

Real-world evidence of advanced non-small cell lung carcinoma treated with an immune checkpoint inhibitor plus chemotherapy

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Abstract. Immunotherapy is an effective treatment strategy for patients with advanced non-small cell lung cancer (NSCLC). Although clinical trials on immunotherapy have provided promising results, real-world research in clinical practice is needed to assess the effectiveness and safety of immunotherapy. The present study aimed to characterize real-world outcomes in patients with advanced NSCLC treated with immune checkpoint inhibitor (ICI)-based regimens. The medical records of patients with advanced NSCLC, who were treated with programmed cell death protein-1 (PD-1)/programmed cell death 1 ligand 1 (PD-L1) inhibitors, were reviewed for data collection. The primary objectives were to evaluate progression-free survival (PFS) and overall survival (OS). Therefore, multiple Cox regression models were used to investigate the predictive factors for survival outcomes. Furthermore, survival curves for PFS and OS were created using Kaplan-Meier estimates and compared using the log-rank test. The present study included a total of 133 patients with advanced NSCLC who received therapy with ICIs between January 1, 2019 and December 31, 2022. The final follow-up date was August 24, 2023. The median PFS and OS times were 9.8 and 27.2 months, respectively. Univariate Cox regression analysis demonstrated that sex, clinical stage, PD-L1 status, previous systemic therapy, and brain and liver metastases were associated with PFS, while Eastern Cooperative Oncology

Group (ECOG) status, clinical stage, PD-L1 status and brain metastasis were associated with OS. Furthermore, multivariate Cox regression analysis demonstrated that a PD-L1 tumor proportion score (TPS) of $\geq 50\%$ was an indicator of favorable PFS and OS. An ECOG performance status score of ≥ 1 was also associated with poor OS but not with PFS. Furthermore, brain metastasis was an indicator for poor PFS and OS, while liver metastasis was only associated with a poor PFS. Finally, the results of the present study demonstrated that PD-L1 status was an independent predictor for PFS and OS in patients with advanced NSCLC, especially adenocarcinoma, who were treated with ICIs plus chemotherapy. The results also suggested that patients with a PD-L1 TPS of $\geq 50\%$ could benefit when the aforementioned regimens were administered as a first-line or later-line therapy.

Introduction

Lung cancer is the most common malignancy worldwide, and non-small cell lung cancer (NSCLC) accounts for 85-90% of all lung cancer cases. The histological subtypes of NSCLC are adenocarcinoma, squamous cell carcinoma and large cell carcinoma (1). It has been reported that $\sim 50\%$ of patients with newly diagnosed NSCLC present with metastasis, and the prognosis of these patients is poor, with a 5-year survival rate of $< 5\%$ (2,3).

For advanced NSCLC without driver gene alterations, such as those in EGFR, KRAS, ALK, ROS1 and BRAF, platinum-based doublet chemotherapy is considered to be the most common standard first-line treatment approach (4). In patients with advanced non-squamous carcinoma NSCLC, the treatment can be combined with bevacizumab and maintained with pemetrexed or bevacizumab following standard therapy (5-7). For patients with driver gene alterations, targeted therapy is often the first treatment approach, since the relevant agents can improve overall survival (OS) and the overall response rate (ORR). However, several patients cannot benefit from target therapy due to the occurrence of therapeutic resistance (8).

With increasing awareness of tumor immune escape mechanisms, immunotherapy has become an effective

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treatment approach for patients with NSCLC (9). To avoid elimination by immune cells, the programmed cell death protein-1 (PD-1)/programmed cell death 1 ligand 1 (D-L1) pathway serves a notable role in tumor cells. PD-L1 is expressed by tumor cells and binds to PD-1, which is expressed by CD4⁺/CD8⁺ T cells, which suppresses T cell proliferation and cytokine secretion. Therefore, the immune system cannot recognize and target the cancer cells for clearance (10,11). Over the last decade, immune checkpoint inhibitors (ICIs) targeting PD-1/PD-L1 have been widely used to treat cancer worldwide. ICI monotherapy or ICIs combined with chemotherapy have become the novel standard treatment strategy for advanced NSCLC without driver gene mutations (9). Previous clinical studies, such as KEYNOTE-024, KEYNOTE-042, IMpower110, ORIENT-11 and OAK, have demonstrated that ICIs could improve the prognosis of patients with advanced NSCLC compared with chemotherapy (12-16). Therefore, immunotherapy is considered to be an effective treatment strategy for patients with advanced NSCLC.

Despite the promising results that have been reported for aforementioned clinical trials on immunotherapy, it should be noted that the participants in these trials, who are selected based on strict criteria, are commonly in good physical condition and of a younger median age compared with patients in real-world clinical settings. Therefore, real-world studies in clinical settings are required to assess the effectiveness and safety of immunotherapy. In the present study, a retrospective analysis of data from patients with advanced NSCLC who were treated with PD-1/PD-L1 ICIs at Weifang People's Hospital (The First Affiliated Hospital of Shandong Second Medical University; Weifang, China) was performed to evaluate the efficacy and response of these patients to ICIs in clinical practice. The results of the present study were then compared with previous research data.

Materials and methods

Patient selection and data collection. Patients who were treated with PD-1/PD-L1 inhibitors at Weifang People's Hospital (The First Affiliated Hospital of Shandong Second Medical University; Weifang, China) between January 1, 2019 and December 31, 2022 were retrospectively included in the present study. The inclusion criteria were as follows: i) Patients with an age of ≥ 18 years; ii) histologically diagnosed with advanced-stage or recurrent NSCLC; iii) treated with PD-1/PD-L1 inhibitors combined with or without chemotherapy; iv) patients with asymptomatic or stable brain metastasis were included; and v) those with measurable disease based on the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) (17). Patients who received < 2 cycles of immunotherapy or those with other types of tumors were excluded from the study. Clinical data, including age, sex, smoking status, Eastern Cooperative Oncology Group (ECOG) score (18), histology, stage (19), EGFR mutation, PD-L1 status, previous systemic therapy, radiotherapy status, brain/liver metastases upon starting ICIs and PD-1/PD-L1 drugs, were collected from electronic medical records. Due to tissue puncture or patient refusal, the PD-L1 status was unknown in 22 cases.

Response evaluation and endpoint. Disease responses were assessed using RECIST (version 1.1) and classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). The primary endpoint was progression-free survival (PFS) and OS. PFS was defined as the time from the start of ICI therapy to radiologically confirmed PD or death due to any cause. Furthermore, OS was defined as the time from the start of ICI treatment to death due to any cause. Secondary objectives included the ORR and disease control rate (DCR). ORR was defined as the percentage of patients who displayed confirmed CR or PR, while DCR was defined as the percentage of patients with confirmed CR, PR or SD.

Statistical analysis. All statistical analyses were performed using SPSS 26.0 software (IBM Corp.) and GraphPad Prism 9.0 (Dotmatics). Data are presented as the median (interquartile range). The survival curves for PFS and OS were drawn using Kaplan-Meier estimates and compared using log-rank tests. Significant prognostic factors were identified using univariate and multivariate Cox regression analyses. A two-sided $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. A total of 133 patients with advanced-stage NSCLC, who received ICI therapy between January 1, 2019 and December 31, 2022, were included in the present study. The final follow-up date was August 24, 2023. The baseline demographic and clinical characteristics of patients are listed in Table I. The median age at the start of ICI treatment was 63 years (range, 32-83 years). More than half of patients ($n=83$; 62.41%) had an ECOG score of 0 and the remaining 50 patients (37.59%) had an ECOG score of ≥ 1 . A total of 104 patients (78.20%) were men and 91 patients (68.42%) were smokers. The majority of patients ($n=113$; 84.96%) had stage IV cancer, with at least one organ metastasis. The remaining 20 patients had stage III cancer, with only lymph node metastasis. Among patients who experienced organ metastasis, 38 (28.57%) and 26 (19.55%) patients exhibited brain and liver metastasis, respectively. Furthermore, 90 patients (67.67%) were diagnosed with adenocarcinoma, while the remaining 43 (32.33%) were diagnosed with squamous cell carcinoma. Among the 109 patients who underwent EGFR testing, 23 patients (17.29%) tested positive for EGFR mutations. All patients had previously received at least one first-line chemotherapy and 51 patients (38.35%) had received ≥ 2 systemic therapy lines. A total of 47 patients (35.34%) underwent radiotherapy. The PD-L1 status was assessed as the percentage of tumor cell and immune cell areas [tumor proportion score (TPS)] showing PD-L1 staining (20). A total of 111 patients (83.46%) accepted PD-L1 testing in the current study. Among these patients, 13 (9.77%) had a TPS of $< 1\%$. In 46 patients (34.59%), the TPS ranged between 1 and 49%, and 52 patients (39.10%) had a TPS $\geq 50\%$. The majority of patients ($n=114$; 85.71%) received either camrelizumab, sintilimab or tislelizumab, which were the three main ICIs used at Weifang People's Hospital (The First Affiliated Hospital of Shandong Second Medical University; Weifang, China).

Table I. Patient characteristics (n=133).

Characteristics	Value
Median age, years (range)	63 (32-83)
Sex, n (%)	
Male	104 (78.20)
Female	29 (21.80)
Smoking status, n (%)	
Smoker	91 (68.42)
Non-smoker	42 (31.58)
ECOG PS score, n (%)	
0	83 (62.41)
≥1	50 (37.59)
Histology, n (%)	
Adenocarcinoma	90 (67.67)
Squamous cell carcinoma	43 (32.33)
Stage, n (%)	
III	20 (15.04)
IV	113 (84.96)
EGFR mutation, n (%)	
Wild-type	86 (64.66)
Mutation	23 (17.29)
Unknown	24 (18.05)
PD-L1 status, n (%)	
<1%	13 (9.77)
1-49%	46 (34.59)
≥50%	52 (39.10)
Unknown	22 (16.54)
Previous systemic therapy, n (%)	
<2	82 (61.65)
≥2	51 (38.35)
Radiotherapy status, n (%)	
No	86 (64.66)
Yes	47 (35.34)
Brain metastasis, n (%)	
No	95 (71.43)
Yes	38 (28.57)
Liver metastasis, n (%)	
No	107 (80.45)
Yes	26 (19.55)
PD-1/PD-L1 drugs, n (%)	
Camrelizumab	41 (30.83)
Sintilimab	37 (27.82)
Tislelizumab	36 (27.07)
Toripalimab	8 (6.02)
Pembrolizumab	8 (6.02)
Durvalumab	2 (1.50)
Nivolumab	1 (0.75)

ECOG PS, Eastern Cooperative Oncology Group performance status; PD-1, programmed cell death protein-1; PD-L1, programmed cell death 1 ligand 1.

Table II. Treatment response.

Response	No. (%)
Complete response	2 (1.5)
Partial response	54 (40.6)
Stable disease	60 (45.1)
Progressive disease	17 (12.8)
Overall response rate	56 (42.1)
Disease control rate	116 (87.2)

Clinical efficacy. The median follow-up period was 14.1 months (range, 1.2-53.2 months). As shown in Table II, 2, 54, 60 and 17 patients achieved CR, PR, SD and PD, respectively, yielding an ORR of 42.1% and DCR of 87.2%. The median PFS and OS times were 9.8 and 27.2 months, respectively (Fig. 1A and B).

Prognostic significance. To assess the association between patient characteristics and PFS and OS, univariate and multivariate Cox regression analyses were performed. Univariate Cox regression analysis demonstrated that sex, clinical stage, PD-L1 status, previous systemic therapy, and brain and liver metastases were associated with PFS (Table III). Furthermore, ECOG status, clinical stage, PD-L1 status and brain metastasis were associated with OS (Table IV). In multivariate Cox regression analysis, only PD-L1 status (TPS ≥50%) was considered to be a significant indicator for both favorable PFS and OS. Furthermore, an ECOG score of ≥1 was associated with decreased OS. Based on the Cox regression analysis results, subgroup and Kaplan-Meier analyses of PFS and OS were performed.

The effect of treatment lines on PFS and OS was analyzed, and the results demonstrated that patients who were treated with ICIs as first-line therapy had a significantly longer PFS compared with patients who were treated with ICIs as a second-line or later therapy. However, no significant difference in terms of OS was observed (Fig. 2).

PD-L1 status (TPS <50%) was a poor prognostic factor associated with PFS and OS (Fig. 3). Patients with a PD-L1 TPS of ≥50% had a significantly longer PFS, regardless of the previous systemic therapy compared with patients with a PD-L1 TPS of <50% (Fig. 3A, C and E). For OS, patients with a PD-L1 TPS of ≥50% had a good prognosis (Fig. 3B), whereas no significant difference was observed between groups based on PD-L1 status in patients treated with ICIs as a first-line therapy (Fig. 3D), while patients with a PD-L1 TPS of ≥50% treated with ICIs as a second-line and subsequent therapies had a significantly longer OS compared with patients with a PD-L1 TPS of <50% (Fig. 3F).

Patients were then further subdivided into two subgroups based on the histopathological type, and the association between the PD-L1 TPS and PFS and OS was assessed. The results demonstrated that in patients with adenocarcinoma, those with a PD-L1 TPS of ≥50% had significantly longer PFS and OS times compared with patients with a PD-L1 TPS of <50% (Fig. 4A and B), while the PD-L1 TPS status had no significant impact on PFS and OS in patients with squamous cell carcinoma (Fig. 4C and D).

Table III. Univariate and multivariate Cox regression analysis of factors associated with progression-free survival.

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Age (<63 vs. ≥63 years)	0.783	0.523-1.173	0.236			
Sex (male vs. female)	1.796	1.128-2.860	0.014	1.309	0.780-2.197	0.309
Smoking history (smoker vs. non-smoker)	0.748	0.487-1.149	0.185			
ECOG status (0 vs. ≥1)	1.108	0.733-1.677	0.626			
Stage (III vs. IV)	3.781	1.743-8.204	0.001	1.938	0.822-4.573	0.131
Histology (adenocarcinoma vs. squamous cell carcinoma)	1.192	0.788-1.803	0.406			
EGFR status (wild-type vs. mutation)	1.626	0.973-2.718	0.064			
PD-L1 status (<50% vs. ≥50%)	0.501	0.314-0.800	0.004	0.493	0.306-0.795	0.004
Previous systemic therapy (<2 vs. ≥2)	1.567	1.044-2.350	0.030	1.206	0.752-1.933	0.437
Radiotherapy status (no vs. yes)	1.012	0.668-1.533	0.955			
Brain metastases (no vs. yes)	1.816	1.185-2.782	0.006	1.331	0.822-2.153	0.245
Liver metastases (no vs. yes)	1.765	1.101-2.831	0.018	1.406	0.814-2.428	0.221

ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PD-L1, programmed cell death 1 ligand 1.

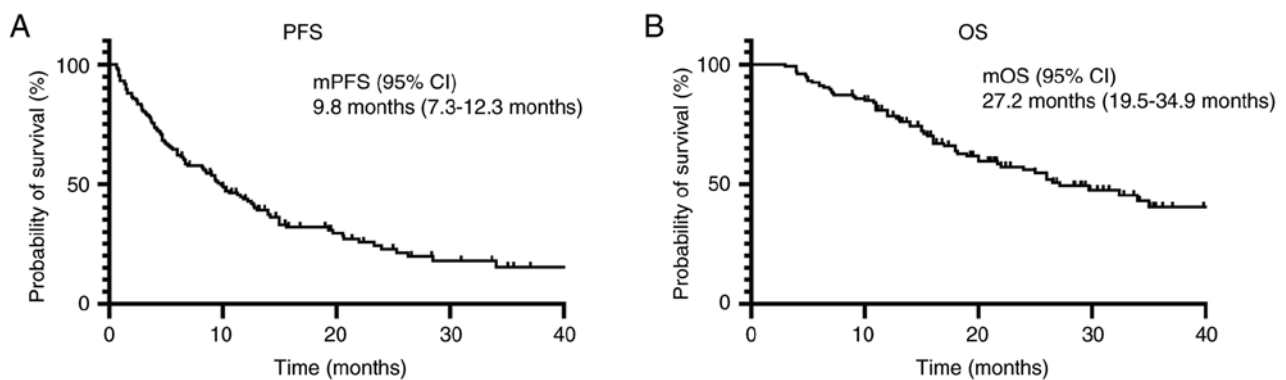


Figure 1. PFS and OS. Kaplan-Meier estimates of (A) PFS and (B) OS. m, median; OS, overall survival; PFS, progression-free survival.

The PFS and OS of patients with brain and liver metastasis was assessed. It was demonstrated that patients with brain metastasis had significantly shorter PFS and OS times compared with patients without brain metastases (Fig. 5A and B). Furthermore, patients with liver metastasis had a significantly shorter PFS compared with patients without liver metastases; however, no significant difference was observed in terms of OS (Fig. 5C and D).

Discussion

The advent of immunotherapy has addressed the shortcomings in the treatment of patients with advanced NSCLC without specific driver gene mutations. Numerous large-scale clinical studies have suggested that ICIs could notably prolong the survival of patients with advanced NSCLC, thus heralding a novel era in cancer treatment (12,13,21,22). However, in the real world, clinicians often encounter a broader and unselected group of patients with lung cancer, while data on the real-world use of immunotherapy are limited. Therefore, further evaluation of the outcomes

observed in clinical trials within the practical context is imperative.

The median age of patients in the present study was 63 years, which was higher compared with the median ages (≤60 years) of patients enrolled in phase III clinical trials, and allowed for a more accurate depiction of the real-world treatment conditions by not selecting patients (22,23). The present results demonstrated that, among 133 patients treated with ICIs, the median PFS and OS times were 9.8 and 27.2 months, respectively, while the ORR was 42.1%. Furthermore, among patients who received ICIs as a first-line therapy, the median PFS and OS times were 12.5 and 34.0 months, respectively. In the KEYNOTE 189 study (21), patients treated with pembrolizumab in combination with chemotherapy as a first-line therapy for metastatic non-squamous NSCLC had a median PFS of 9.0 months, a median OS of 22.0 months and an ORR of 47.6%. Compared with the KEYNOTE 189 study, the present study included patients with squamous or non-squamous NSCLC and revealed moderately improved PFS and OS. Furthermore, among patients treated with ICIs as second- or later-line

Table IV. Univariate and multivariate Cox regression analysis of factors associated with overall survival.

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Age (<63 vs. ≥63 years)	1.013	0.603-1.703	0.960			
Sex (male vs. female)	1.373	0.774-2.435	0.279			
Smoking history (smoker vs. non-smoker)	0.772	0.457-1.306	0.335			
ECOG status (0 vs. ≥1)	1.685	1.002-2.833	0.049	2.118	1.176-3.816	0.012
Stage (III vs. IV)	4.087	1.278-13.069	0.018	2.654	0.630-11.176	0.183
Histology (adenocarcinoma vs. squamous cell carcinoma)	1.185	0.697-2.016	0.531			
EGFR status (wild-type vs. mutation)	1.576	0.859-2.893	0.142			
PD-L1 status (<50% vs. ≥50%)	0.465	0.260-0.831	0.010	0.432	0.238-0.783	0.006
Previous systemic therapy (<2 vs. ≥2)	1.372	0.824-2.284	0.224			
Radiotherapy status (no vs. yes)	0.879	0.517-1.496	0.635			
Brain metastases (no vs. yes)	1.807	1.073-3.042	0.026	1.123	0.622-2.026	0.700
Liver metastases (no vs. yes)	1.735	0.976-3.082	0.060			

ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PD-L1, programmed cell death 1 ligand 1.

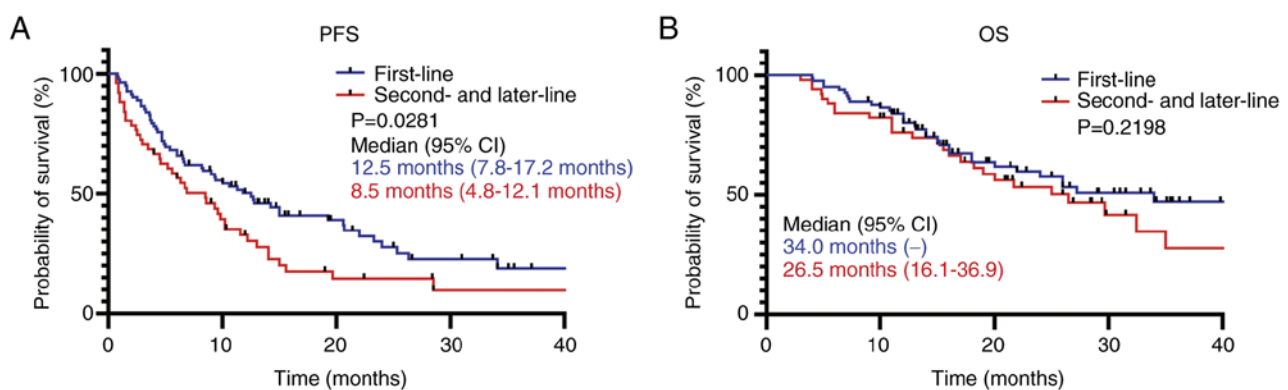


Figure 2. Kaplan-Meier estimates of (A) PFS and (B) OS stratified by immune checkpoint inhibitor therapy line. OS, overall survival; PFS, progression-free survival.

therapy, a median PFS time of 8.5 months and a median OS time of 26.5 months were observed. Based on long-term follow-up data for ICIs as a second-line therapy, the phase III clinical trial CheckMate 078 (22) assessed the efficacy and safety of nivolumab in the treatment of patients with advanced NSCLC, with a median PFS time of 2.8 months and a median OS time of 12.0 months reported in patients in the nivolumab group. In the present study, the follow-up data for second- and later-line treatments demonstrated improved PFS and OS compared with the existing clinical research data. Patients with EGFR/ALK alterations were excluded in the CheckMate 078 trial, while these were included in the present study. It was demonstrated that the EGFR mutation status did not affect the efficacy of later-line ICI treatment. In terms of ICI efficacy as first- or later-line therapies, the results of the present study demonstrated that patients treated with first-line ICIs had a longer PFS time compared with those treated with ICIs as second- or later-line therapy. In summary, first-line therapy with ICIs exhibited superior efficacy compared with second-line ICI treatment.

Numerous prior studies have demonstrated that combining immunotherapy with chemotherapy could extend the survival of patients with advanced NSCLC compared with chemotherapy alone. Furthermore, higher PD-L1 expression levels were associated with more pronounced survival benefits (21,23,24).

In the present study, among all patients who received ICIs, 83.46% underwent PD-L1 TPS testing. The present study aimed to assess the association between PD-L1 expression in tumors and the prognosis of patients with NSCLC treated with immunotherapy. The results of the present study demonstrated that patients with a PD-L1 TPS ≥50% had a significantly longer median PFS and OS time compared with patients with a PD-L1 TPS <50%. Survival analysis of patients treated with first-line ICI therapy also demonstrated a longer PFS time in patients with a PD-L1 TPS ≥50%. However, no significant difference was observed in this group for OS. Furthermore, in terms of later-line treatment, patients with a PD-L1 TPS ≥50% exhibited a significantly longer median PFS and OS time. These findings suggested

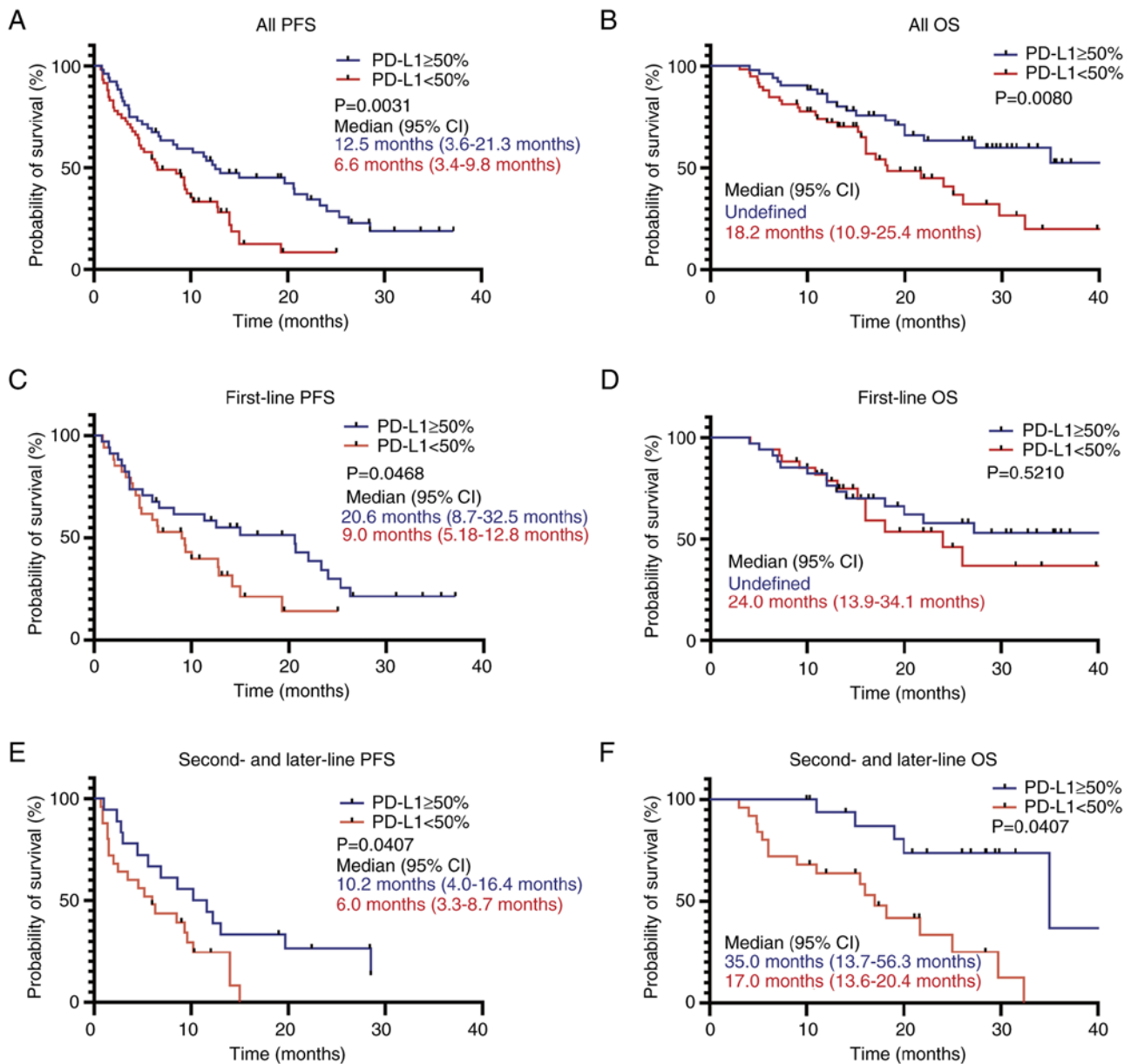


Figure 3. Kaplan-Meier estimates of (A) PFS and (B) OS stratified by PD-L1 status. Kaplan-Meier estimates of (C) PFS and (D) OS of patients who used immunotherapy plus chemotherapy as first-line treatment stratified by PD-L1 status. Kaplan-Meier estimates of (E) PFS and (F) OS of patients who used immunotherapy plus chemotherapy as second- and later-line therapy stratified by PD-L1 status. OS, overall survival; PD-L1, programmed cell death 1 ligand 1; PFS, progression-free survival.

that in second-line and subsequent immunotherapy treatments, individuals with high PD-L1 expression could notably benefit from ICI treatment compared with those with low or no PD-L1 expression. Furthermore, multivariate analysis further verified that PD-L1 TPS was a significant independent prognostic predictor for both PFS and OS. Furthermore, the proportion of patients with a PD-L1 TPS $\geq 50\%$ was $\sim 20\%$ in patients with NSCLC, as confirmed by immunohistochemistry in a previous study (25). In the present study, a number of patients with a PD-L1 TPS $< 50\%$ did not receive ICI treatment due to financial reasons, whereas patients with PD-L1 TPS $\geq 50\%$ were more willing to use the immunotherapy; therefore, the proportion of patients with a PD-L1 TPS $\geq 50\%$ will be higher in the present study compared with the proportion of patients confirmed by immunohistochemistry

in a previous study (25). This may be the reason why the PFS and OS were superior in the present study compared with the results of the clinical trials. In the real-world setting, the aforementioned findings substantiated the potential use of high PD-L1 expression in tumors as a biomarker for the selection of patients with advanced NSCLC who could benefit from immunotherapy.

In the present study, no association between the PD-L1 TPS and the effectiveness of ICIs was observed in patients with squamous cell carcinoma. This finding was consistent with the outcomes of two prior clinical trials, which compared the efficiency of nivolumab with docetaxel in patients with advanced NSCLC (26,27). The CheckMate 017 study, which focused on patients with squamous cell carcinoma, reported that the treatment efficacy was not associated with the PD-L1

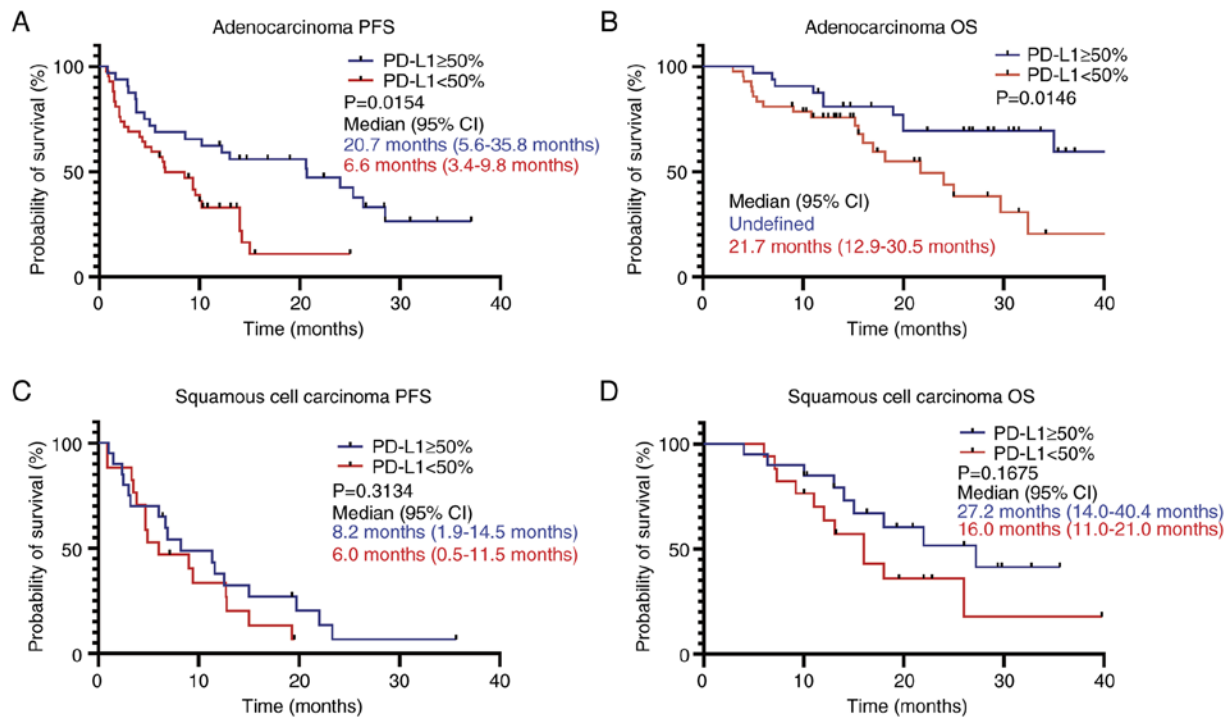


Figure 4. Kaplan-Meier estimates of (A) PFS and (B) OS of patients with adenocarcinoma stratified by PD-L1 status. Kaplan-Meier estimates of (C) PFS and (D) OS of patients with squamous cell carcinoma stratified by PD-L1 status. OS, overall survival; PD-L1, programmed cell death 1 ligand 1; PFS, progression-free survival.

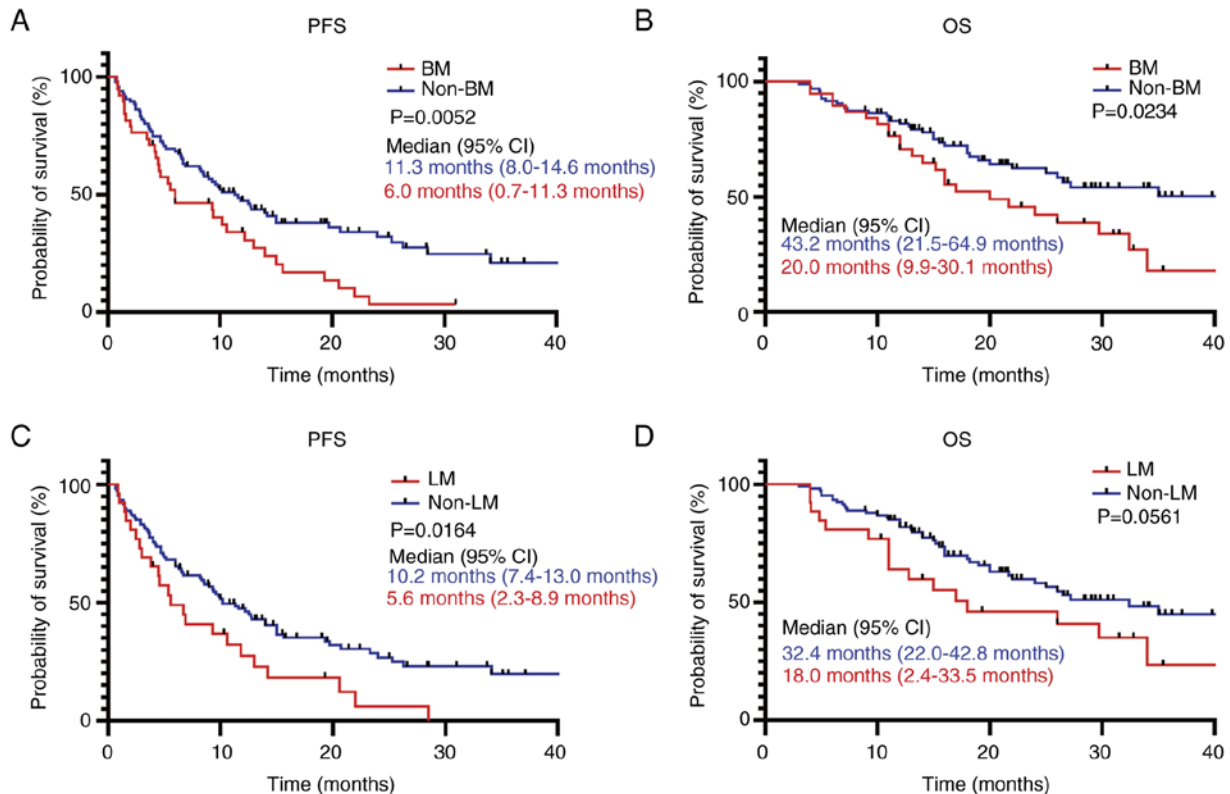


Figure 5. Kaplan-Meier estimates of (A) PFS and (B) OS stratified by BM. Kaplan-Meier estimates of (C) PFS and (D) OS stratified by LM. BM, brain metastasis; LM, liver metastasis; OS, overall survival; PFS, progression-free survival.

TPS. By contrast, the CheckMate 057 study, which enrolled patients with adenocarcinoma, demonstrated an association

between treatment efficacy and the PD-L1 TPS, thus the present study verified these previously reported results.

The majority of patients with NSCLC with brain metastasis were excluded from previous clinical trials (28-30). Therefore, data on the effectiveness and safety of immunotherapy in patients with NSCLC exhibiting brain metastasis are limited. Thus, patients with asymptomatic or stable brain metastasis were included. In the present study, ~28.57% of the patients exhibited brain metastasis, which is a higher percentage compared with what has been commonly recorded in several large-scale clinical trials (23). The results of the present study demonstrated that patients with brain metastasis had a shorter PFS and OS time in the overall population that was treated with immunotherapy. This aligned with the results of a study by Waterhouse *et al* (31), which reported that brain metastasis was associated with reduced OS in patients with squamous cell carcinoma NSCLC treated with either a single-agent immunotherapy or with immunotherapy combined with chemotherapy. Similar findings were obtained in patients with non-squamous cell carcinoma treated with immunotherapy combined with chemotherapy (12,21). The KEYNOTE-189 trial reported that, in a subgroup of patients with brain and liver metastasis, patients who received pembrolizumab in combination with chemotherapy exhibited improved PFS and OS compared with those treated with placebo combined with chemotherapy (21). However, when the results of two other studies, namely IMpower130 (26) and IMpower132 (32), were reviewed, the results demonstrated that patients in the liver metastasis subgroup did not exhibit survival benefits from immunotherapy combined with chemotherapy. Notably, in these studies, patients with metastasis in one or multiple organs were also included, which would affect the prognosis of patients. Consequently, further clinical research is needed to verify the response of patients with advanced NSCLC and liver metastasis to immunotherapy. The results of the present study also demonstrated that patients without liver metastasis had a longer PFS time compared with those with liver metastasis. Consistently, previous studies indicated that liver metastasis was closely associated with worse survival outcomes in patients receiving nivolumab, with a noticeably longer median PFS time observed in patients without liver metastasis compared with those with liver metastasis (33,34).

The current published immunotherapy data from real-world patients with lung cancer have some limitations (35-37). Firstly, the sample sizes were commonly small (<100 patients), and the studies only included a particular subgroup of patients, such as elderly patients, those treated with PD-1/PD-L1 monotherapy or patients experiencing immune-related adverse events. Although data from several large studies were extracted from the corresponding databases, the detailed patient records were not always available (31,38).

In summary, in the present study, the inclusion criteria resulted in a more comprehensive cohort and relevant subgroup analyses were also conducted, which could assist clinicians in assessing the safety and efficacy of ICIs in the treatment of patients with advanced lung cancer in routine oncology practice.

However, the present study has some limitations. This was a small, single-center, retrospective study, which could be affected by inherent selection bias. Furthermore, seven types of ICIs were used in present study, which may have resulted in differences in efficacy among patients who received

different treatments. Furthermore, patients treated with both single-agent and combination immunotherapy, with varying treatment regimens and multiple confounding factors, were included, thus possibly affecting the assessment of immunotherapy efficacy. Therefore, larger, multicenter, prospective studies are required to further confirm the results of the present study and provide a more solid basis for identifying potential benefits of immunotherapy.

In conclusion, the present study demonstrated that PD-L1 status was an independent predictor for PFS and OS in patients who were treated with ICIs plus chemotherapy with advanced adenocarcinoma, but not in those with squamous cell carcinoma. When the aforementioned regimens were used as first-line therapy, an increase in PFS but not OS was observed. An increase in PFS was also demonstrated in patients treated with first-line ICI therapy with a PD-L1 TPS of $\geq 50\%$. Furthermore, when the ICIs were used as second- or later-line therapy, the PFS and OS were both significantly increased in patients with a PD-L1 TPS $\geq 50\%$. Patients with brain metastasis had a shorter PFS and OS time compared with those without metastases. Patients with liver metastasis showed poor PFS; however, it was not significantly associated with OS. Finally, although the present study had some limitations, these results may aid clinicians in decision-making and provide other options 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

ZX, HZ and GM contributed to the response evaluation and data analysis. ZX, HZ, WM, JD, XW, BY, NW, YD, QZ and NL performed the data collection and analysis. ZX and ZL wrote and edited the manuscript. ZX, HZ and ZL confirm the authenticity of all the raw data. XZ, GY, SL and ZL designed the present study. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Weifang People's Hospital (The First Affiliated Hospital of Shandong Second Medical University) (approval no. KYLL20230112-1; Weifang, China) and was performed according to the Declaration of Helsinki. Informed consent was not required, since patient data were de-identified prior to receipt, and the requirement for informed consent was waived by the Ethics Committee of Weifang People's Hospital

(The First Affiliated Hospital of Shandong Second Medical University).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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