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Patterns of failure and the subsequent treatment after progression on first-line immunotherapy monotherapy in advanced non-small cell lung cancer: a retrospective study

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Abstract

Background Immune checkpoint inhibitors (ICIs) have become the recommended first-line treatment for advanced non-small cell lung cancer (NSCLC) without driver gene mutations. However, data on the failure patterns of first-line ICIs monotherapy is limited, and the optimal strategy for subsequent treatment remains controversial.

Methods Advanced NSCLC patients receiving first-line ICIs monotherapy at Guangdong Lung Cancer Institute between December 2017 and October 2021 were identified. The progressive sites were recorded to analyze failure patterns. Post-progression survival (PPS) was compared between different treatment regimens.

Results A total of 121 patients receiving first-line ICIs monotherapy were identified, with a median progression-free survival of 8.6 months. Sixty-five patients had available imaging at diagnosis as well as progressive disease, with 56.9% showing oligoprogression. For those with progression in existing lesions, the most common sites were the liver (77.8%) and lung parenchyma (62.5%), while progression with new lesions frequently occurred in the liver (32.0%). Fifty patients with recorded subsequent treatment were included in the analysis of subsequent treatment patterns. Patients treated with anti-angiogenesis therapy could get better PPS (HR: 0.275, $P=0.013$). Isolated oligoprogression occurred most often in the lung parenchyma and intracranial lesions. More than half of these patients continued immunotherapy after local treatment, with a 2.5-year PPS rate of 51.4%.

Conclusion The liver was the most common site of progression on first-line ICIs monotherapy. Anti-angiogenesis-based therapy might be an optimal regimen at the time of progression. Patients with isolated oligoprogressive could still benefit from immunotherapy after local treatment.

Keywords Progression, Anti-angiogenesis, Oligoprogression, Local treatment, Immune checkpoint inhibitors

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Introduction

Since pembrolizumab was first approved for first-line treatment in advanced non-squamous non-small cell lung cancer (NSCLC) by the Food and Drug Administration in 2016, the administration of immune checkpoint inhibitors (ICIs) either alone or combined with chemotherapy has become the recommended therapy for advanced NSCLC without driver gene mutations [1, 2]. The increasing application of ICIs in first-line treatment has extended both progression-free survival (PFS) and overall survival (OS) in patients with advanced NSCLC [3].

Despite these advances, almost all patients will inevitably experience disease progression (PD) and require additional therapeutic options after progression [4, 5]. PD could be categorized as polyprogression or oligoprogression based on the number of progressive sites in any organ [6]. A few studies have explored the frequency of different failure patterns and their correlation with OS. It has been reported that oligoprogression is more common in NSCLC treated with ICIs, with an incidence ranging from 40 to 62% [7–9]. Since previous studies always included mixed treatment lines or various ICIs-based regimens, more data specifically on first-line ICIs monotherapy is needed.

For those with oligoprogression, where PD is confined to a limited number of disease sites, local treatment may be a viable option to eliminate tumor cell populations resistant to previous systemic therapy and allow the continuation of treatment [6, 7]. Local therapy has been shown to prolong survival in NSCLC patients with oligoprogression to first-line pembrolizumab. As oligoprogression seems to benefit from the continuation of ICIs as resistance was limited to a limited number of lesions, the benefit for those with polyprogression from the original ICIs remains unclear. Switching to second-line systemic therapy is still the standard approach for PD according to guidelines. For those progressing on first-line immunotherapy monotherapy, optional second-line systemic therapies include chemotherapy, anti-angiogenesis therapy, other ICIs, and combinations of initial ICIs with chemotherapy or anti-angiogenesis therapy [10, 11]. Since the efficacy data for these regimens is largely derived from clinical trials conducted before the introduction of ICIs, evidence to guide treatment selection for these patients is limited, and the optimal strategy after progression on first-line ICIs remains controversial.

Given this unmet need, we report data on failure patterns in advanced NSCLC receiving first-line immunotherapy alone and the subsequent treatment patterns to explore the optimal therapeutic strategy related to different failure patterns.

Materials and methods

Study population

Consecutive patients with advanced NSCLC receiving first-line ICIs monotherapy at Guangdong Provincial People's Hospital between December 2017 and October 2021 were identified in a database approved by the Ethics and Scientific Committees of Guangdong Provincial People's Hospital. The inclusion criteria were: (I) biopsy-proven NSCLC; (II) diagnosis of treatment-naïve advanced NSCLC; (III) receiving at least one course of ICIs monotherapy in a first-line setting. The exclusion criteria were: (I) patients without metastatic sites; (II) patients with SCLC; (III) targetable actionable mutations treated with first-line small molecule inhibitors. All patients meeting these criteria were included in the real-world clinical outcomes analysis. Among them, those with available imaging at diagnosis and PD were included in the patterns of failure analysis. Those with recorded subsequent treatment received at the time of progression were included in the subsequent treatment patterns analysis.

Clinical characteristics data including age, sex, Eastern Cooperative Oncology Group Performance Status (ECOG PS), smoking history, pathology, PD-L1 expression, and sites of disease at diagnosis were retrieved from the patients' medical records. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics and Scientific Committees of Guangdong Provincial People's Hospital [approval number: GDREC2019304H(R1)]. The ethics committee waived individual consent due to the retrospective nature of the study.

Real-world clinical outcomes analysis

All patients eligible for the criteria were included in the real-world clinical outcomes analysis. At the initial diagnosis, enhanced computed tomography (CT) of the chest and abdomen, enhanced magnetic resonance imaging (MRI) of the head, and whole-body bone scan by emission computed tomography (ECT) imaging, or whole-body positron emission tomography (PET)/CT plus head-enhanced MRI were required to determine staging. Sites of disease at diagnosis were recorded in the medical records. Radiographic PD was identified based on the RECIST 1.1 by the reviewing physician [12]. The final follow-up date was January 31, 2024. PFS was defined as the time from the first ICIs prescription date to the day of physician assessment of PD or death from any cause. OS was defined as the time from the first ICIs prescription date to either the date of death or the final follow-up date. The data of patients who survived were censored.

Patterns of failure analysis

Enrolled patients with available imaging materials at diagnosis as well as radiographic PD were included in the patterns of failure analysis. At the time of PD, patient imaging was reviewed by physicians, and the progressive sites were recorded. To understand the failure patterns among these patients, new lesions of failure were defined as tumors not present before ICIs treatment, while existing lesions were sites that responded to treatment but then progressed. Combination refers to disease growth in both existing and new lesions simultaneously at the time of PD. The number of progression sites after ICIs therapy was also recorded. Patients were classified as oligoprogressive (≤3 distinct sites of progression in any organs) or polyprogressive (>3 sites of progression, including malignant pleural or pericardial effusion/studding, leptomeningeal spread, or lymphangitic parenchymal disease) [7].

Subsequent treatment patterns analysis

Enrolled patients with recorded subsequent treatments received at the time of progression were included in the subsequent treatment patterns analysis. Based on the drugs used, patients were divided into groups with or without anti-angiogenesis therapy, chemotherapy, and immunotherapy. The frequency of anti-angiogenesis therapy, chemotherapy, and immunotherapy used at the time of progression was calculated. Post-progression survival (PPS) was evaluated for those receiving treatment beyond progression on first-line ICIs (calculated from the date of progression on ICIs to death from any cause, with surviving patients censored at the time of the last follow-up). The differences in PPS between those receiving anti-angiogenesis therapy, chemotherapy, and immunotherapy were analyzed. We The effect of local treatment at progression on first-line ICIs monotherapy was also evaluated.

Table 1 Baseline patient and tumor characteristics

Characteristics	Total population ($n=121$)
Age, years, median (range)	66 (39, 86)
Gender, No. (%)	
Male	105 (86.8)
Female	16 (13.2)
Smoking history, No. (%)	
Current/ Former	88 (72.7)
Never	33 (27.3)
ECOG PS, No. (%)	
0–1	107 (92.6)
2	9 (7.4)
Pathologic subtypes, No. (%)	
Adenocarcinoma	75 (62.0)
Squamous	30 (24.8)
Others	16 (13.2)
Sites of disease at diagnosis, No. (%)	
Lung	115 (95.0)
LNs	101 (83.5)
Bone	51 (42.1)
Pleura	35 (28.9)
Adrenal	28 (23.1)
Brain	28 (23.1)
Others	21 (17.4)
Liver	18 (14.9)
PD-L1, No. (%)	
TPS ≥ 50%	100 (82.6)
TPS < 50%, ≥ 1%	10 (8.3)
TPS < 1%	3 (2.5)
Unknow	8 (6.6)

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Science (SPSS) software (version 23) and GraphPad Prism software (Version 8). The Kaplan-Meier method was used to analyze the survival probability, and the log-rank test was used to calculate the significance of differences. The Cox proportional hazard model was applied for the univariate and multivariate analyses to calculate the hazard ratios (HRs) and 95% confidence intervals (95% CIs). Two-sided *P* values < 0.05 were considered statistically significant.

Results

Baseline patient characteristics

A total of 121 patients with advanced NSCLC meeting the criteria were enrolled to assess the clinical outcomes of first-line ICIs monotherapy in a real-world setting. The patients' clinical characteristics are summarized in Table 1 in detail. All of them received anti-PD-1 inhibitors (including pembrolizumab and sintilimab) monotherapy (Supplementary Table 1). The median age was 66 years (range, 39–86), 86.8% ($n=105$) were male, 72.7% ($n=88$) had a smoking history, and 92.6% ($n=107$) had an ECOG PS of 0 to 1. Most tumors were adenocarcinomas ($n=75$, 62.0%) with PD-L1 TPS ≥ 50% ($n=100$, 82.6%). The majority had disease lesions in the lung parenchyma ($n=115$, 95.0%), including primary or metastatic sites. The most common distant metastases were bone metastases ($n=51$, 42.1%), followed by adrenal metastases ($n=28$, 23.1%) and brain metastases ($n=28$, 23.1%).

Real-world clinical outcomes in advanced NSCLC receiving first-line immunotherapy monotherapy

After a follow-up of 31.8 months, the median PFS was 8.6 months and the median OS was 21.4 months for those receiving first-line immunotherapy monotherapy(Fig. 1A and B). Univariate and multivariate analyses identified factors associated with the efficacy of first-line ICIs monotherapy. Patients without liver metastases had significantly longer PFS (univariate: HR 0.614, $P=0.001$; multivariate: HR 0.697, $P=0.001$) and OS (univariate: HR

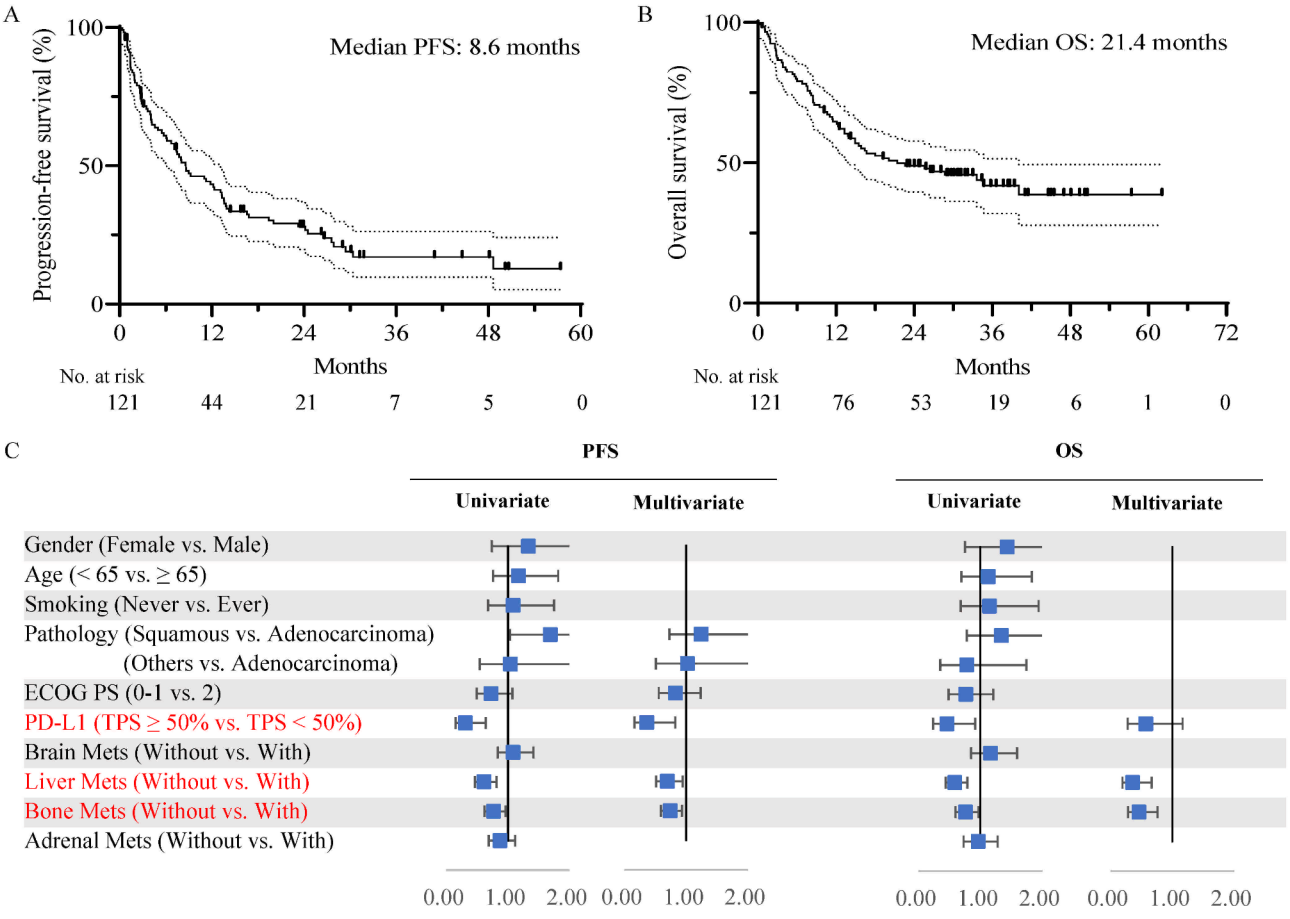
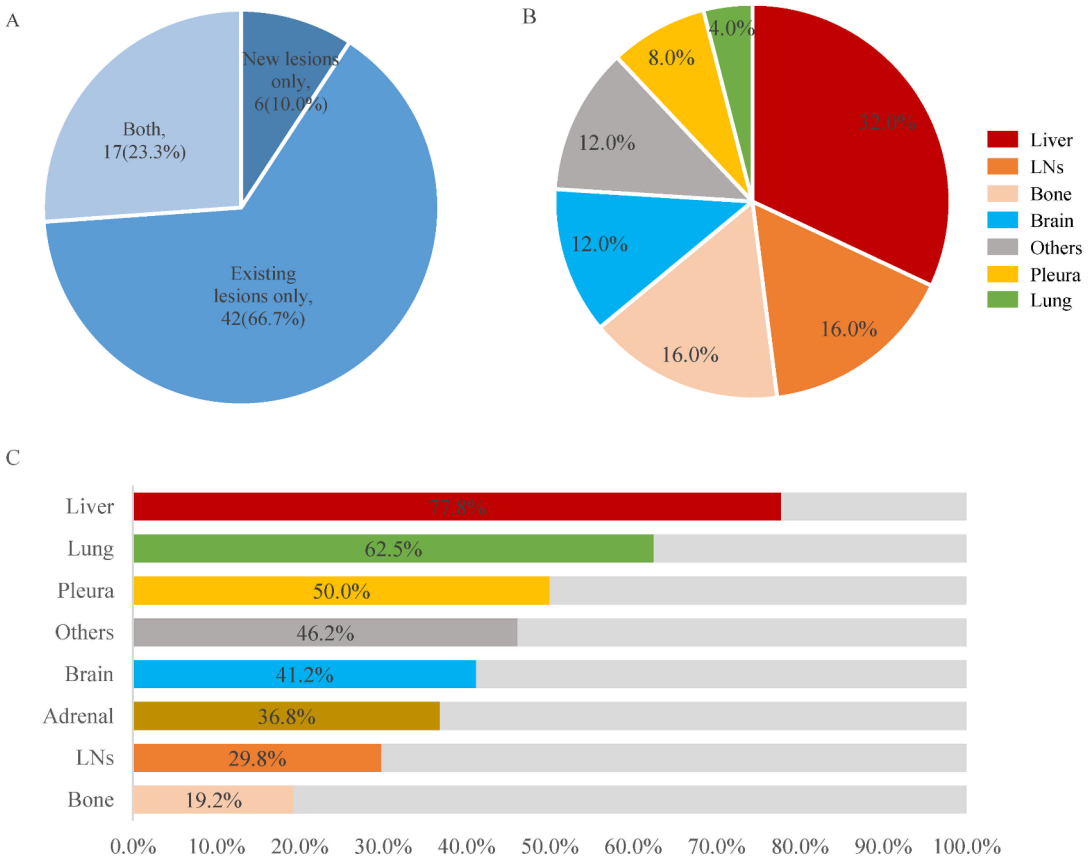


Fig. 1 Real-world clinical outcomes in advanced NSCLC receiving first-line immunotherapy monotherapy. (**A**) Kaplan-Meier curves for PFS. (**B**) Kaplan-Meier curves for OS. (**C**) Forest plots of the effects of clinical factors on PFS and OS. Mets: metastases

0.588, P=0.001; multivariate: HR 0.359, P=0.001) compared to those with liver metastases. Bone metastases showed a similar pattern, indicating that liver and bone metastases were independent factors associated with poor survival in NSCLC patients treated with first-line ICIs monotherapy Patients with high PD-L1 expression (TPS≥50%) could get better PFS (univariate: HR 0.313, P=0.017; multivariate: HR 0.363, P=0.024), but not OS (univariate: HR 0.462, P=0.027; multivariate: HR 0.572, P=0.125) benefits in our analysis. No significant differences were observed concerning other clinical parameters including age, gender, smoking history, pathological types, or the presence of brain metastases or adrenal metastases in our cohort (Fig. 1C, Supplementary Tables 2 and 3).

Patterns of failure of first-line immunotherapy monotherapy in advanced NSCLC

To understand the patterns of failure in those receiving first-line immunotherapy monotherapy, we collected data on patients with available imaging at diagnosis as well as PD. Of the 121 enrolled patients, 83 (68.6%) had recorded PFS events, among which 65 (78.3%) had radiological evidence of PD, 1 (1.2%) had clinical deterioration of disease, and the other 17 (20.5%) had documented death record (Supplementary Table 4). Finally, sixty-five patients were included in the patterns of failure analysis. Among them, most failures occurred in existing lesions alone (n=42, 66.7%), followed by a combination of new and existing lesions (n=17, 23.3%), and in new lesions alone (n=6, 10.0%) (Fig. 2A). For those with new lesions, progression frequently occurred in the liver (n=8, 32.0%), LNs (n=4, 16.0%), and bone (n=4, 16.0%) (Fig. 2B). As for those with failure in existing lesions, the most common progression sites were liver (77.8%), lung parenchyma (62.5%), and pleura (50.0%) (Fig. 2C). Additionally, 56.9% (n=37) of these patients showed oligoprogression, while the others had progression in more than three sites (Fig. 2D), suggesting that oligoprogression was more common. Those with oligoprogression had longer OS than those with polyprogression (median OS: 40.1 vs. 13.2 months, P=0.007) (Fig. 2E). Isolated oligoprogression occurred in 35.5% (n=22) of these patients, and most often in the lung parenchyma (n=9) and intracranial lesions (n=5).



Count	Liver	Lung	Pleura	Others	Brain	Adrenal	LNs	Bone
Sites of progression, n	7	40	10	6	7	7	17	5
Sites of disease at diagnosis, n	9	64	20	13	17	19	57	26

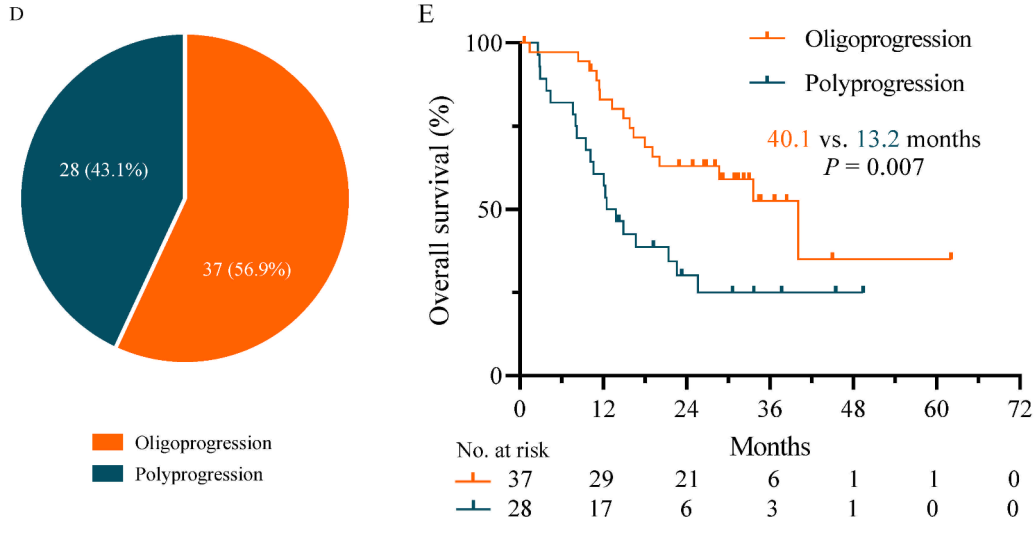


Fig. 2 Patterns of failure of first-line immunotherapy monotherapy in advanced NSCLC. (**A**) Pie chart showing the distribution of failure in existing lesions only, new lesions only, and both. (**B**) Pie chart showing the distribution of each organ with new lesions. (**C**) Frequency of each organ with progression in existing lesions. (**D**) Pie chart showing the distribution of oligoprogression and polyprogression. (**E**) Kaplan-Meier curves for OS stratified by oligoprogression and polyprogression. LNs: lymph nodes

Subsequent treatment patterns after progression on first-line immunotherapy monotherapy

We then analyzed the subsequent treatment patterns after progression on first-line immunotherapy monotherapy. Fifty patients with recorded treatments received at the time of progression were included in this part of the analysis. In these patients, the median OS was 34.7 months (Supplementary Fig. 1). Based on the drugs used, patients were divided into groups with or without anti-angiogenesis therapy, chemotherapy, and immunotherapy. The clinical characteristics including ECOG PS and pathological types among participants between groups were similar (Table 2). The frequency of anti-angiogenesis therapy (including bevacizumab and anlotinib), chemotherapy (including pemetrexed ± platinum, paclitaxel ± platinum, and gemcitabine + platinum), and immunotherapy used at the time of progression was 38.0%, 56%, and 64%, respectively (Supplementary Table 1). Half of the patients ($n=27$, 54.0%) were treated with a combination of local treatment, other anti-tumor agents, or both, based on the original ICIs. Local treatment, including palliative surgical resection or radiotherapy, was most common for intracranial lesions ($n=4$), followed by lung parenchyma ($n=3$), bone ($n=2$), and adrenal ($n=2$).

Univariate and multivariate analyses were then performed to determine the factors associated with PPS. As shown in Table 3, patients with a good performance status had significantly better PPS (univariate: HR 0.187, $P<0.001$; multivariate: HR 0.162, $P<0.001$). In terms of different treatment strategies, patients treated with anti-angiogenesis therapy could get better PPS (univariate: HR 0.315, $P=0.024$; multivariate: HR 0.275, $P=0.013$) compared to those without anti-angiogenesis therapy. In contrast, no significant differences were observed based on whether chemotherapy or immunotherapy was used, nor were there differences in other clinical parameters including age, gender, smoking history, pathological types, PD-L1 expression, metastatic sites, or patterns of failure in our cohort. Interestingly, although the *P*-value was not significant, the Kaplan-Meier survival curve stratified by liver metastases showed a tendency to separate (median: 15.9 vs. 21.6 months, $P=0.374$, Supplementary Fig. 2).

Optimal therapeutic strategies according to different patterns of failure

We showed the sites of progression and the treatments received at the time of progression for each case in Fig. 3A. As mentioned above, oligoprogression was more common. In the subsequent treatment patterns analysis cohort, thirty-one patients exhibited oligoprogression. These patients could still benefit from immunotherapy with a median PPS of 32.1 months, which was significantly longer than those without immunotherapy after failure to first-line ICIs monotherapy (10.3 months, $P=0.021$, Fig. 3B). For those with polyprogression, no significant difference was observed between those who received second-line immunotherapy and those who did not ($P=0.979$). Among patients with isolated oligoprogression, more than half ($n=11$) received local treatment along with the original ICIs as the subsequent treatment at the time of progression on first-line ICIs monotherapy. Local treatment significantly prolonged PPS, with a 2.5-year PPS of 51.4%, compared to those without local treatment ($P=0.007$) in patients with isolated oligoprogression (Fig. 3C).

The application of anti-angiogenesis therapy significantly prolonged PPS (median: not reached vs. 15.9 months, $P=0.017$, Fig. 3D). Given the high frequency of progression in the liver and the positive impact of anti-angiogenesis therapy on ICIs efficacy in NSCLC patients with liver metastases as reported, we analyzed the efficacy of anti-angiogenesis therapy in a subgroup analysis. It was shown that those with liver progression benefited from anti-angiogenesis therapy, with a 1-year-PPS of 75.0%, while the median PPS for those without anti-angiogenesis therapy was 6.5 months (Supplementary Fig. 3).

Discussion

In this analysis, we focused on the patterns of failure and subsequent treatments after progression on first-line ICIs in advanced NSCLC patients. A relatively homogeneous population of patients receiving first-line ICIs alone was included. This is also the first study analyzing optimal therapeutic strategies according to different patterns of failure. We found that the liver was the most common site of progression, both in patients with failure in existing lesions and those with new lesions. Anti-angiogenesis-based therapy might be an optimal regimen at the time of progression, even for those with progression in liver. Oligoprogression was more common, and patients with oligoprogression rather than polyprogression could benefit from the subsequent immunotherapy. Isolated oligoprogression most often occurred in the lung parenchyma and intracranial lesions, and these patients could still benefit from the original ICIs after local treatment.

ICIs monotherapy has been widely used in real-world clinical practice for those with PD-L1 TPS ≥ 1%. According to the KEYNOTE-024 and KEYNOTE-042 trials, the median OS of first-line pembrolizumab monotherapy was 26.3 months and 16.4 months, respectively [13, 14]. In our clinical cohort, the OS was 21.4 months, and baseline liver metastases and bone metastases were correlated with poor OS via Cox proportional hazards modeling. These findings align with published data [15–18]. PD-L1 expression is recommended as a predictive biomarker for selecting patients who derive the most benefit from

Table 2 Clinical characteristics between groups in PPS

	Anti-angiogenesis therapy			Chemotherapy			Immunotherapy		
	With	Without	*P*	With	Without	*P*	With	Without	*P*
Gender									
Female	1 (5.3%)	4 (12.9%)	0.382	4 (14.3%)	1 (4.5%)	0.254	4 (12.5%)	1 (5.6%)	0.432
Male	18 (94.7%)	27 (87.1%)		24 (85.7%)	21 (95.5%)		28 (87.5%)	17 (94.4%)	
Age									
< 65	7 (36.8%)	17 (54.8%)	0.216	17 (60.7%)	7 (31.8%)	0.052	15 (46.9%)	9 (50.0%)	0.832
≥ 65	12 (63.2%)	14 (45.2%)		11 (39.3%)	15 (68.2%)		17 (53.1%)	9 (50.0%)	
Smoking									
Never	4 (21.1%)	6 (19.4%)	0.884	8 (28.6%)	2 (9.1%)	0.154	5 (15.6%)	5 (27.8%)	0.302
Ever	15 (78.9%)	25 (80.6%)		20 (71.4%)	20 (90.9%)		27 (84.4%)	13 (72.2%)	
Pathology									
Squamous	4 (21.0%)	14 (45.2%)	0.219	9 (32.1%)	9 (40.9%)	0.496	13 (40.6%)	5 (27.8%)	0.656
Adeno-carcinoma	12 (63.2%)	13 (41.9%)		16 (57.1%)	9 (40.9%)		15 (46.9%)	10 (55.6%)	
Others	3 (15.8%)	4 (12.9%)		3 (10.7%)	4 (18.2%)		4 (12.5%)	3 (16.6%)	
ECOG PS									
0–1	17 (89.5%)	27 (87.1%)	0.802	24 (85.7%)	20 (90.9%)	0.575	30 (93.8%)	14 (77.8%)	0.095
2	2 (10.5%)	4 (12.9%)		4 (14.3%)	2 (9.1%)		2 (6.2%)	4 (22.2%)	
PD-L1, TPS									
≥ 50%	14 (73.7%)	27 (87.1%)	0.465	23 (82.1%)	18 (81.8%)	0.955	25 (78.1%)	16 (88.8%)	0.629
< 50%	3 (15.8%)	2 (6.5%)		3 (10.7%)	2 (9.1%)		4 (12.5%)	1 (5.6%)	
Unknow	2 (10.5%)	2 (6.5%)		2 (7.1%)	2 (9.1%)		3 (9.4%)	1 (5.6%)	
Brain Metastases									
With	5 (26.3%)	9 (29.0%)	0.836	5 (17.9%)	9 (40.9%)	0.113	8 (25.0%)	6 (33.3%)	0.529
Without	14 (73.7%)	22 (71.0%)		23 (82.1%)	13 (59.1%)		24 (75.0%)	12 (66.7%)	
Liver Metastases									
With	4 (21.1%)	6 (19.4%)	0.884	6 (21.4%)	4 (18.2%)	0.776	7 (21.9%)	3 (16.7%)	0.659
Without	15 (78.9%)	25 (80.6%)		22 (78.6%)	18 (81.8%)		25 (78.1%)	15 (83.3%)	
Bone Metastases									
With	8 (42.1%)	15 (48.4%)	0.665	12 (42.9%)	11 (50.0%)	0.615	15 (46.9%)	8 (44.4%)	0.869
Without	11 (57.9%)	16 (51.6%)		16 (57.1%)	11 (50.0%)		17 (53.1%)	10 (55.6%)	
Adrenal Metastases									
With	4 (21.1%)	13 (41.9%)	0.130	8 (28.6%)	9 (40.9%)	0.361	13 (40.6%)	4 (22.2%)	0.187
Without	15 (78.9%)	18 (58.1%)		20 (71.4%)	13 (59.1%)		19 (59.4%)	14 (77.8%)	

Table 3 Univariate and multivariate analyses of clinical parameters on PPS in NSCLC patients after progression on first-line ICIs monotherapy

Factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Gender						
Female vs. Male	0.780	0.181–3.364	0.739			
Age						
< 65 vs. ≥ 65	1.092	0.480–2.487	0.834			
Smoking						
Never vs. Ever	0.868	0.293–2.573	0.798			
Pathology						
Squamous vs. Adenocarcinoma	1.115	0.470–2.643	0.805			
Others vs. Adenocarcinoma	0.871	0.242–3.131	0.832			
ECOG PS						
0–1 vs. 2–3	0.187	0.089–0.396	< 0.001	0.162	0.072–0.364	< 0.001
PD-L1, TPS						
≥ 50% vs. < 50%	0.959	0.284–3.238	0.946			
Brain Metastases						
Without vs. With	0.824	0.529–1.282	0.390			
Liver Metastases						
Without vs. With	0.794	0.475–1.327	0.379			
Bone Metastases						
Without vs. With	1.007	0.670–1.513	0.974			
Adrenal Metastases						
Without vs. With	0.852	0.559–1.298	0.455			
Anti- angiogenesis therapy						
With vs. Without	0.315	0.116–0.856	0.024	0.275	0.099–0.762	0.013
Chemotherapy						
With vs. Without	1.893	0.808–4.437	0.142			
Immunotherapy						
With vs. Without	0.508	0.223–1.160	0.108			
Failure patterns						
Polyprogression vs. Oligoprogression	1.956	0.858–4.460	0.110			

ICIs monotherapy [19]. Here PD-L1 expression was correlated with PFS rather than OS in multivariate analysis, which might be due to the small sample of patients with PD-L1 < 50% in our cohort.

Several studies have described the patterns of failure of ICIs, but these often included mixed treatment lines or different regimens (including monotherapy and chemoimmunotherapy) [7, 9, 20]. In our study, we limited the analysis to patients receiving first-line ICIs monotherapy. It was found that 66.7% of failures occurred in existing lesions alone, which was relatively higher than the incidence reported in patients receiving first-line pembrolizumab alone or chemoimmunotherapy (33%) [7], but similar to those receiving first or second-line ICIs alone (58%) [9]. Since the natural history of disease responsive to the addition of cytotoxic chemotherapy on the basis of ICIs may differ from ICIs alone, patterns of failure could vary between different ICIs-based regimens. Additionally, the treatment line might also influence the patterns of failure, as previous treatments may affect the efficacy of subsequent therapies [21]. Therefore, we described the patterns of failure in a relatively homogeneous population of patients receiving only first-line ICIs monotherapy.

The liver was identified as the most common site of progression on first-line ICIs alone, in both existing and new lesions. Previous studies compared the counts of different progressing sites and reported that the lung parenchyma had the highest number of patients with progression, especially in those with progression in existing lesions [7, 9]. However, it is important to note that the number of patients with lung parenchyma lesions at diagnosis was also higher than at other sites in lung cancer. Here, we reported the proportion of progressive lesions in a specific site, highlighting the high proportion of progressive liver lesions. The management of metastatic liver lesions during immunotherapy should be taken seriously. Studies have shown that liver metastases might get limited benefit from immunotherapy monotherapy, indicating the need for more aggressive combination strategies [16, 22]. Liver metastases are associated with shorter OS. In this study, liver metastases were not significantly

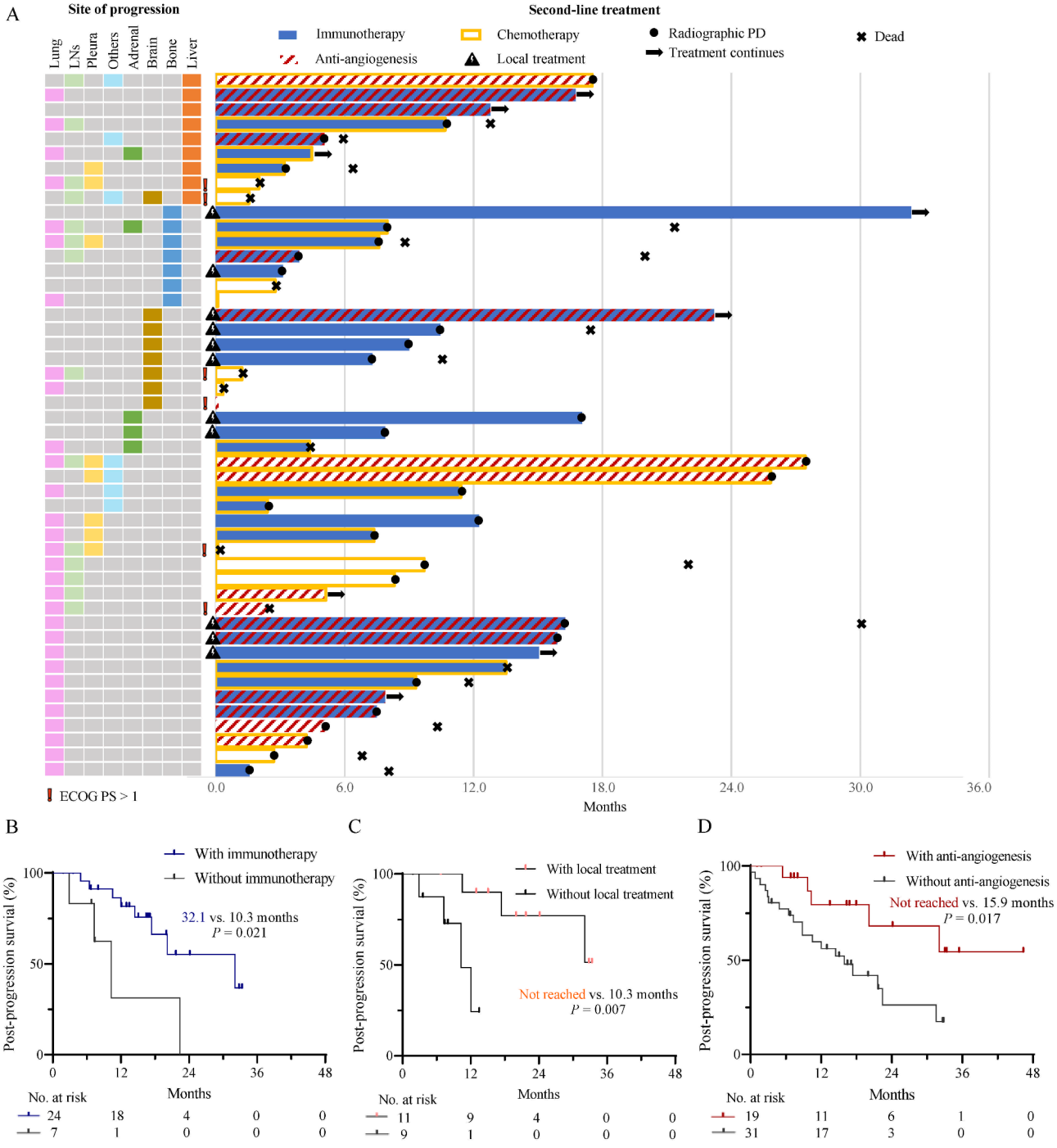


Fig. 3 Subsequent treatment after progression on first-line immunotherapy monotherapy. (**A**) Treatment courses received at the time of progression on first-line ICIs monotherapy and clinical outcomes of the subsequent treatment patterns analysis subset. (**B**) Kaplan-Meier curves for PPS in patients with oligoprogression stratified by with or without second-line immunotherapy. (**C**) Kaplan-Meier curves for PPS in patients with isolated oligoprogression stratified by with or without local treatment. (**D**) Kaplan-Meier curves for PPS stratified by with or without anti-angiogenesis agents received at time of progression

associated with PPS in univariate and multivariate analyses, but the Kaplan-Meier survival curve stratified by liver metastases showed a tendency to separate, which might be due to the limited sample size. The Impower150 trial showed the numerical improvement in OS with the addition of an anti-angiogenesis drug to immunotherapy in the liver metastases subgroup, suggesting anti-angiogenesis-based therapy for these patients in clinical practice [23]. Here, we reported that anti-angiogenesis therapy after progression on first-line ICIs alone could

improve PPS, even in those with liver progression. Anti-angiogenesis agents, such as bevacizumab and anlotinib, play an important role treating advanced NSCLC [24]. Previous studies have demonstrated that the abnormal angiogenesis state of tumors can suppress the anti-tumor immune response through multiple mechanisms and is related to immunotherapy resistance. Anti-angiogenesis treatment can inhibit tumor growth and promote the normalization of tumor blood vessels to reconstitute the tumor microenvironment [25]. Clinical effects of ICIs and anti-angiogenesis treatment were observed when anti-angiogenesis treatment was administered concomitantly and immediately after ICIs, supporting its application after progression on ICIs [21].

The frequency of oligoprogression was relatively higher than polyprogression in our study. Consistent with our findings, oligoprogression is more common in NSCLC treated with ICIs in several studies, with incidence rates varying from 40 to 62% [7–9]. However, it should be noted that there might be a potential overestimation of oligoprogression because patients who progressed systemically may omit radiological evaluation. Previous studies have reported that patients with oligoprogression treated with local treatments, such as palliative surgical resection or radiotherapy, showed significant improvement in survival [7, 8, 26]. Importantly, eliminating tumor cell populations resistant to prior systemic therapy through local treatment can allow the continuation of the original immunotherapy [27]. Our study also indicated that patients with oligoprogression rather than polyprogression could benefit from subsequent immunotherapy. These findings support considering patterns of failure when making decisions on subsequent treatment in clinical practice.

This study has several limitations. Given the nature of a single-center retrospective study, there might be potential bias. We compared patients' characteristics between groups to ensure inter-group comparability. We categorized patients into groups with or without anti-angiogenesis therapy, chemotherapy, and immunotherapy in the subsequent treatment setting, though multiple regimens might be combined in clinical practice. We did not analyze which combination was optimal due to the limited sample size. In addition, we included only those receiving first-line ICIs monotherapy to improve population homogeneity, but a large proportion of patients receive ICIs-based combination therapy in the real world. It should be noted that patterns of failure might differ between monotherapy and combination therapy. Further studies are needed to compare the differences between various ICIs treatment strategies.

Conclusions

In conclusion, our findings summarize the patterns of failure and the optimal subsequent therapeutic strategies after progression on first-line ICIs monotherapy in advanced NSCLC patients. It increases the focus on the liver for the high proportion of progressive liver lesions on first-line ICIs monotherapy. In addition, patterns of failure should be considered when making decisions on subsequent treatment in clinical practice. Our study provides valuable insights into treatment decisions after immunotherapy resistance in clinical practice.

Supplementary Information

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Supplementary Material 1

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Author contributions

JY.D.: Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Visualization, Writing–original draft, Writing–review & editing. MY.Y.: Data curation, Investigation, Writing–review & editing. XR.Y.: Formal analysis, Writing–review & editing. ZH.C.: Resources, Funding acquisition. CR.X.: Conceptualization, Data Curation, Writing–review & editing. Q.Z.: Conceptualization, Investigation, Supervision, Writing–original draft, Writing–review & editing, Project administration, Funding acquisition. All authors reviewed the manuscript.

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Data availability

Data relevant to the study are included in the article or uploaded as supplementary information. All other relevant data are available from the corresponding author of this study (Qing Zhou, gzzhouqing@126.com) upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics and Scientific Committees of Guangdong Provincial People's Hospital [approval number: GDREC2019304H(R1)]. The ethics committee waived the individual consent due to the retrospective nature of the study.

Consent for publication

Not applicable.

Conflict of interest

Not applicable.

Competing interests

Prof. Qing Zhou reports honoraria from AstraZeneca, Boehringer Ingelheim, BMS, Eli Lilly, MSD, Pfizer, Roche, and Sanofi outside the submitted work. The other authors have no competing interests to declare.

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References

1. Pai-Scherf L, Blumenthal GM, Li H, Subramaniam S, Mishra-Kalyani PS, He K, Zhao H, Yu J, Paciga M, Goldberg KB, et al. FDA approval Summary: Pembrolizumab for treatment of metastatic non-small cell Lung Cancer: First-Line Therapy and Beyond. Oncologist. 2017;22(11):1392–9.
2. Lahiri A, Maji A, Potdar PD, Singh N, Parikh P, Bisht B, Mukherjee A, Paul MK. Lung cancer immunotherapy: progress, pitfalls, and promises. Mol Cancer. 2023;22(1):40.
3. Reck M, Remon J, Hellmann MD. First-line immunotherapy for non-small-cell Lung Cancer. J Clin Oncol. 2022;40(6):586–97.
4. Horvath L, Thienpont B, Zhao L, Wolf D, Pircher A. Overcoming immunotherapy resistance in non-small cell lung cancer (NSCLC) - novel approaches and future outlook. Mol Cancer. 2020;19(1):141.
5. Leal TA, Dasgupta A, Latremouille-Viau D, Rossi C, Rai P, Barlesi F, Liu SV. Real-world treatment patterns and clinical outcomes after platinum-Doublet Chemotherapy and Immunotherapy in Metastatic Non-small Cell Lung Cancer: a Multiregional Chart Review in the United States, Europe, and Japan. JCO Glob Oncol. 2024;10:e2300483.
6. Patel PH, Palma D, McDonald F, Tree AC. The Dandelion Dilemma Revisited for Oligoprogression: treat the whole lawn or weed selectively? Clin Oncol (R Coll Radiol). 2019;31(12):824–33.
7. Friedes C, Yegya-Raman N, Zhang S, Iocolano M, Cohen RB, Aggarwal C, Thompson JC, Marmarelis ME, Levin WP, Cengel KA, et al. Patterns of failure in metastatic NSCLC treated with First Line Pembrolizumab and Use of local therapy in patients with oligoprogression. Clin Lung Cancer. 2024;25(1):50–e6056.
8. Schoenfeld AJ, Rizvi HA, Memon D, Shaverdian N, Bott MJ, Sauter JL, Tsai CJ, Lihm J, Hoyos D, Plodkowski AJ, et al. Systemic and oligo-acquired resistance to PD-(L)1 blockade in Lung Cancer. Clin Cancer Res. 2022;28(17):3797–803.
9. Chai R, Yin Y, Cai X, Fu X, Zhang Q. Patterns of failure in patients with Advanced Non-small Cell Lung Cancer treated with Immune Checkpoint inhibitors. Front Oncol. 2021;11:724722.
10. Passaro A, Brahmer J, Antonia S, Mok T, Peters S. Managing resistance to Immune checkpoint inhibitors in Lung Cancer: treatment and novel strategies. J Clin Oncol. 2022;40(6):598–610.
11. Popat S, Grohe C, Corral J, Reck M, Novello S, Gottfried M, Radonjic D, Kaiser R. Anti-angiogenic agents in the age of resistance to immune checkpoint inhibitors: do they have a role in non-oncogene-addicted non-small cell lung cancer? Lung Cancer. 2020;144:76–84.
12. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228–47.
13. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, Gottfried M, Peled N, Tafreshi A, Cuffe S, 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(21):2339–49.
14. de Castro G Jr., Kudaba I, Wu YL, Lopes G, Kowalski DM, Turna HZ, Caglevic C, Zhang L, Karaszewska B, Laktionov KK, et al. Five-year outcomes with Pembrolizumab Versus Chemotherapy as First-Line therapy in patients with non-small-cell lung Cancer and programmed death Ligand-1 tumor proportion score >/= 1% in the KEYNOTE-042 study. J Clin Oncol. 2023;41(11):1986–91.
15. Perol M, Felip E, Dafni U, Polito L, Pal N, Tsourti Z, Ton TGN, Merritt D, Morris S, Stahel R, et al. Effectiveness of PD-(L)1 inhibitors alone or in combination with platinum-doublet chemotherapy in first-line (1L) non-squamous non-small-cell lung cancer (Nsq-NSCLC) with PD-L1-high expression using real-world data. Ann Oncol. 2022;33(5):511–21.
16. Deng J, Gao M, Gou Q, Xu C, Yan H, Yang M, Li J, Yang X, Wei X, Zhou Q. Organ-specific efficacy in advanced non-small cell lung cancer patients treated with first-line single-agent immune checkpoint inhibitors. Chin Med J (Engl). 2022;135(12):1404–13.
17. Maggie Liu SY, Huang J, Deng JY, Xu CR, Yan HH, Yang MY, Li YS, Ke EE, Zheng MY, Wang Z, et al. PD-L1 expression guidance on sintilimab versus pembrolizumab with or without platinum-doublet chemotherapy in untreated patients with advanced non-small cell lung cancer (CTONG1901): a phase 2, randomized, controlled trial. Sci Bull (Beijing). 2024;69(4):535–43.
18. Landi L, D'Inca F, Gelibter A, Chiari R, Grossi F, Delmonte A, Passaro A, Signorelli D, Gelsomino F, Galetta D, et al. Bone metastases and immunotherapy in patients with advanced non-small-cell lung cancer. J Immunother Cancer. 2019;7(1):316.
19. Brody R, Zhang Y, Ballas M, Siddiqui MK, Gupta P, Barker C, Midha A, Walker J. PD-L1 expression in advanced NSCLC: insights into risk stratification and treatment selection from a systematic literature review. Lung Cancer. 2017;112:200–15.
20. Hosoya K, Fujimoto D, Morimoto T, Kumagai T, Tamiya A, Taniguchi Y, Yokoyama T, Ishida T, Matsumoto H, Hirano K, et al. Clinical factors associated with shorter durable response, and patterns of acquired resistance to first-line pembrolizumab monotherapy in PD-L1-positive non-small-cell lung cancer patients: a retrospective multicenter study. BMC Cancer. 2021;21(1):346.
21. Matsumoto K, Shiroyama T, Kuge T, Miyake K, Yamamoto Y, Yoneda M, Yamamoto M, Naito Y, Suga Y, Fukushima K, et al. Impact of treatment timing and sequence of immune checkpoint inhibitors and anti-angiogenic agents for advanced non-small cell lung cancer: a systematic review and meta-analysis. Lung Cancer. 2021;162:175–84.
22. Funazo T, Nomizo T, Kim YH. Liver metastasis is Associated with poor progression-free survival in patients with Non-small Cell Lung Cancer treated with Nivolumab. J Thorac Oncol. 2017;12(9):e140–1.
23. Nogami N, Barlesi F, Socinski MA, Reck M, Thomas CA, Cappuzzo F, Mok TSK, Finley G, Aerts JG, Orlandi F, et al. IMpower150 final exploratory analyses for Atezolizumab Plus Bevacizumab and Chemotherapy in Key NSCLC patient subgroups with EGFR mutations or metastases in the liver or brain. J Thorac Oncol. 2022;17(2):309–23.
24. Choi SH, Yoo SS, Lee SY, Park JY. Anti-angiogenesis revisited: reshaping the treatment landscape of advanced non-small cell lung cancer. Arch Pharm Res. 2022;45(4):263–79.
25. Yi M, Jiao D, Qin S, Chu Q, Wu K, Li A. Synergistic effect of immune checkpoint blockade and anti-angiogenesis in cancer treatment. Mol Cancer. 2019;18(1):60.
26. Friedes C, Mai N, Fu W, Hu C, Hazell SZ, Han P, McNutt TR, Forde PM, Redmond KJ, Voong KR, et al. Isolated progression of metastatic lung cancer: clinical outcomes associated with definitive radiotherapy. Cancer. 2020;126(20):4572–83.
27. Cortellini A, Cannita K, Tiseo M, Cortinovis DL, Aerts J, Baldessari C, Giusti R, Ferrara MG, D'Argento E, Grossi F, et al. Post-progression outcomes of NSCLC patients with PD-L1 expression >/= 50% receiving first-line single-agent pembrolizumab in a large multicentre real-world study. Eur J Cancer. 2021;148:24–35.

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