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Original Article

Efficacy of continuing pembrolizumab after progression on first-line treatment in stage IV non-small cell lung cancer: a prospective real-world study

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Abstract: This prospective observational study investigated the efficacy of pembrolizumab administered as first-line therapy and the survival outcomes of continuing or combining it with other agents after disease progression in patients with stage IV non-small cell lung cancer (NSCLC). A total of 63 patients who experienced disease progression following pembrolizumab-based first-line treatment between February 2019 and July 2024 were prospectively enrolled. Patients were randomized into two cohorts based on treatment strategy: a treated beyond progression (TBP) group (n = 39) to receive continued pembrolizumab monotherapy or pembrolizumab-based combination regimens after disease progression, and a non-TBP (NTBP) group (n = 24), which discontinued pembrolizumab upon progression. The primary endpoint was overall survival (OS), and secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR). The median PFS during first-line therapy (mPFS1) was 6.97 months. In the TBP group, the median PFS from first-line initiation to progression after second-line therapy (mPFS2) was 17.6 months, with an ORR of 20.5% and a DCR of 74.4%. OS in the TBP group was significantly longer than that in NTBP group (29.4 vs. 12.4 months, $P < 0.001$). Multivariate Cox regression analysis identified continued pembrolizumab use and favorable ECOG performance status as independent predictors of prolonged OS. These findings suggest that continued pembrolizumab use or combination therapy after disease progression significantly enhances survival benefits in advanced NSCLC, underscoring the importance of individualized treatment strategies based on clinical characteristics and treatment response.

Keywords: Non-small cell lung cancer, pembrolizumab, first-line treatment, treated beyond progression, treatment efficacy evaluation

Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide and continues to impose a considerable burden on public health [1]. Non-small cell lung cancer (NSCLC), which constitutes nearly 85% of all lung cancer cases, has therefore become the focus of most clinical and translational research [2-4]. In recent years, immune checkpoint inhibitors

(ICIs) have reshaped treatment paradigms for advanced NSCLC, with pembrolizumab demonstrating particularly meaningful clinical benefits [5-7]. By blocking the PD-1/PD-L1 axis, pembrolizumab can enhance antitumor immunity and lead to prolonged survival. Landmark trials such as KEYNOTE-407 and KEYNOTE-189 have demonstrated that combining pembrolizumab with chemotherapy as a first-line regimen yields significant improvements in overall survival (OS) for patients with advanced NSCLC [8, 9].

Nevertheless, disease progression during or after immunotherapy remains a critical therapeutic dilemma. After progression on ICIs, cytotoxic chemotherapy is typically administered, but its clinical benefit is modest [3, 10, 11]. Against this backdrop, continuation or re-initiation of ICIs has attracted increasing attention. Early evidence suggests that re-exposure to PD-1 blockade may confer clinical benefit in selected patients who previously received immunotherapy [12, 13]. Notably, the phase III OAK trial reported that patients who continued atezolizumab after radiographic progression achieved longer OS compared with those who discontinued treatment [14]. However, evidence regarding the efficacy and safety of continuing pembrolizumab after progression on first-line therapy remains limited.

To address this gap, we evaluated the clinical outcomes of pembrolizumab re-treatment in patients with advanced NSCLC who progressed on first-line therapy. Using real-world data, we analyzed objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS), while exploring associations between baseline characteristics and treatment outcomes. These findings aim to provide evidence-based guidance for individualized therapeutic strategies for advanced NSCLC.

Materials and methods

Participants

This research was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (Approval No.: (2020)IIT-556). Written informed consent was obtained from all participants prior to enrollment. The study was also registered at ClinicalTrials.gov (NCT04153097).

Inclusion criteria: Patients with untreated stage IV NSCLC between February 2019 and July 2024 who had received at least one cycle of pembrolizumab, either as monotherapy or in combination with chemotherapy and/or angiogenesis inhibitors as their first-line treatment; Patients who experienced progressive disease (PD) after first-line treatment during the subsequent follow-up. Exclusion criteria: Patients permanently discontinued pembrolizumab due to ≥ Grade 3 immune-related adverse events, lost to follow-up before the first efficacy assessment, or enrolled in other clinical trials after disease progression were excluded from this study. Follow-up ended on December 31, 2024.

Since this is a real-world prospective observational study, no formal sample size calculation was performed, and the sample size (n = 63) was exclusively based on the number of eligible patients consecutively enrolled during the study period. Patients who continued pembrolizumab treatment for at least two cycles after first-line treatment progression were classified into the treated beyond progression (TBP) group (n = 39), consistent with previously published TBP studies that used this threshold to indicate meaningful continuation of therapy [15]. Patients who discontinued pembrolizumab treatment after first-line treatment progression were categorized into the non-TBP (NTBP) group (n = 24).

Covariates and outcome definitions

Patient clinical data were collected via the electronic medical record system, including age, sex, histological type, smoking status, presence of distant metastases, and Eastern Cooperative Oncology Group performance status (ECOG PS). Follow-up treatment and survival status after discharge were monitored through telephone interviews. The primary endpoint of this study was OS, defined as the time from the initiation of initial treatment to death from any cause. The secondary endpoints included PFS, ORR, and DCR. Specifically, PFS1 referred to the duration from initiation of first-line treatment to disease progression; and PFS2 was defined as the duration from the initiation of first-line treatment until disease progression on second-line therapy. In this study, partial response (PR), stable disease (SD), and PD were assessed and classified according to Response Evaluation Criteria in Solid Tumors

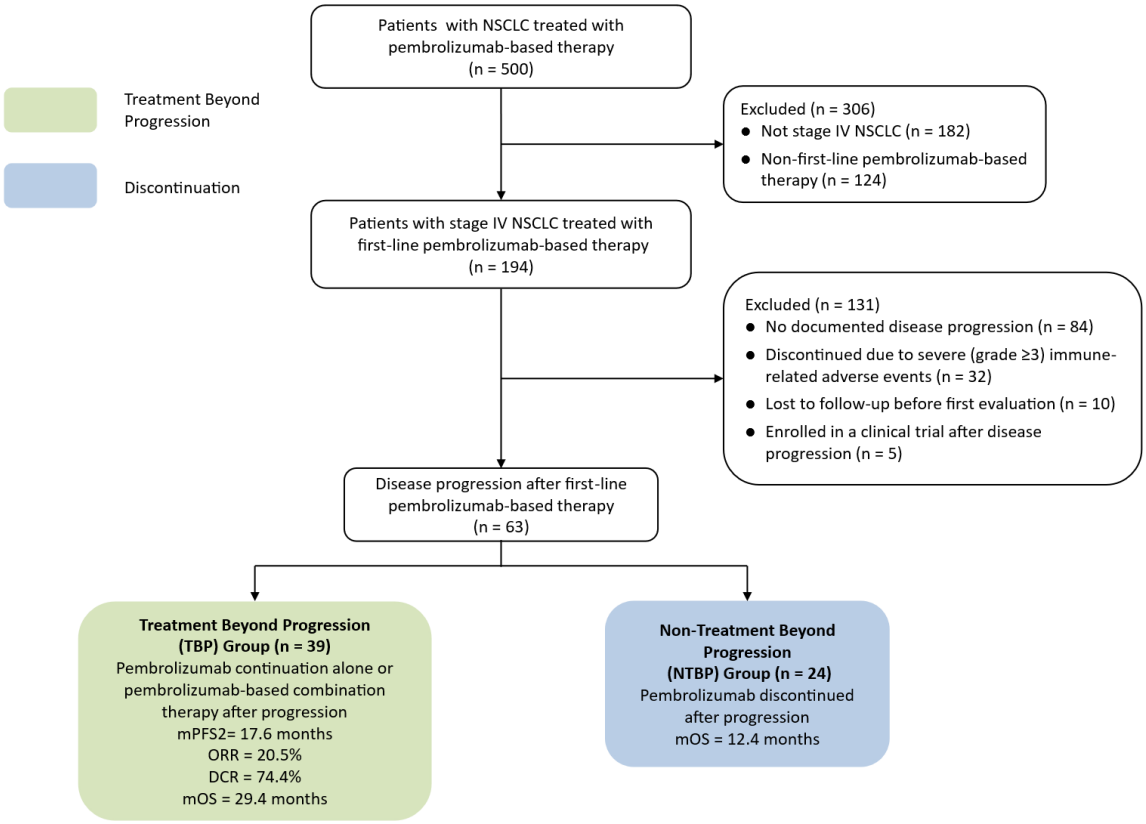

Figure 1. Participant enrollment flow diagram.

(RECIST) version 1.1 criteria. Specifically, radiologic evaluations were performed every 6 weeks using CT scans. All imaging data were independently reviewed by two experienced oncologists who were blinded to the treatment allocation and clinical data. In cases of discrepancy, a consensus decision was reached after discussion. ORR was defined as the proportion of patients achieving PR, and DCR was defined as the proportion of patients achieving either PR or SD.

Statistical analysis

All statistical analyses were performed using R statistical software (version 4.2.2). Continuous variables were summarized as medians, while categorical variables were presented as counts and percentages. Comparisons of categorical variables between groups were performed using the chi-square test or Fisher's exact test, as appropriate. The 95% confidence intervals (CI) for OS, PFS1, and PFS2 were calculated using the Kaplan-Meier method, with comparisons made using the log-rank test. Median follow-up was estimated using the reverse Kaplan-Meier method. Best overall response (BOR), ORR, and DCR were assessed according to RECIST 1.1 criteria. Covariates including age, ECOG PS, BOR, sex, histology, smoking status, liver metastasis, bone metastasis, and brain metastasis were incorporated into Cox proportional hazards models. Hazard ratios (HR), along with their 95% CIs and *p*-values, were calculated using univariate and multivariate models to assess the correlation of these variables with patient OS. A p-value < 0.05 was considered statistically significant.

Results

Study population and clinical characteristics

This study enrolled 63 patients with stage IV NSCLC who received pembrolizumab as first-line treatment between February 2019 and July 2024 and subsequently experienced PD (**Figure 1**). At the data cutoff date (December 31, 2024), the median follow-up duration was 42.3 months (95% CI: 29.6-NA). The upper limit of

Table 1. Baseline demographics and clinical characteristics of enrolled patients

Characteristics	All patients (N = 63)	TBP (N = 39)	NTBP (N = 24)	*p* value
Age, years				
Median	66	67	65	
Range	41-85	41-81	57-85	
< 65	27 (42.9%)	17 (43.6%)	10 (41.7%)	1.000
≥ 65	36 (57.1%)	22 (56.4%)	14 (58.3%)	
Sex				
Male	56 (88.9%)	33 (84.6%)	23 (95.8%)	0.336
Female	7 (11.1%)	6 (15.4%)	1 (4.2%)	
Histological subtype				
Squamous carcinoma	31 (49.2%)	18 (46.2%)	13 (54.2%)	0.720
Non-Squamous carcinoma	32 (50.8%)	21 (53.8%)	11 (45.8%)	
Smoking status				
Smoker	45 (71.4%)	23 (59.0%)	22 (91.7%)	0.012
Never	18 (28.6%)	16 (41.0%)	2 (8.3%)	
ECOG PS				
0-1	47 (74.6%)	31 (79.5%)	16 (66.7%)	0.402
2-4	16 (25.4%)	8 (20.5%)	8 (33.3%)	
Metastatic site				
Liver	8 (12.7%)	3 (7.7%)	5 (20.8%)	0.440
Bone	22 (34.9%)	14 (35.9%)	8 (33.3%)	
Brain	11 (17.5%)	6 (15.4%)	5 (20.8%)	

ECOG PS, Eastern Cooperative Oncology Group performance status.

the confidence interval could not be estimated because most patients were still under follow-up. The shortest follow-up was 5 months, corresponding to patients enrolled most recently. **Table 1** presents the clinical characteristics of all patients, including age, sex, histological subtype, smoking history, ECOG PS, and metastasis sites. The median age of enrolled patients was 66 years, with males constituting the vast majority (88.9%). Most patients (71.4%) had a history of smoking, and 74.6% had an ECOG PS score of 0 or 1 before treatment. The liver, bone, and brain were the most common sites of metastasis.

Regarding clinical characteristics, there were a higher proportion of smokers in the NTBP group (P = 0.012). However, no significant differences were observed between the two groups in age, sex, histological subtype, ECOG PS score, or metastasis sites (p-values: 1.000, 0.336, 0.720, 0.402, and 0.440, respectively).

Efficacy analysis of first-line and subsequent treatment regimens in stage IV NSCLC patients

This study conducted an in-depth analysis of 63 stage IV NSCLC patients who received pembrolizumab as first-line treatment between February 2019 and July 2024, focusing on evaluating the efficacy of subsequent treatment regimens following disease progression. Detailed treatment regimens are shown in Supplementary Table 1. Most patients (48 out of 63, 76.2%) were treated with a combination of pembrolizumab and chemotherapy during first-line treatment. The median PFS1 (mPFS1) during first-line treatment was 6.97 months (95% CI: 5.9-8.5 months) (**Figure 2**). According to RECIST 1.1 criteria, 28 patients achieved PR, 32 had SD, and 3 experienced PD during first-line therapy.

Following progression on first-line treatment, 39 patients continued pembrolizumab for at least two additional cycles during the second-line treatment. All these received pembrolizumab in combination with other systemic therapies. In the NTBP group, 24 patients discontinued pembrolizumab after first-line treatment progression. Among them, 17 received only systemic therapy, including 12 with chemotherapy, 4 with an angiogenesis inhibitor, and 1 with a combination of chemotherapy and angiogenesis inhibitor. Four patients under-

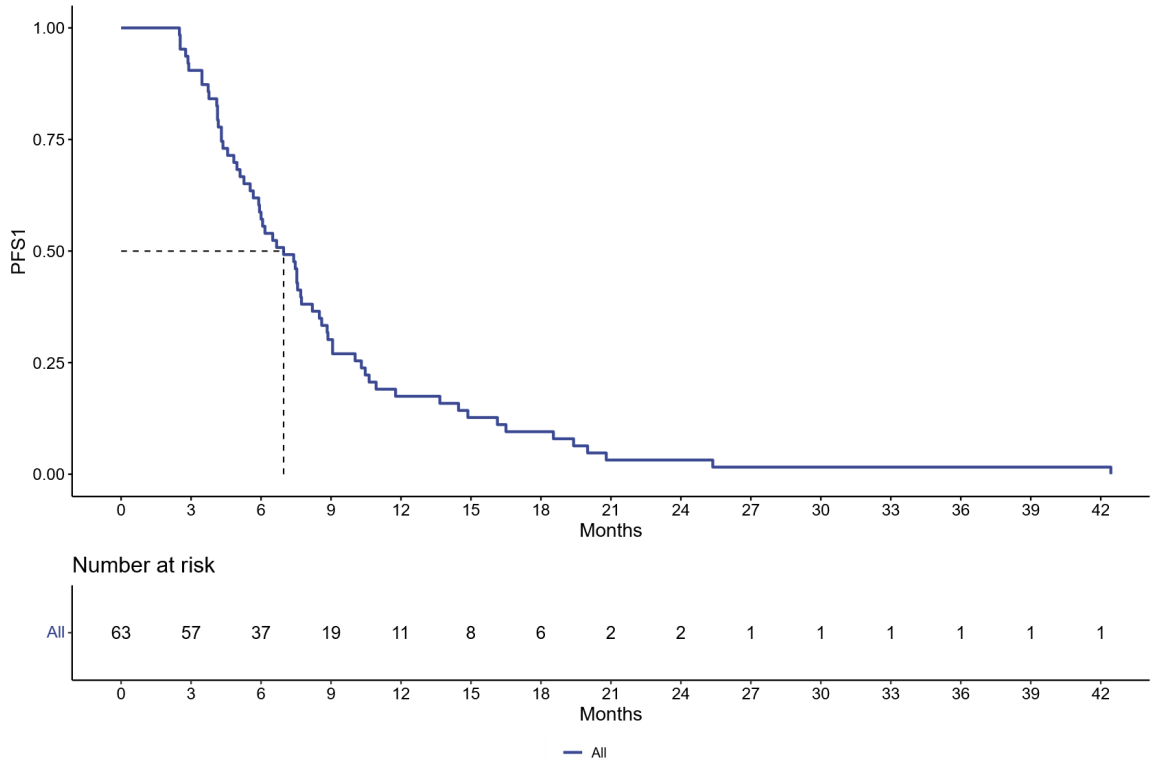

Figure 2. Progression-free survival of patients during first-line pembrolizumab treatment. Abbreviations: PFS1, time from the initiation of treatment until the progression of the disease during first-line therapy.

went local radiotherapy, three received the best supportive care, hoping to resume systemic therapy upon disease improvement or stabilization.

In summary, this study demonstrates the widespread application of pembrolizumab combined with chemotherapy as a first-line treatment for stage IV NSCLC patients, with diverse subsequent treatment strategies. Although some patients continued pembrolizumab after progression on first-line therapy, treatment selection still require individualized decision-making based on patient's specific condition and treatment response.

Evaluation of second-line treatment efficacy following progression in stage IV NSCLC patients receiving first-line therapy

This study further analyzed the efficacy and survival outcomes of patients in TBP group who received pembrolizumab as second-line treatment.

The mPFS2 in the TBP group was 17.6 months (95% CI: 15.1-21.9 months) (**Figure 3**). After second-line treatment, 8 patients achieved PR, 21 achieved SD, and 10 experienced PD, with an ORR of 20.5% (8/39) and a DCR of 74.4% (29/39) (Supplementary Table 2). The PFS1 was similar between the TBP and NTBP groups (mPFS1: 6.97 vs. 6.98 months, P = 0.73). Furthermore, no statistically significant differences were observed among patients receiving different first-line combination regimens in the TBP group (P = 0.1), suggesting that the type of combination regimen did not significantly affect PFS1 in this cohort (Supplementary Figure 1). The median overall survival (mOS) was significantly longer in the TBP group compared to the NTBP group (29.4 vs. 12.4 months, P < 0.001) (**Figure 4A**, **4B**). Multivariate analysis, adjusting for other covariates, found that continued pembrolizumab used after progression on first-line therapy (HR, 0.3; 95% CI, 0.16-0.55, P < 0.001) and a better ECOG PS (0-1) were associated with improved OS (HR, 0.51; 95% CI, 0.26-0.97, P = 0.041). Age, sex, histological subtype, and organ metastases did not significantly affect OS (**Table 2**). The treatment duration in TBP group is depicted in **Figure 5**.

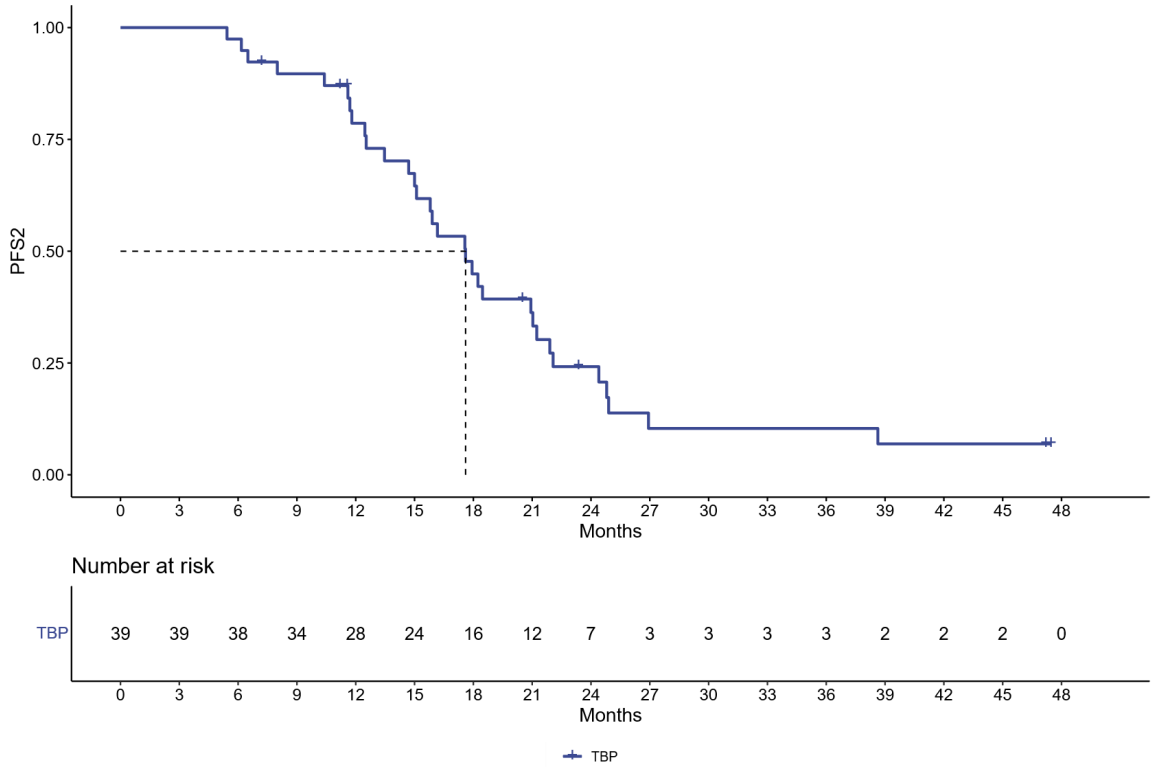

Figure 3. Progression-free survival of patients with continued pembrolizumab treatment after progression during second-line pembrolizumab treatment. Abbreviations: PFS2, time from the initiation of first-line treatment until the progression of the disease during second-line therapy; TBP, patients with pembrolizumab treatment beyond progression of first-line treatment.

In addition, treatment-related adverse events (any grade) were observed in 20.8% of patients in the NTBP group and 23.1% in the TBP group. No treatment-related deaths were observed in either group.

In summary, these findings underscore the significant efficacy of continuing pembrolizumab as a second-line treatment in improving survival outcomes for stage IV NSCLC patients who progressed after first-line treatment.

Discussion

Previous studies on continuing immunotherapy after progression have yielded inconsistent findings. A large U.S. real-world analysis involving over 4,000 patients reported that individuals who remained on ICIs after progression experienced markedly longer OS than those who discontinued treatment (11.5 vs. 5.1 months) [16]. Similar findings were observed in an Italian multicenter cohort, which demonstrated that nivolumab continuation after progression was associated with improved OS (17.8 vs. 3.7 months) [17]. Several earlier reports have also suggested that certain clinical profiles - such as oligoprogression or absence of visceral metastases - may predict potential benefit from continued immunotherapy [18, 19]. However, inconsistencies exist across studies. For instance, a phase II trial failed to identify survival differences between TBP and non-TBP groups [20]. Similarly, the EMPOWER-Lung 1 study similarly showed no OS advantage for patients continuing ICIs with chemotherapy compared with those who received chemotherapy alone [21]. Therefore, existing evidence remains uncertain, and the true benefit of immunotherapy after NSCLC progression has not been fully established.

Within this context, our study provides prospective observational data specifically evaluating the continued use of pembrolizumab after progression on first-line therapy. Our findings demonstrate a notable OS advantage in the TBP cohort (mOS: 29.4 vs. 12.4 months), especially among patients with preserved ECOG PS. Variations in treatment settings may partly

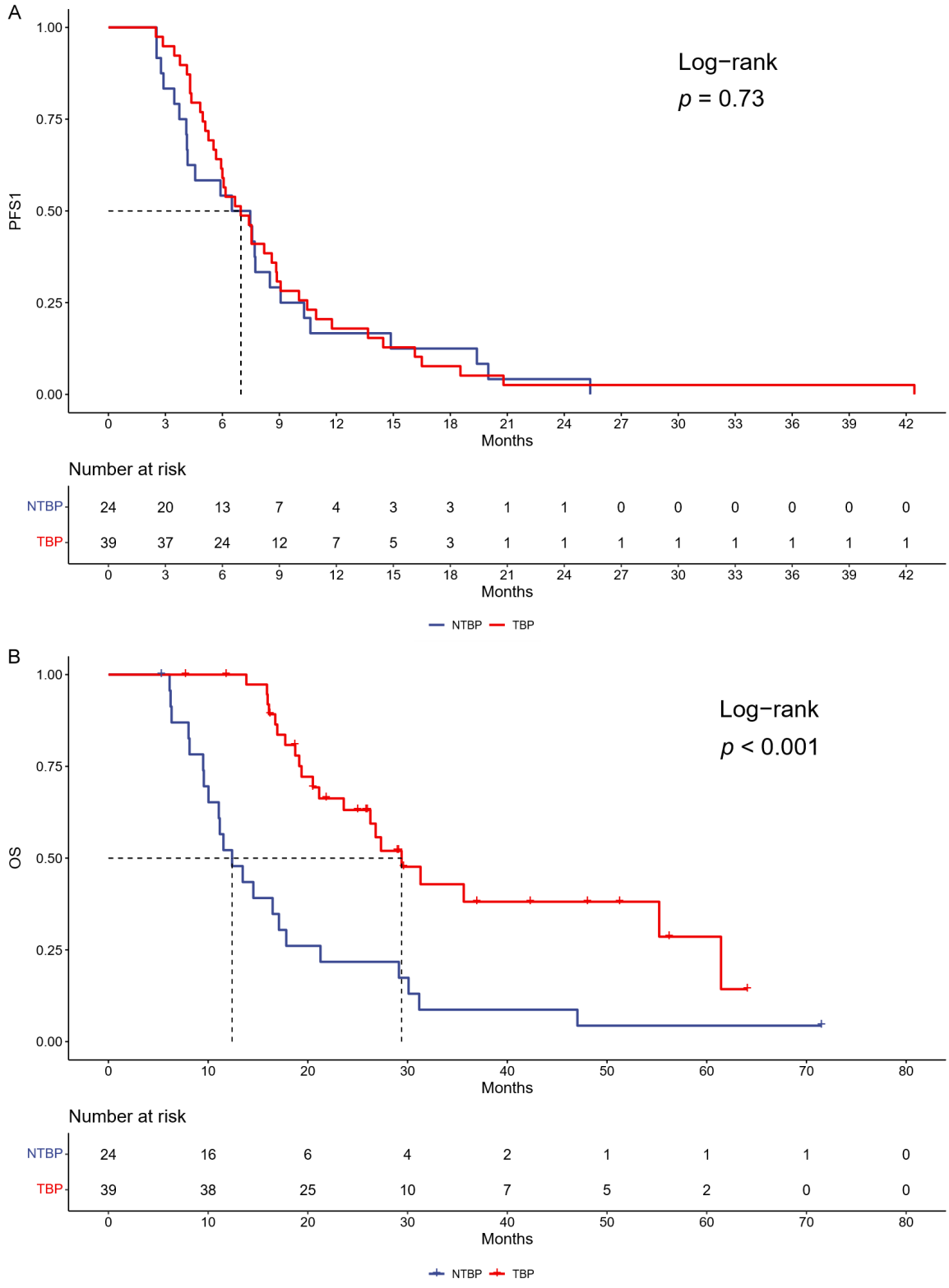

Figure 4. Progression-free survival during first-line pembrolizumab treatment (A) and overall survival (B). Abbreviations: PFS1, time from the initiation of treatment until the progression of the disease during first-line therapy; OS, overall survival; TBP, patients with pembrolizumab treatment beyond progression of first-line treatment; NTBP, patients without pembrolizumab treatment beyond progression of first-line treatment.

Table 2. Univariate and multivariate analyses of clinical characteristics and treatment regimens on mOS in patients with advanced NSCLC

Characteristics	Group 1	Group 2	Univariate		Multivariate	
			Crude HR (95% CI)	*p*-value	Crude HR (95% CI)	*p*-value
Age, years	< 65	≥ 65	1.51 (0.71-3.22)	0.280		
Gender	Male	Female	0.29 (0.07-1.22)	0.093		
Histological subtype	Squamous carcinoma	Non-squamous carcinoma	0.83 (0.45-1.53)	0.555		
Smoking status	Smoker	Never	0.59 (0.29-1.2)	0.146		
ECOG PS	2-4	0-1	0.51 (0.27-0.98)	0.042	0.51 (0.26-0.97)	0.041
Liver metastasis	Yes	No	0.56 (0.23-1.34)	0.190		
Bone metastasis	Yes	No	0.84 (0.44-1.6)	0.600		
Brain metastasis	Yes	No	0.99 (0.44-2.22)	0.972		
Group	NTBF	TBF	0.3 (0.16-0.55)	< 0.001	0.3 (0.16-0.55)	< 0.001

ECOG NSCLC, Non-small Cell Lung Cancer; PS, Eastern Cooperative Oncology Group performance status.

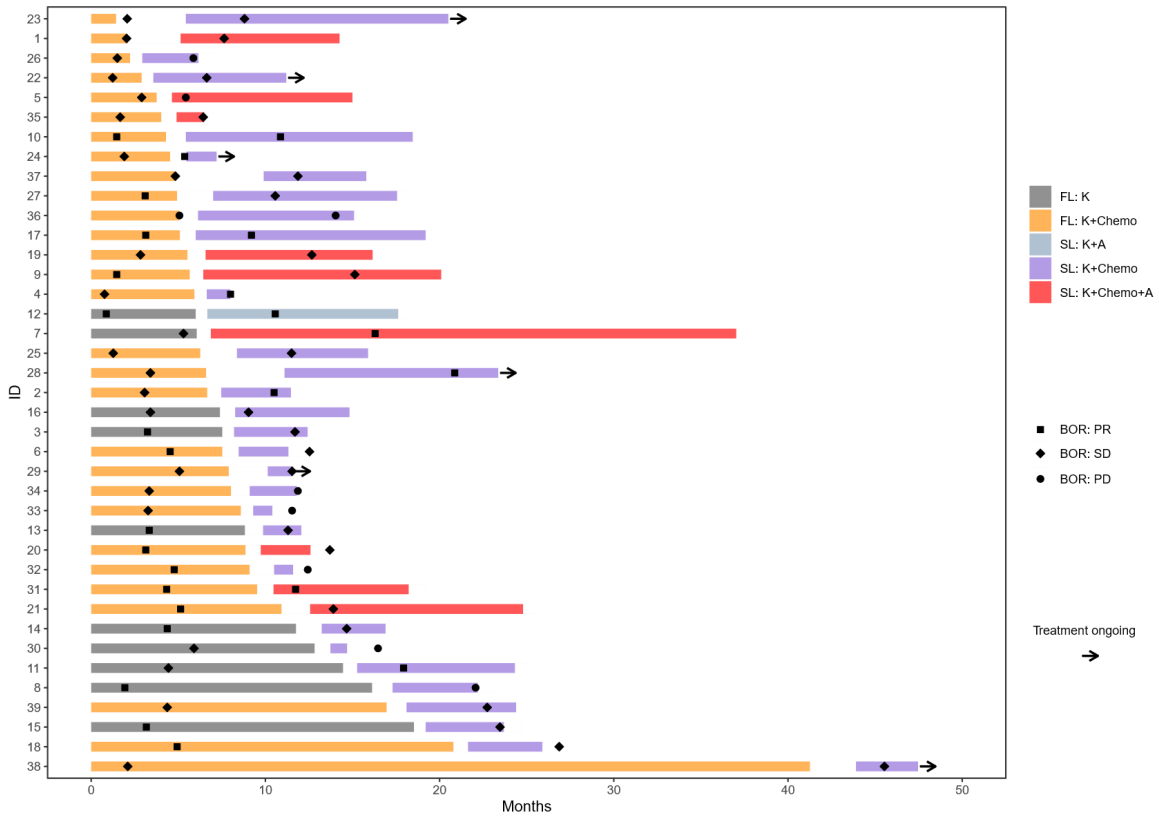

Figure 5. Summary of treatment duration of patients who received continued pembrolizumab treatment after progression on first-line treatment. Abbreviations: FL, first-line treatment; SL, second-line treatment; K, pembrolizumab; Chemo, chemotherapy; A, angiogenesis inhibitors; BOR, best overall response; PD, progressive disease; PR, partial response; SD, stable disease.

account for the differences in mOS across studies. In the US cohort, patients were treated with multiple ICIs and did not receive immunotherapy as first-line therapy, whereas in the Italian cohort, nivolumab was administered post-progression rather than as an initial treatment. In contrast, our study involved patients who received pembrolizumab as first-line therapy and continued with the same agent after progression, potentially contributing to the significantly prolonged survival observed. Furthermore, the ORR in TBP group during second-line

treatment reached 20.5% (8/39), significantly higher than the ORR of 9%-14% observed with second-line docetaxel chemotherapy in earlier trials [12, 22-24].

Several biological mechanisms may account for the apparent benefit of continued PD-1 blockades. Chemotherapy can alter tumor immunogenicity and reshape the tumor microenvironment, thereby enhancing ICI activity. Prior research has demonstrated that chemotherapy may enhance the efficacy of immunotherapy by increasing the production of tumor-associated neoantigens, disrupting stromal architecture to promote T-cell infiltration, and reducing the number of immunosuppressive cell populations such as regulatory T cells and myeloid-derived suppressor cells (MDSCs) [25-29]. Studies by Guo et al. and Song et al. revealed that neoadjuvant chemotherapy increased PD-L1 expression on lung cancer cells, potentially enhancing the efficacy of ICIs [30, 31].

However, this study has several limitations. First, although the mOS in the TBP group was 29.4 months, interpretation should consider that some patients, particularly those enrolled most recently, had relatively short follow-up durations. Nevertheless, the overall follow-up time has covered the majority of observed events, and the survival estimates remain informative for the study cohort. Second, exclusion of patients who discontinued pembrolizumab due to severe immune-related adverse events (grade ≥ 3) precluded comprehensive assessment of the incidence of grade 3-4 or severe adverse events, affecting the completeness of treatment safety outcomes. Third, the study population may not be fully representative due to potential selection bias, as participants were not randomly selected. The small sample size limits our ability to conduct deeper analyses, such as subgroup analyses for different NSCLC subtypes. Therefore, our findings require further validation in larger-scale studies.

Future research should aim to address these limitations and further clarify the role of pembrolizumab in the management of advanced NSCLC. Larger, well-designed prospective studies are needed to verify our observations and to generate more robust evidence supporting continued pembrolizumab use after disease progression on first-line therapy. In addition, future investigations should prioritize the heterogeneity of NSCLC by analyzing different pathological subtypes, molecular characteristics, and baseline clinical features to identify patient populations most likely to benefit from continued immunotherapy. Such efforts will deepen our understanding of how to optimally integrate pembrolizumab into treatment strategies, thereby improving patient outcomes.

Conclusion

In the treatment of stage IV NSCLC, pembrolizumab delivers significant clinical benefit both as first-line therapy and when continued after disease progression. Treatment decisions should comprehensively consider patients' baseline clinical characteristics and treatment response. Continuation of pembrolizumab and maintenance of good ECOG PS scores are critical to achieving improved survival outcomes.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. First-line and follow-up treatment regimens

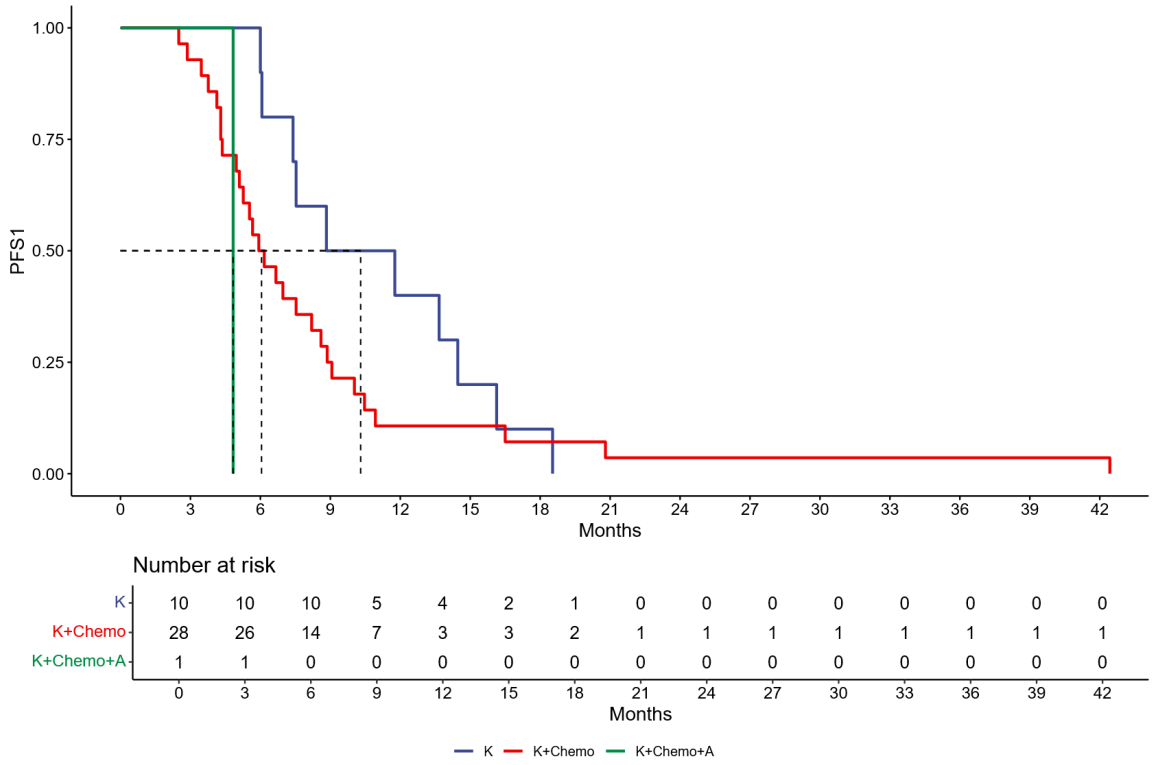
	All patients (N = 63)	TBP (N = 39)	NTBP (N = 24)
First-line immunotherapy regimen			
Pembrolizumab monotherapy	15 (23.8%)	10 (25.6%)	5 (20.8%)
Combined with nab-Pacilitaxel ± carboplatin/cisplatin	25 (39.7%)	14 (35.9%)	11 (45.8%)
Combined with pemetrexed + carboplatin/cisplatin	20 (31.7%)	13 (33.3%)	7 (29.2%)
Combined with gemcitabine + carboplatin	1 (1.6%)	1 (2.6%)	0 (0.0%)
Combined with pemetrexed + carboplatin + Bevacizumab	2 (3.2%)	1 (2.6%)	1 (4.2%)
Follow-up treatment regimen			
Other systemic treatment	56 (88.9%)	39 (100.0%)	17 (70.8%)
Local radiation treatment	4 (6.3%)	0 (0.0%)	4 (16.7%)
Best supportive care*	3 (4.8%)	0 (0.0%)	3 (12.5%)

*Allow and encourage patients to continue systemic treatment after their states improve or symptoms stabilize.

Supplementary Table 2. Summary of efficacy of pembrolizumab in TBP second-line treatment

Best overall response	TBP
Partial response	8
Stable disease	21
Progressive disease	10
Objective response rate	8/39 (20.5%)
Disease control rate	29/39 (74.4%)
mPFS2 (95% CI), months	17.6 (15.1-21.9)

mPFS2, the median time between the initiation of first-line treatment until the progression of second-line therapy.



Supplementary Figure 1. Impact of different first-line combination regimens on PFS1 and the benefits of TBP. Abbreviations: PFS1, time from the initiation of treatment until the progression of the disease during first-line therapy; TBP, patients with pembrolizumab treatment beyond progression of first-line treatment; K, pembrolizumab; Chemo, chemotherapy; A, angiogenesis inhibitors.