, Yang K, et al. Immune checkpoint inhibitor rechallenge in advanced or metastatic non-small cell lung cancer: a retrospective cohort study. J Cancer Res Clin Oncol 2022;148:3081-9.
30. Tian T, Yu M, Yu Y, et al. Immune checkpoint inhibitor (ICI)-based treatment beyond progression with prior immunotherapy in patients with stage IV non-small cell lung cancer: a retrospective study. Transl Lung Cancer Res 2022;11:1027-37.
31. Katayama Y, Shimamoto T, Yamada T, et al. Retrospective Efficacy Analysis of Immune Checkpoint Inhibitor Rechallenge in Patients with Non-Small Cell Lung Cancer. J Clin Med 2019;9:102.
32. Giaj Levra M, Cotté FE, Corre R, et al. Immunotherapy rechallenge after nivolumab treatment in advanced non-small cell lung cancer in the real-world setting: A national data base analysis. Lung Cancer 2020;140:99-106.

Cite this article as: Fu S, Lu Z, Wei S, Chen Z, Tang J, Wang J. The prognostic factors of clinical outcomes in non-small cell lung cancer patients receiving subsequent treatments after progression on initial immunotherapy. J Thorac Dis 2024;16(9):6012-6023. doi: 10.21037/jtd-24-57