



# Efficacy and safety profile of combining programmed cell death-1 (PD-1) inhibitors and antiangiogenic targeting agents as subsequent therapy for advanced or metastatic non-small cell lung cancer (NSCLC)

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## Abstract

**Background:** Previous studies have demonstrated that PD-1 inhibitors are effective in the treatment of advanced or metastatic non-small cell lung cancer (NSCLC). However, whether the combination of PD-1 inhibitors and antiangiogenic agents benefit advanced NSCLC patients as subsequent therapy remains unknown. In this study, we retrospectively reviewed the efficacy and safety profile of this combination strategy as subsequent therapy for NSCLC patients in a real-world setting.

**Methods:** A total of 30 patients with advanced NSCLC, who progressed after at least two cycles of platinum-based chemotherapy or targeted therapy and subsequently received combination therapy with a PD-1 inhibitor and antiangiogenic agent, were included in this study. The safety profile and efficacy were also investigated.

**Results:** At the time of a median follow-up period of 10.7 months, 28 patients had experienced progression of disease and 16 patients had died. The median progression-free survival (mPFS) was 5.0 months (95% confidence interval [CI]: 3.179–6.821), and the median overall survival (mOS) was 14.3 months (95% CI: 8.912–19.659). The objective response rate (ORR) and the disease control rate (DCR) were 10.3% and 72.4%, respectively (0 complete remission, three partial responses and 18 stable disease in 29 patients with measurable lesions). Patients with PD-L1 expression of at least 1% of tumor cells ( $n = 5$ ) had relatively longer mPFS compared to those with PD-L1-negative tumors ( $n = 14$ ), (11.6 months vs. 3.7 months). Treatment was suspended in two patients due to grade 3 immune-related pneumonia and pancreatitis, respectively. No novel adverse events (AEs) or grade 4 AEs were observed.

**Conclusions:** A combination of PD-1 inhibitors and antiangiogenic targeting agents may be beneficial for patients with advanced or metastatic NSCLC as subsequent treatment, especially for patients with PD-L1 protein expression positive, and treatment is well tolerated.

## KEYWORDS

advanced or metastatic non-small-cell lung cancer (NSCLC), antiangiogenic targeting agents, combination therapy, programmed cell death-1 (PD-1) inhibitors, subsequent therapy

Junling Li and Puyuan Xing contribute equally to this manuscript as co-corresponding authors.

## INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases, and among them,

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around 40% of patients are diagnosed with advanced or metastatic disease, with a poor prognosis.<sup>1</sup> Standard systemic treatment strategies for advanced or metastatic NSCLC include platinum-based chemotherapy, with or without bevacizumab, and targeted therapy for those harboring driver gene mutations such as epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), and c-ros oncogene 1 (*ROS1*). Second-line treatments include docetaxel or pemetrexed, which provide limited clinical benefits to the population.<sup>2</sup>

For patients with advanced NSCLC, especially those without driver gene mutations, or those who have progressed on previous treatment including targeted therapy and platinum-based chemotherapy, novel agents have been associated with long-term survival in some clinical trials. These agents mainly fall into two categories: immunotherapy such as immune checkpoint inhibitors (ICI) including programmed cell death-1 (PD-1) inhibitors and programmed cell death ligand-1 (PD-L1) inhibitors, and antiangiogenic agents consisting of monoclonal antibodies (mAbs) targeting vascular endothelial growth factor (VEGF), or vascular endothelial growth factor receptor (VEGFR), and small-molecular tyrosine kinase inhibitors (TKIs) targeting multiple angiogenic and proliferative pathways. PD-1 inhibitors have been recommended as preferred agents for metastatic lung cancer patients with improved response and survival comparing cytotoxic chemotherapy including docetaxel, gemcitabine, and pemetrexed according to a series of phase III trials, either as monotherapy or combined with platinum-based chemotherapy.<sup>3,4</sup> However, the median progression-free survival (mPFS) obtained by PD-1 inhibitor monotherapy has been reported to range from only 2.3 to 3.7 months.<sup>5,6</sup> A randomized phase III clinical trial, OAK, also showed that regardless of the expression level of PD-L1, the survival rate following atezolizumab treatment was significantly improved compared with docetaxel.<sup>7</sup> For long-term survivors in the atezolizumab group, the objective response rate (ORR) was 14% and the median overall survival (mOS) was 13.8 months (95% confidence interval [CI]: 11.8–15.7). Based on the OAK findings, atezolizumab has been approved by the FDA and the EMA for further treatment of those patients previously treated for advanced NSCLC.

A combination of immune checkpoint blockade therapies and antiangiogenic targeting agents has been speculated to induce synergistic effects on advanced NSCLC, thereby improving treatment outcomes. Preclinical experiments have shown that antiangiogenic therapies could prevent cancer cells from acquiring an aggressive phenotype associated with a hypoxic microenvironment by vascular normalization, targeting VEGF, platelet-derived growth factor (PDGF), and so on, and thus inducing a synergistic effect on immune therapy.<sup>8,9</sup> In phase I clinical trials, this combination therapy has also showed favorable results, with mPFS of 15 months and an ORR of 72.7% in treatment-naïve advanced NSCLC patients.<sup>10</sup> The efficacy and safety of a combination of PD-L1 inhibitor and bevacizumab plus chemotherapy has also been

revealed by the phase 3 randomized clinical trial IMpower 150.<sup>11</sup> However, evidence of the clinical efficacy and safety of this combination therapy in the real-world is still scarce. For those patients who have been diagnosed with metastatic NSCLC, or who have experienced disease recurrence, it is essential that novel treatment strategies to improve their long-term outcome are determined. In this retrospective study, we therefore mainly focus on the effect of PD-1 inhibitors combining antiangiogenic targeting agents as second-line or later therapy for advanced or metastatic NSCLC, and explore the potential optimal therapy for this group of patients who have progressed after prior treatments.

## METHODS

### Patients

Patients diagnosed with advanced or metastatic NSCLC who underwent PD-1 combined with antiangiogenic treatment as second-line or later therapy in the Chinese Academy of Medical Sciences (CAMS) were included in this retrospective study, during July 2018 to August 2020. We collected the clinicopathological features including their smoking history, family history, Eastern Cooperative Oncology Group performance status (ECOG PS), and number of metastatic sites, as well as their prior treatments such as EGFR-TKI treatment and localized radiotherapy. Those who received PD-1 inhibitors and antiangiogenic treatment as maintenance therapy after standard therapy of PD-1, antiangiogenic agents, and albumin-bound paclitaxel or pemetrexed combination were not included in the study.

This study was approved by the Ethics Committee of the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (approval no. 19-096-1881). All patients alive at the time of this study signed an informed consent before enrollment.

### Efficacy and safety

The assessment of treatment efficacy was based on The Response Evaluation Criteria of Solid Tumors (RECIST) 1.1 version.<sup>12</sup> The tumor responses of target lesions were evaluated and categorized into complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD). The ORR was defined as the sum of CR and PR, and disease control rate (DCR) as the sum of CR, PR, and SD. Progression-free survival (PFS) was measured from the time of initiation of combination therapy to PD or death from any cause, and overall survival (OS) was defined as the period from the initiation of combination strategy to death from any cause, or the last follow-up. Any adverse events (AEs) related to medication which occurred were recorded, and the grading of AEs was based on the

Common Terminology Criteria for Adverse Events (CTCAE, version 4.0).

## Statistical analysis

Median PFS was calculated with Kaplan–Meier product limit method. Risk factors for PFS and OS were analyzed with the univariate Cox proportional hazards regression model (COX). Clinical characteristics and responses to therapy of patients were analyzed with descriptive methods. Continuous variables were compared using *t* tests, and categorical variables using  $\chi^2$  tests. All statistical analysis was performed using SPSS version 23.0, and a *p*-value <0.05 was considered statistically significant.

## RESULTS

### Patient characteristics

A total of 30 evaluable advanced NSCLC patients who were undergoing, or had received combination therapy of PD-1 inhibitors and antiangiogenic agents as subsequent treatment, were enrolled in the study. Among these 30 patients, 21 patients (70.0%) were diagnosed as stage IV NSCLC at first, and the remaining nine patients (30.0%) experienced recurrence of disease after resection and adjuvant therapies. The median age when receiving combination therapy was 57 (range 37–75) years. PD-L1 expression was evaluated in 19 patients (63.3%),

of which there were five patients (26.3%) with PD-L1 expression of at least 1% of tumor cells, and 14 patients (73.7%) with PD-L1-negative tumors (PD-L1 expression of less than 1% of tumor cells). The other 11 patients did not undergo PD-L1 testing mainly due to the insufficiency of biopsy tissue, or because their disease had been diagnosed by cytohistology, which was not eligible for 22C3 assay. Three patients (10.0%) harbored epidermal growth factor receptor (*EGFR*) exon 21 L858R mutations, two patients (6.7%) harbored *EGFR* exon 19 deletion mutation, and another six patients (20.0%) harbored *KRAS* exon 2 mutation. The clinicopathological characteristics of these patients are listed in Table 1, and gene mutation status at baseline is shown in Table 2.

### Treatment

In total, 10 patients (33.3%) received the combination regimen as second-line treatment, and the remaining 20 patients (66.7%) received the combination therapy as third-line or later treatment. The agents used in the combination strategy are shown in Table 3. Anlotinib was the most frequently-used antiangiogenic agent, with 18 patients (60.0%) receiving a combined PD-1 inhibitor and anlotinib only, and 10 patients (33.3%) receiving bevacizumab as combination therapy. Other patients also received apatinib, a small molecular TKI targeting VEGFR. Eight patients had previously been administered *EGFR*-TKIs, among whom two patients without *EGFR* mutation also tried afatinib, a second-generation *EGFR*-TKI as late line therapy.

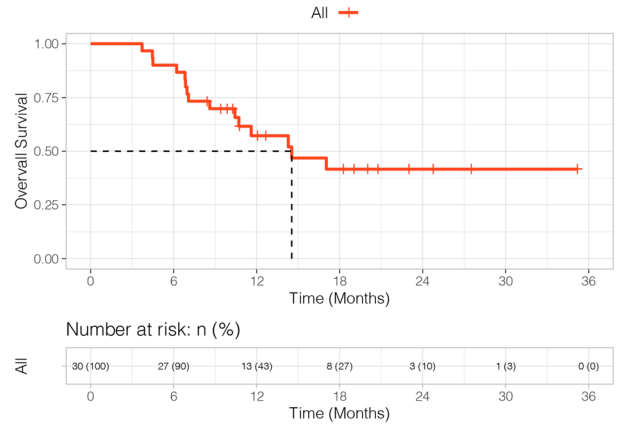
**TABLE 1** Clinicopathological features of all advanced NSCLC patients who received PD-1/PD-L1 inhibitors and antiangiogenic combined therapy

Characteristics	n (%)	Characteristics	n (%)
Age		Metastatic sites	
Median	57	≤ 2	10 (33.3)
Range	37–75	> 2	20 (66.7)
Gender		Number of previous treatments	
Male	22(73.3)	≤ 2	10 (33.3)
Female	8 (26.7)	> 2	20 (66.7)
Location		Prior radiotherapy	
Left	13 (43.3)	Yes	15 (50.0)
Right	16 (53.4)	No	15 (50.0)
Anterior mediastinum	1 (3.3)	Prior <i>EGFR</i> -TKIs	
Smoking history		Yes	8 (26.7)
Never smoker	13(43.3)	No	22 (73.3)
Current/former smoker	17 (56.7)	Histology	
Family history of tumor		Adenocarcinoma	25(83.3)
Yes	7 (23.3)	Squamous cell carcinoma	5 (16.7)
No	23 (76.7)	PD-L1 expression	
ECOG PS		≤ 1%	14 (46.7)
≤ 1	18 (60.0)	>1%	5 (16.7)
> 1	12 (40.0)	Unknown	11 (36.6)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; *EGFR*, epidermal growth factor receptor; n, number; TKI, tyrosine kinase inhibitors.

**TABLE 2** Baseline gene mutation status of patients who received a combination strategy of PD-1 inhibitors and antiangiogenic targeted therapy

Gene mutation	n (%)
<b>EGFR mutation</b>	
Exon19 deletion	2 (6.7)
Exon 21 mutation (L858R)	3 (10.0)
EGFR 18 mutation	1 (3.3)
<b>KRAS mutation</b>	
Exon 2 p.G12A	1 (3.3)
Exon 2 p.G12C	4 (13.4)
Exon 2 p.G12D	1 (3.3)
HER2 mutation	1 (3.3)
RET fusion mutation	1 (3.3)
Wild-type	17 (53.4)



**FIGURE 2** Kaplan–Meier curves for overall survival (OS) for the entire population

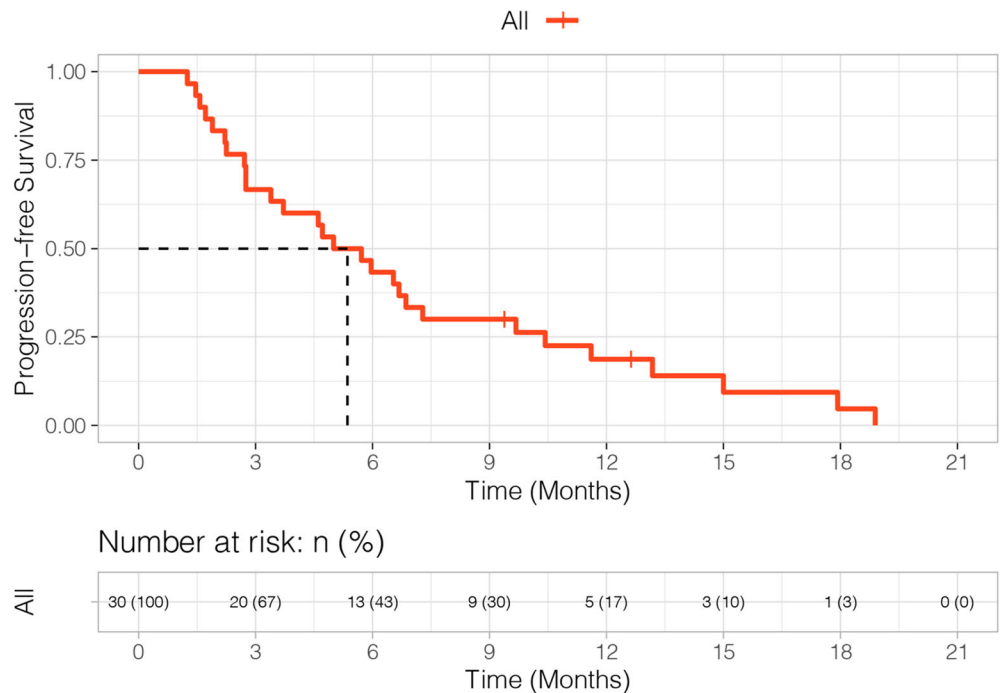
**TABLE 3** Agents used in the combination treatment of PD-1 inhibitors and antiangiogenic targeted therapy

Agents of combination strategy	n (%)
Nivolumab + bevacizumab	7 (23.3)
Nivolumab + anlotinib	5 (16.7)
Nivolumab + apatinib	1(3.3)
Pembrolizumab + bevacizumab	2(6.8)
Pembrolizumab + anlotinib	5 (16.7)
Sintilimab + anlotinib	7(23.3)
Toripalimab + bevacizumab	1(3.3)
Toripalimab + anlotinib	1(3.3)
Camrelizumab + apatinib	1(3.3)

**TABLE 4** Treatment outcome of 29 advanced NSCLC patients with targetable lesions who received PD-1 inhibitors and antiangiogenic combined therapy

Overall best response	n (%)
CR	0
PR	3 (10.3)
SD	18 (62.1)
PD	8 (27.6)
ORR	3 (10.3)
DCR	22 (72.4)

Abbreviations: CR, complete remission; DCR, disease control rate (DCR = CR + PR + SD); n, number; ORR, objective response rate (ORR = CR + PR); PD, progression disease; PR, partial response; SD, stable disease.

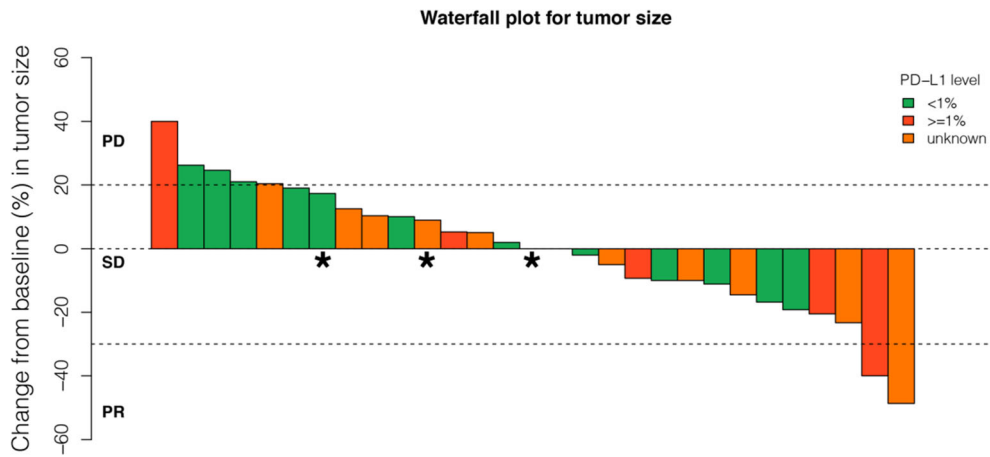


**FIGURE 1** Kaplan–Meier curves for progression-free survival (PFS) for the entire population

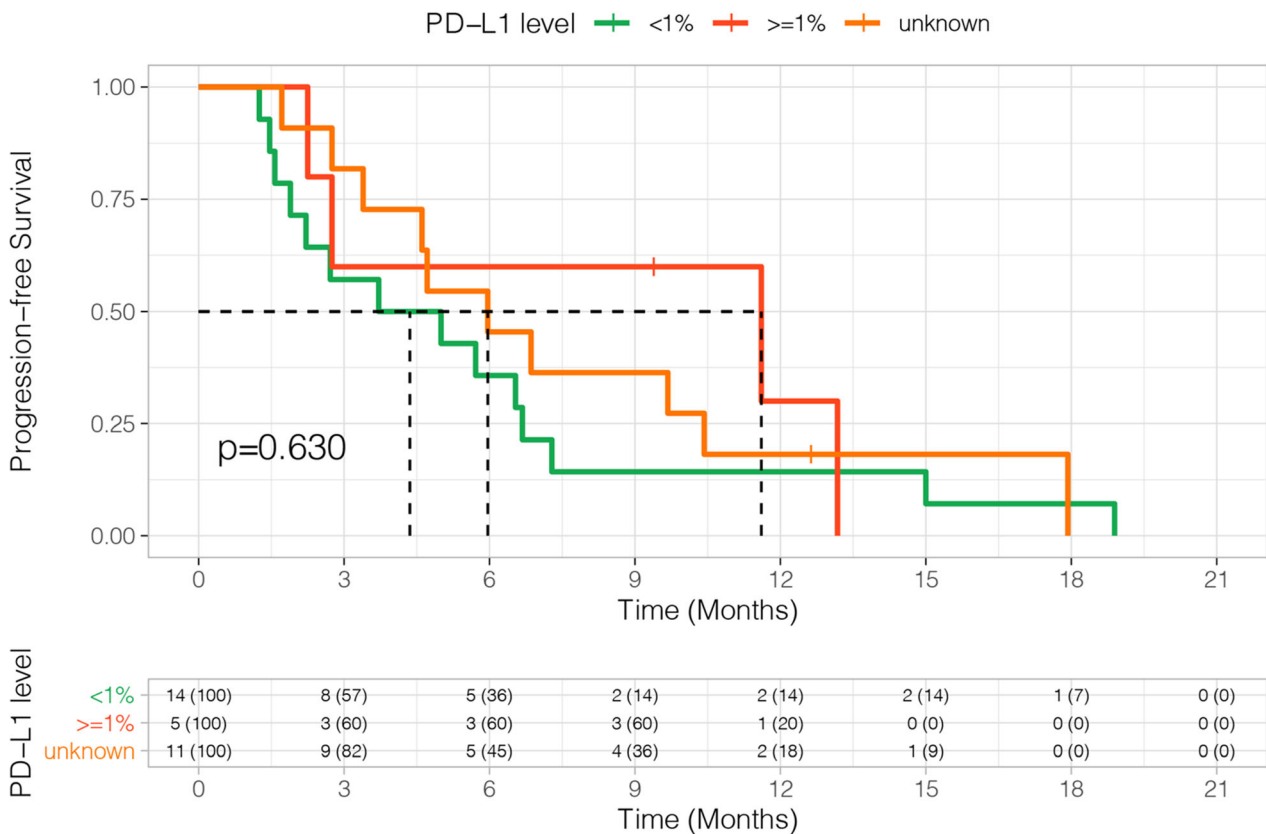
### Survival and response

From 11<sup>th</sup> March, 2021, the median follow-up period was 10.7 months (range 3.7–35.1 months). In total, 28 patients

experienced progression of disease and 16 patients died of disease. The median PFS (mPFS) was 5.0 months (95% CI: 3.179–6.821), as shown in Figure 1, and the median OS (mOS) was 14.3 months (8.912–19.659), as shown in



**FIGURE 3** Maximum tumor size change from baseline by the best overall response, as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 in 29 patients with at least one measurable target lesion, who received a PD-1 inhibitor and antiangiogenic agent as subsequent therapy. Each bar represents the maximum change in the sum of the diameters of the target lesions of an individual patient. \*Progressive disease (PD) was considered in three cases with the appearance of one or more new lesions while no more than 20% increase was observed in the sum of diameters of target lesions in three cases



**FIGURE 4** Progression-free survival (PFS) curves for patients with diverse level of PD-L1 expression using univariate analysis in Cox proportional hazards regression model

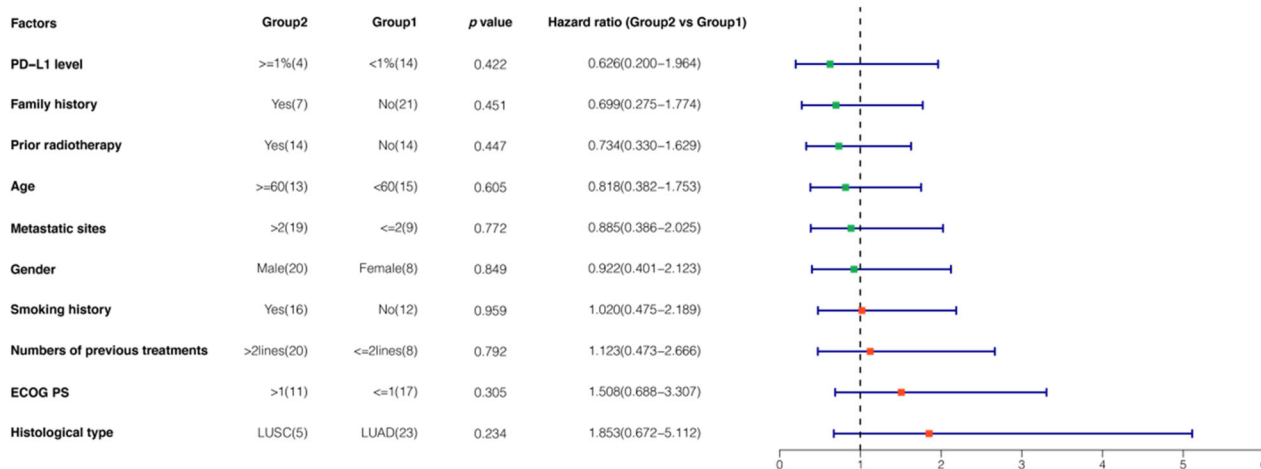


FIGURE 5 Hazard ratio of progression-free survival in patients with different characteristics. A hazard ratio less than 1 implies a lower risk of disease progression or death of group 2 compared with group 1. The number of cases that had progressive disease is shown in each group of every characteristic

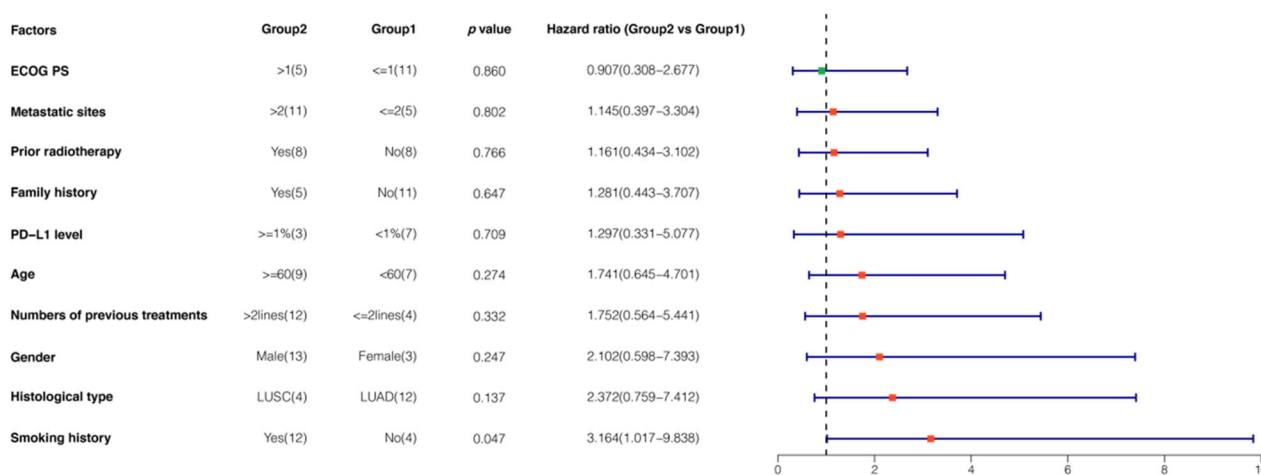


FIGURE 6 Hazard ratio of overall survival in patients with different characteristics. A hazard ratio less than 1 implies a lower risk of disease progression or death of group 2 compared with group 1. The number of cases that had progressive disease is shown in each group of every characteristic

Figure 2. There were 0 CR, three PR and 18 SD in 29 patients with measurable lesions. The ORR and the DCR were 10.3% and 72.4%, respectively, as shown in Table 4 and Figure 3.

## Risk factors for PFS and OS

The relationship between PFS and clinicopathological characteristics including age, gender, smoking history, family history of cancer, ECOG PS, histology type, prior *EGFR* TKI treatment or radiotherapy, and number of previous treatments was analyzed. Different levels of PD-L1 protein expression were also analyzed as a factor. Based on univariate Cox proportional hazards regression model (COX) analysis, no significant difference was found in any of the characteristics included. However, patients with PD-L1 expression of at least 1% of tumor cells had relatively longer mPFS compared to those with PD-L1-negative tumors,

although no significant difference was observed (11.6 months vs. 3.7 months, HR 0.626, 95% CI: 0.200–1.964), as shown in Figure 4. Figures 5 and 6 show the hazard ratio of PFS and OS in patients with different characteristics, respectively.

## Safety and tolerability

AEs that occurred during combination therapy were recorded and are shown in Table 5. In this study, any grade of toxicity occurred in 53.3% (16/30). The most frequently seen AEs were dermatological, such as pruritus, rash, and hand-foot syndrome (HFS), seen in 30.0% of patients (9/30), followed by fatigue, which occurred in 13.3% (4/30) of patients. Shortness of breath (SOB) was seen in 10.0% of patients (3/30), grade 1/2 diarrhea in 10.0% of patients (3/30), and grade 1/2 mucositis oral in three patients (10.0%)



**TABLE 5** Treatment-related adverse events (AEs) in all advanced NSCLC patients who received combination therapy of PD-1 inhibitors and antiangiogenic agents

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4
	n (%)	n (%)	n (%)	n (%)
Hemorrhage	2 (6.7)			
General disorders				
SOB	1 (3.3)	1 (3.3)	1 (3.3)	
Fatigue	4 (13.3)			
Headache	1 (3.3)			
Fever	1 (3.3)	1 (3.3)		
Hematological toxicity				
Leukopenia	1 (3.3)			
Dermatological toxicity				
Rash	3 (10.0)	2 (6.7)		
Pruritus	3 (10.0)	2 (6.9)		
HFS	2 (6.7)	1 (3.3)		
Pulmonary toxicity				
Pneumonitis	1 (3.3)	1 (3.3)	1 (3.3)	
Gastrointestinal toxicity				
Mucositis oral	1 (3.3)	2 (6.7)		
Diarrhea	2 (6.7)	1 (3.3)		
Hepatic toxicity	1 (3.3)	1 (3.3)		
Pancreatitis			1 (3.3)	
Endocrine toxicity				
Hypothyroidism	2 (6.7)			
Thyrotoxicosis	1 (3.3)			
Renal toxicity				
Proteinuria		1 (3.3)		

Abbreviations: HFS, hand-foot syndrome; n, number; SOB, shortness of breath.

caused by the administration of anlotinib. Endocrine toxicity was seen in two patients, consisting of grade 1/2 hypothyroidism and thyrotoxicosis. All patients were permitted to remain on combination therapy after appropriate management. One patient had to discontinue treatment because of grade 3 immune-mediated pneumonia and subsequently received steroids, and another patient discontinued combination therapy as a result of grade 3 immune-related pancreatitis. Another two patients who reported grade 1/2 pneumonia continued therapy without any administration of steroids. One patient discontinued therapy because of grade 2 liver toxicity. Only two patients reported mild hemoptysis, both from gingival hemorrhage. Grade 1 hypertension (HTN) was reported in one patient being treated with a combined PD-1 inhibitor and bevacizumab.

## DISCUSSION

Immune checkpoint inhibitors and antiangiogenic targeting agents have been proven to have potential in the treatment

of advanced NSCLC patients.<sup>13,14</sup> The combination therapy of PD-1 inhibitors and antiangiogenic agents has been reported to be favorable in clinical use with the support of some preclinical data on their effect and safety,<sup>8,9</sup> and has been shown to be effective as first-line therapy for advanced NSCLC in clinical use.<sup>11</sup> A recent phase Ib clinical trial from China has released the initial outcome of combining PD-1 and anlotinib as first-line therapy for advanced NSCLC, with ORR of 72.7% (16/22 PR, 6/22 SD), and DCR of 100%.<sup>15</sup> Further analysis showed that mPFS was 15 months, and the one-year PFS rate was 71.4%. Also, no novel adverse events have been observed in this combination therapy as first-line treatment, which has provided evidence for the efficacy and safety in combining PD-1 inhibitors and antiangiogenic targeting agents treating patients with advanced NSCLC. For second-line or later therapy in advanced or metastatic NSCLC patients, combination therapy provides more potential than cytotoxic agents, due to the limited efficacy and obvious toxicity of the latter treatment. However, the role of combination therapy of PD-1 and antiangiogenic agents in subsequent therapy of advanced lung cancer still remains to be further investigated.

Second-line and beyond systemic therapy has recently been referred to as subsequent therapy, and chemotherapy such as docetaxel has been proven to have a poor response and limited efficacy for improving survival by a median of 3.0 months.<sup>16</sup> Oral TKI erlotinib alone has a mPFS of only 2.2 months and a response rate of 8.9% in previously treated NSCLC patients.<sup>17</sup> Our study showed an ORR of 10.0%, DCR of 73.3%, and mPFS of 5.0 months, which provides evidence that this combination therapy is promising compared to the strategies mentioned above. Moreover, our results have shown that mPFS was relatively longer in second-line therapy than in later lines. A similar trend was observed in a real-world study which enrolled 69 patients who received PD-1 inhibitor plus antiangiogenic therapy. Median PFS was 6.0 months in patients who received the combination strategy as subsequent therapy, while longer in first-line therapy (13.1 months, 95% CI: 9.0–17.2 months).<sup>18</sup> However, this study failed to reveal the relationship between PD-L1 expression level and treatment efficacy and has possibly overestimated the efficacy of this combination strategy because there were 39 enrolled patients who also received chemotherapy in addition to immunotherapy and antiangiogenic therapy.

The level of PD-L1 expression may affect the immune effects in first-line therapy, with PD-1 inhibiting treatment of PD-L1 positive (tumor proportion score  $\geq 50\%$ ) advanced NSCLC achieving longer PFS than platinum-based chemotherapy.<sup>19</sup> A combination of PD-L1 inhibitor atezolizumab and chemotherapy regimen also improved the OS and PFS of advanced lung cancer patients whose PD-L1 expression was less than 50% or unknown, compared with the control arm of chemotherapy/bevacizumab as first-line treatment, according to the result of Impower 150.<sup>11</sup> However, it remains unknown whether the expression level of PD-L1 has any influence on the effect of PD-1/PD-L1 inhibitors in

subsequent treatments, and testing for PD-L1 protein expression was not required before prescription according to NCCN guidelines. In addition, multiple factors influence the accuracy of PD-L1 expression testing, which limits its predictive value on immunotherapy efficacy.<sup>20</sup> The inadequacy of samples that underwent PD-L1 expression testing were mainly as a result of insufficient biopsy tissue, or because some patients were diagnosed by cytohistology, which was not eligible for 22C3 testing assay. This also limited the precision of analyzing the possible relationship between this factor and the outcome. Despite these limitations, the results from this study still indicated that the expression level of PD-L1 might be correlated with the efficacy of immunotherapy, even in subsequent treatment. Further studies should be conducted with a greater number of samples to explore whether the expression level of PD-L1 protein would influence the efficacy of PD-1 inhibitors and antiangiogenic combination in subsequent therapy of advanced NSCLC.

The irAEs of PD-1 inhibitors may occur in different systems, and severe irAEs may lead to discontinuation of immune therapy. According to previous reports, one of the most common toxicities of immune checkpoint inhibitors is diarrhea, which has been reported to occur in approximately 8%–10% of patients exposed to nivolumab,<sup>21</sup> and approximately 8% of those receiving pembrolizumab.<sup>20,22</sup> The data in our study is parallel to previous studies, and the clinical conditions were all reversible. Skin events such as rash and pruritus are also commonly seen, and HFS, the cutaneous event that manifests as erythema, dysesthesia, pain, and cracking on palms and soles, greatly affects the quality of life in patients, although it is also reversible.<sup>23</sup> In our study, the most frequently seen irAE was skin toxicity, while no patient discontinued therapy due to dermatological events, showing the importance of early-stage management. As for pulmonary toxicities, around 5% of the cases are described as immune-mediated pneumonia using PD-1 inhibitors, and even cases of death from treatment-related pulmonary toxicities have been reported in clinical trials.<sup>5,22</sup> Although 10.0% of patients had shortness of breath (SOB) during or after immunotherapy in our study, only one of our patients had to discontinue treatment because of grade 3 immune-mediated pneumonia and subsequently received steroids as further treatment. AEs that are related to antiangiogenic treatment mainly include HTN, hemorrhage, and proteinuria. The incidence of hemorrhagic events may be life-threatening in the case of important organs.<sup>24</sup> In our study, only two cases of mild hemorrhagia were observed, a syndrome known as hemoptysis. In summary, all of the AEs which occurred in patients included in this study were manageable, and no novel AEs were observed.

There are several limitations in this study. First, the sample is not large enough as a retrospective study, especially for subgroup analysis, so more studies especially large-sample randomized clinical studies are needed to verify the conclusion. Our multicenter prospective interventional study is now recruiting patients, based on the results of this

retrospective study, with the aim of providing more evidence for the efficacy and safety of PD-1 inhibitors and antiangiogenic treatment in advanced nonsquamous NSCLC patients (NCT04670913). It is also notable that the onset of irAEs may vary among different kinds of drugs, and further follow-up of late-onset AEs is needed to study the safety of this strategy.

In conclusion, our study indicates that combination therapy of PD-1 inhibitors and antiangiogenic targeting agents may be beneficial for patients with advanced or metastatic NSCLC as second-line or later treatment, especially for patients with PD-L1 protein expression positive, and is well tolerated.

## CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest that might be relevant to the content of this manuscript. The abstract of this paper was presented at the IASLC 2020 World Conference on Lung Cancer as a poster presentation with interim findings. The poster's abstract was published in "Poster Abstracts" in *Journal of Thoracic Oncology*: DOI:<https://doi.org/10.1016/j.jtho.2021.01.1199>.

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