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The prognostic impact of immune checkpoint inhibitors for the treatment of pulmonary sarcomatoid carcinoma: A multicenter retrospective study

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Pulmonary sarcomatoid carcinoma (PSC) is an aggressive and poorly differentiated type of non-small cell lung carcinoma. Because of the rarity of PSC, the efficacy and toxicity of immunotherapy remain unclear. Hence, the aim of this study was to evaluate the efficacy and safety of immune checkpoint inhibitors (ICIs) for the treatment of advanced PSC. The study cohort was limited to 33 patients with pathologically confirmed PSC treated with ICIs in four hospitals in China from March 2018 to March 2022. Expression of programmed death ligand 1 (PD-L1) was detected by immunohistochemical analysis. Categorical variables were compared with the Fisher exact test and survival analysis was conducted with the Kaplan-Meier method. Of the 33 PSC patients, 8 (24.2%) received monotherapy with ICIs and 25 (75.8%) received combination therapy with ICIs. The objective response rate (ORR) and disease control rate (DCR) were 36.4% and 78.8%, respectively. The median durations of progression-free survival (PFS) and overall survival (OS) were 6.07 and 21.33 months, respectively. PD-L1 status in 16 available samples was assessed, which included 30.3% PD-L1-positive patients. The ORRs for PD-L1-positive vs. -negative patients were 50.0% and 90.0%, the DCR was 33.3% and 83.3%, and the median PFS was 17.50 and 6.07 months, respectively (p=0.812). The median OS was not reached in PD-L1-positive and -negative patients (p=0.655). The incidence of immune-related adverse (irAEs) was 48.5% and mainly included grade 1 or 2 (39.4%), while the incidence of grade 3 or 4 was 9.1%. Pneumonia (9.1%) and skin rash (9.1%) were the most frequent irAEs. Immunotherapy with ICIs was a promising regimen to improve the prognosis of patients with advanced PSC.

Key words: efficacy, immune checkpoint inhibitors, immune-related adverse events, programmed death ligand 1, pulmonary sarcomatoid carcinoma

Pulmonary sarcomatoid carcinoma (PSC) is an aggressive and poorly differentiated type of non-small cell lung carcinoma (NSCLC), accounting for less than 1% of all lung cancers [1]. PSC is classified into three subtypes based on the 2021 World Health Organization classification of lung tumors: carcinosarcoma, pulmonary blastoma, and pleomorphic carcinoma, which includes giant cell carcinoma and spindle cell carcinoma [2, 3]. Because PSC is not sensitive to traditional radiotherapy or chemotherapy, the prognosis remains relatively poor [4–6]. Hence, it is necessary to develop more effective therapeutic regimens for the treatment of PSC.

The use of immune checkpoint inhibitors (ICIs) has recently changed the therapeutic paradigms for patients with various types of cancer. Along with advances in cancer immunotherapy, ICIs targeting programmed death 1 (PD-1) and PD-ligand 1 (PD-L1) have become promising alternatives for the treatment of various malignant tumors and rapidly changed standard regimens for NSCLC patients. Monotherapy with a PD-1 inhibitor or in combination with

platinum-based regimens has been established as a first-line standard treatment for NSCLC [7, 8]. Several investigators have reported relatively high expression of PD-L1 in about 90% of PSC patients [9, 10]. ICIs are reported to invoke high response rates and prolong the overall survival (OS) of PSC patients [4, 11]. However, because of the rarity of PSC, the efficacy and safety of ICIs remain unclear.

Therefore, the aim of this multicenter retrospective study was to assess the efficacy and safety of ICIs in order to provide recommendations for the treatment of advanced PSC.

Patients and methods

Study design. The medical records of 33 patients with stage IIIC or IV PSC treated with ICIs at Zhejiang Cancer Hospital (Hangzhou, China) and three other centers between March 2018 and March 2022 were retrospectively reviewed. PSC was confirmed by pathological and immunohistochemical (IHC) analyses in accordance with the 2021 World Health Organization classification of lung tumors [3]. IHC analysis of PD-L1 in formalin-fixed paraffin-embedded tissues was performed using the 22C3 pharmDx companion diagnostic assay (Agilent Technologies, Santa Clara, CA, USA). A tumor proportion score (i.e., percentage of positive tumor cells) of ≥ 1% was considered positive. Next-generation sequencing (NGS) was performed to detect genetic mutations. The study protocol was approved by the Institutional Ethics Committee of each participating center and conducted in accordance with the ethical principles for medical research involving human subjects defined in the Declaration of Helsinki (as revised in 2013). Due to the retrospective nature of this study, patient consent was waived.

Assessment of treatment response. All data were extracted from patient medical records. The ICI regimens and dosages complied with the guidelines of the National Comprehensive Cancer Network. Treatment was discontinued due to disease progression or unacceptable toxicity. Clinical efficacy was assessed every two cycles or upon significant disease progression. Tumor responses were evaluated in accordance with the Response Evaluation Criteria in Solid Tumors (version 1.1). Objective tumor responses included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The objective response rate (ORR) was defined as the sum of CR and PR, while the disease control rate (DCR) was defined as the sum of the objective responses and stabilization rates (CR+PR+SD).

Tumor response, progression-free survival (PFS), and OS were evaluated for all patients. OS was defined as the time from the date of confirmation of advanced PSC to death or the last follow-up. PFS was defined as the time from the first day of immunotherapy to documented disease progression or death from any cause or until the date of the last follow-up visit for surviving patients with no disease progression. The follow-up rate was 100%. The median follow-up duration was 19.87 (range, 19.63–20.12) months.

Evaluation of adverse reactions. Toxicity was evaluated in accordance with the Common Terminology Criteria for Adverse Events (version 5.0). Immune-related adverse events (irAEs), which were defined as adverse events with a potential immunological basis that medical oncologists could recognize objectively, were assigned a score ranging from 1 to 5 by two or more independent medical professionals.

Statistical analysis. Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 25.0. (IBM Corporation, Armonk, NY, USA). Categorical variables were compared using the Fisher exact test. PFS and OS were estimated with the Kaplan-Meier method and analyzed using the log-rank test. A two-sided probability (p) value of <0.05 was considered statistically significant.

Results

Clinical characteristics. The study cohort consisted of 33 patients with advanced PSC who received treatment from March 2018 to March 2022. The baseline characteristics of all PSC patients are summarized in Table 1. The median patient age was 61 (range, 15–85) years and 18.2% (6/33) were females. Most patients were smokers (66.7%, 22/33) and median tobacco consumption was 35 (range, 0–110) pack-years. The Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 2 or 3 for 5 (15.2%) patients and 0 or 1 for the other 28 (84.8%). NGS of 25 (75.8%) patients revealed KRAS (Kirsten rat sarcoma virus) mutations in 5 (15.2%) patients, *EGFR* (epidermal growth factor receptor) mutations in 2 (6.1%), and *MET* (hepatocyte growth factor receptor) mutations in 2 (6.1%).

Immunotherapy characteristics are summarized in Table 2. More than half of the patients (57.6%, 19/33) received first-line immunotherapy, while eight (24.2%) received monotherapy with ICIs and 25 (75.8%) received combination therapy with ICIs. PD-L1 expression was detected in 16 (48.5%) patients, including 10 (30.3%) who were PD-L1 positive. Disease status was PR for 12 (36.4%) patients, SD for 14 (42.2%), and PD for 7 (21.2%). In addition, immunotherapy was continued for 12 patients (36.4%). All patients received immunotherapy with PD-1 inhibitors.

Response and survival analyses. Treatment of all 33 patients with ICIs resulted in an ORR of 36.4% (12/33) and a DCR of 78.8% (26/33). The median PFS was 6.07 (95% confidence interval [CI], 2.59–17.41) months with a 1-year PFS rate of 24.2% (8/33) and the median OS was 21.33 (95% CI, 10.43–32.23) months with a 1-year OS rate of 63.6% (21/33). A swimmer plot of the treatment outcomes of patients receiving ICIs is shown in Figure 1.

According to the type of immunotherapy, the patients were divided into two groups: a first-line treatment group and a second or more-line treatment group. Of 19 (57.6%) patients in the first-line treatment group, PR was achieved in 8 (42.1%) and SD in 7 (36.8%). Notably, no patient achieved a CR. The ORR of ICIs as a first-line treatment was higher

Table 1. Baseline characteristics of patients with PSC.

Characteristics	PSC (n=33)	
	n	%
Sex		
Male	27	81.8
Female	6	18.2
Age		
Median age (years, range)	61 (15–85)	
>65	11	33.3
≤65	22	66.7
Smoking history		
Median tobacco consumption (pack-years*, range)	35 (0–110)	
Yes	22	66.7
No	11	33.3
ECOG PS		
0–1	28	84.8
2–3	5	15.2
TNM staging		
III	3	9.1
IV	30	90.0
Diagnosis method		
Surgery	8	24.2
Percutaneous lung biopsy	14	42.4
Bronchial biopsy	5	15.2
Unknown	6	18.2
Mutation status		
EGFR mutation	2	6.1
KRAS mutation	5	15.2
MET mutation	2	6.1
Other mutations	10	30.3
Multiple mutations	4	12.1
No known mutations	9	27.3
Unknown	7	21.2
Extrathoracic metastases		
Yes	26	78.8
No	7	21.2
Previous surgery		
Yes	10	30.3
No	23	69.7
Radiotherapy		
Yes	12	36.4
No	21	63.6

Note:*pack-years: an estimation of lifetime exposure to tobacco, which was the product of packs of cigarettes per day and years of smoking
Abbreviation: ECOG PS-Eastern Cooperative Oncology Group Performance status

Table 2. Baseline characteristics of ICIs for treatment of PSC.

Characteristics	PSC (n=33)	
	n	%
Line of ICIs treatment		
First	19	57.6
Second or more	14	42.4
ICIs regimens		
Monotherapy	8	24.2
Combination treatment	25	75.8
PD-L1 status		
Positive	10	30.3
Negative	6	18.2
Unknown	17	51.5
Best response under ICIs treatment		
Partial response	12	36.4
Stable disease	14	42.4
Progressive disease	7	21.2
Reason for ICIs discontinuation		
Progression	16	48.5
Toxicity	2	6.1
Death	3	9.1
Ongoing	12	36.4
Median PFS (months, 95% CI)	6.07 (2.59–17.41)	
1-year PFS rate	24.2% (8/33)	
Median OS (months, 95% CI)	21.33 (10.43–32.23)	
1-year OS rate	63.6% (21/33)	

Abbreviations: ICIs-immune checkpoint inhibitors; OS-overall survival; PFS-progression-free survival

than that of a second or more-line treatment (42.1% [8/19] vs. 28.6% [4/14], respectively), although this difference was not statistically significant (p=0.665). There was no significant difference in the DCR between the first- and second or more-line treatment groups (78.9% [15/19] vs. 78.6% [11/14], respectively, p=1.000). The median PFS and OS of PSC patients receiving first-line immunotherapy were 11.80 (95% CI, 3.44–20.16) and 21.33 (95% CI, 10.41–32.25) months, respectively. The median PFS and OS of PSC patients receiving second or more-line immunotherapy were 3.40 (95% CI, 0.34–6.46) months and not reached, respectively. There was no significant difference in PFS (p=0.998, Figure 2A) and OS (p=0.819, Figure 2B) between the treatment groups.

All patients were further subdivided into a monotherapy group or combination therapy group based on the use of ICIs. In the combination therapy group, patients received ICIs in combination with chemotherapy or targeted therapy. There was no significant difference in the ORR between the monotherapy and combination therapy groups (37.5% [3/8] vs. 36.0% [9/25], respectively, p=1.000) or in the DCR (75.0% [6/8] vs. 80.0% [20/25], respectively, p=1.000). The median PFS and OS of PSC patients were 6.00 (95% CI, 0.00–12.89) and 20.20 (95% CI, 14.73–25.67) months, respectively, in the monotherapy group, and 6.07 (95% CI, 3.04–9.10) and 28.50 (95% CI, 13.16–43.84) months in the combination group. There were no significant differences in PFS (p=0.499, Figure 2C) and OS (p=0.724, Figure 2D) between the treatment groups.

PD-L1 expression and efficacy analysis. PD-L1 status was assessed for 16 (48.5%) available patient samples, which included 10 (30.3%) PD-L1-positive patients. The ORR and

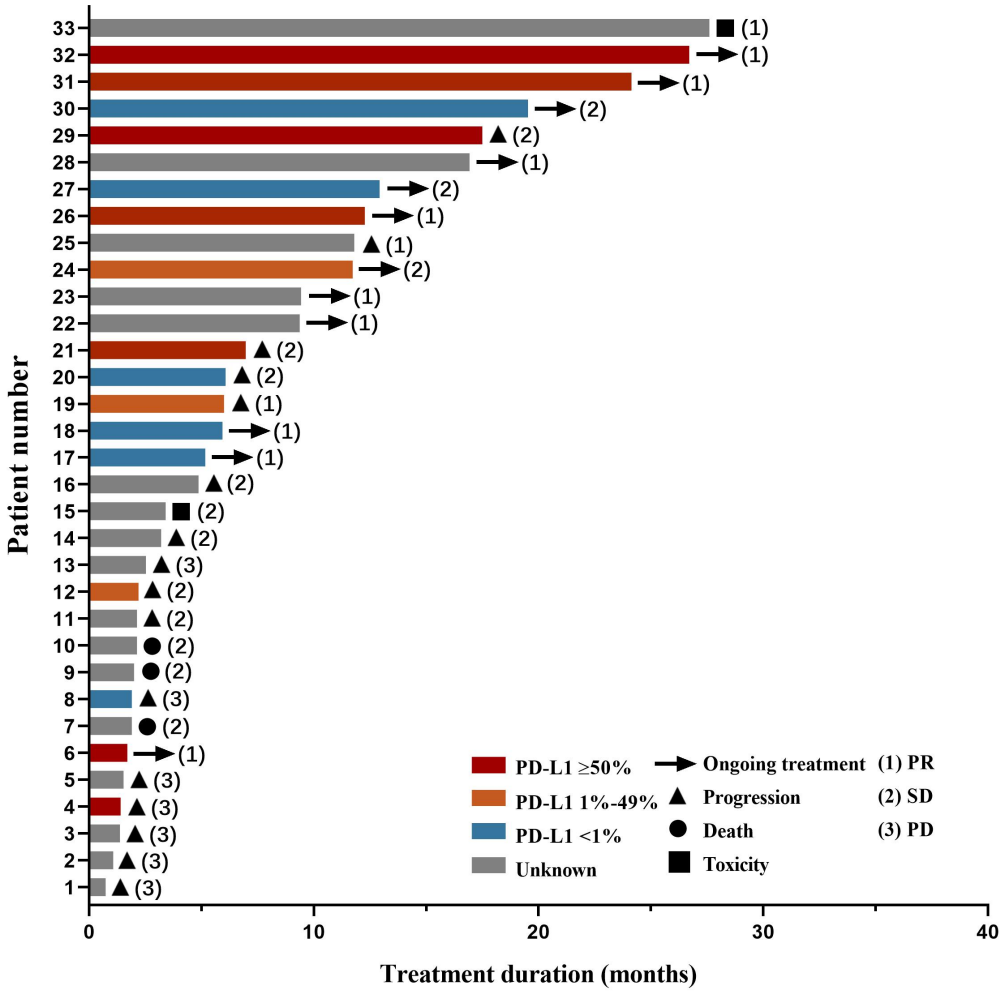

Figure 1. A swimmer plot of treatment outcomes of patients receiving ICIs.

DCR were, respectively, 50.0% (5/10) and 90.0% (9/10) for the PD-L1-positive patients and 33.3% (2/6) and 83.3% (5/6) for the PD-L1-negative patients (Supplementary Figure S1). There was no significant difference in ORR (p=0.896) and DCR (p=1.000) between the PD-L1-positive and -negative patients. Although the median PFS was longer for PD-L1-positive than -negative patients (17.50 [95% CI, 0.00–38.25] vs. 6.07 [95% CI, 5.78–6.36] months, respectively), this difference was not statistically significant (p=0.812; Figure 3A). The median OS of the PD-L1-positive and -negative patients was not reached (p=0.655; Figure 3B).

Toxicity. The observed irAEs of any grade of all 33 PSC patients are summarized in Table 3. The incidence of irAEs was 45.5% (n = 15/33) and mainly included grade 1 or 2 (39.4%,13/33), while the incidence of grade 3 or 4 was 9.1% (3/33). The most frequently observed irAEs were pneumonia (9.1%, 3/33) and skin rash (9.1%, 3/33). Treatment with ICIs was discontinued for 2 (6.1%) patients due to pneumonia and for 2 (6.1%) due to cardiovascular toxicity (one case each of abnormal echocardiography and acute heart failure resulting in death). There was no significant difference in the incidence of irAEs between the monotherapy and combination groups (50.0% [4/8] vs. 48% [12/25], respectively, p=1.000).

Discussion

The results of this study demonstrated that PSC patients could benefit from immunotherapy. For the entire cohort, the ORR and DCR were 36.4% and 78.8%, respectively, and the median PFS and OS were 6.07 and 21.33 months. These results appeared to be superior to those previously observed for PSC patients receiving chemotherapy [12, 13]. Thus, immunotherapy was a promising strategy to improve the prognosis of PSC patients.

In a previous study of 37 PSC patients, the ORR to ICIs was relatively high at 40.5% and the median OS was 12.7 (95% CI,

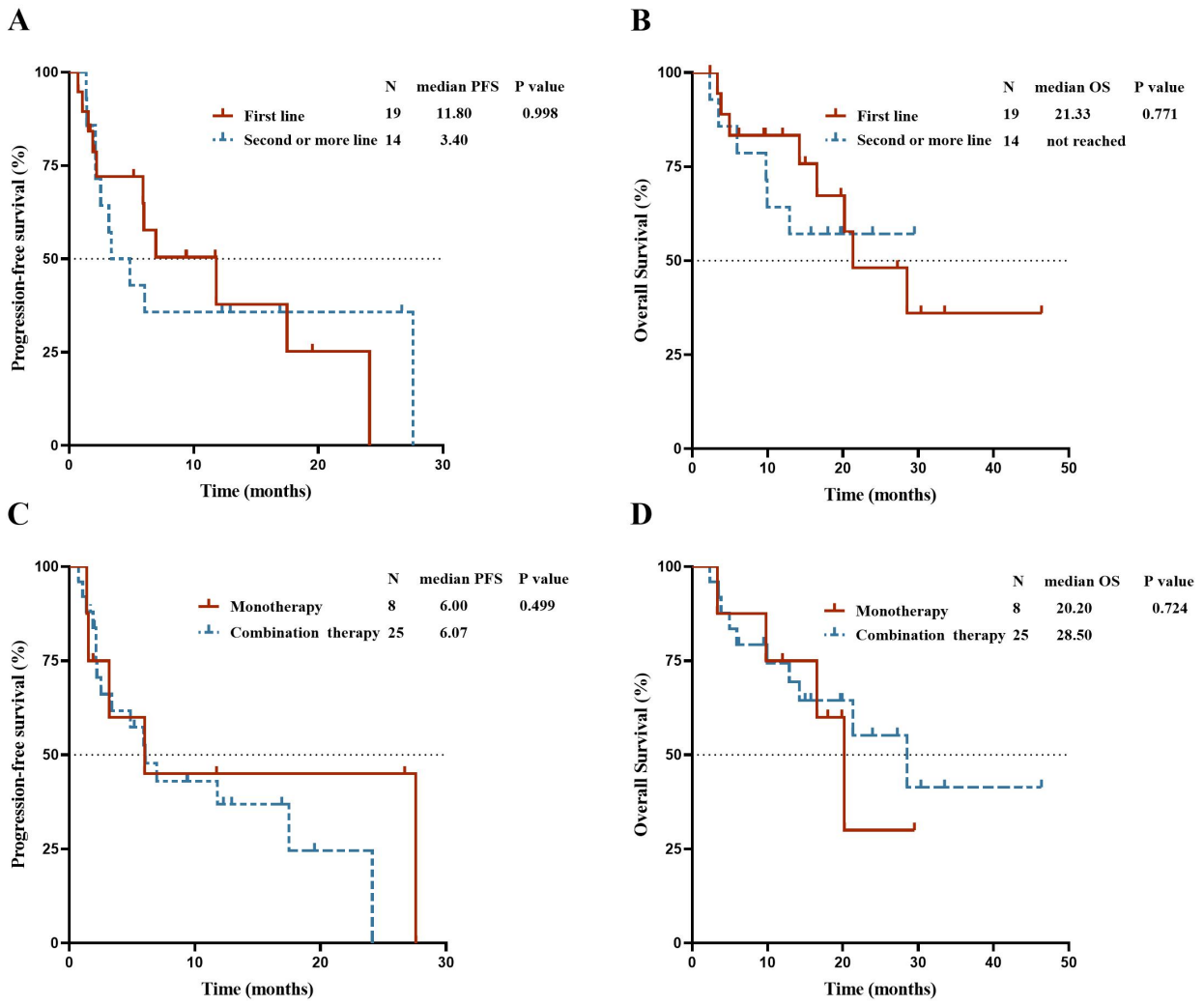

Figure 2. Kaplan-Meier curves of PFS and OS according to the treatment regimen. A) PFS of patients receiving ICIs as a first- vs. second or more-line treatment. B) OS of patients receiving ICIs as a first- vs. second or more-line treatment. C) PFS of patients treated with ICIs as monotherapy vs. combination therapy. D) OS of patients treated with ICIs as monotherapy vs. combination therapy.

0.3–45.7) months, regardless of the PD-L1 status [4]. Lee et al. [9] reported an ORR of 49.0%, median PFS of 7.2 months, and median OS of 22.2 months in 49 patients with pulmonary pleomorphic carcinoma treated with ICIs. In addition, a retrospective review reported similarly good efficacy of PD-1/PD-L1 inhibitors in four (80%) of five patients with advanced PSC, as one achieved a CR and the OS ranged between 14 and 33 months [14]. Hayashi et al. [15] reported similar outcomes for three patients with pleomorphic carcinoma of the lung treated with ICIs. Studies of immunotherapy for PSC conducted over the last 2 years are listed in Supplementary Table S1. The results of the present study showed that the number of lines of immunotherapy and the use of monotherapy vs. combination therapy had little effect on the treatment efficacy.

PD-L1 expression is reportedly higher in PSC than in other NSCLCs [10]. A study by Domblides et al. [4] reported that median PD-L1 expression was 70% (range, 0–100) and the ORR was 58.8% with 0% in both PD-L1-positive and -negative patients (p=0.44) [4]. A study by Lee et al. [9] found that high vs. low/negative/unknown expression of PD-L1 was associated with a longer median PFS (7.2 vs. 1.5 months, respectively, p=0.16) and median OS (22.2 vs. 3.5 months, respectively, p=0.001), thereby confirming an association between positive PD-L1 expression and longer survival after initiation of therapy with ICIs. Similarly, the results of the present study showed that PD-L1 expression tends to increase in reactive diseases. In this study, PD-L1 status was assessed in 16 available samples with 30.3% PD-L1-positive patients. The results showed that PD-L1 expression had little

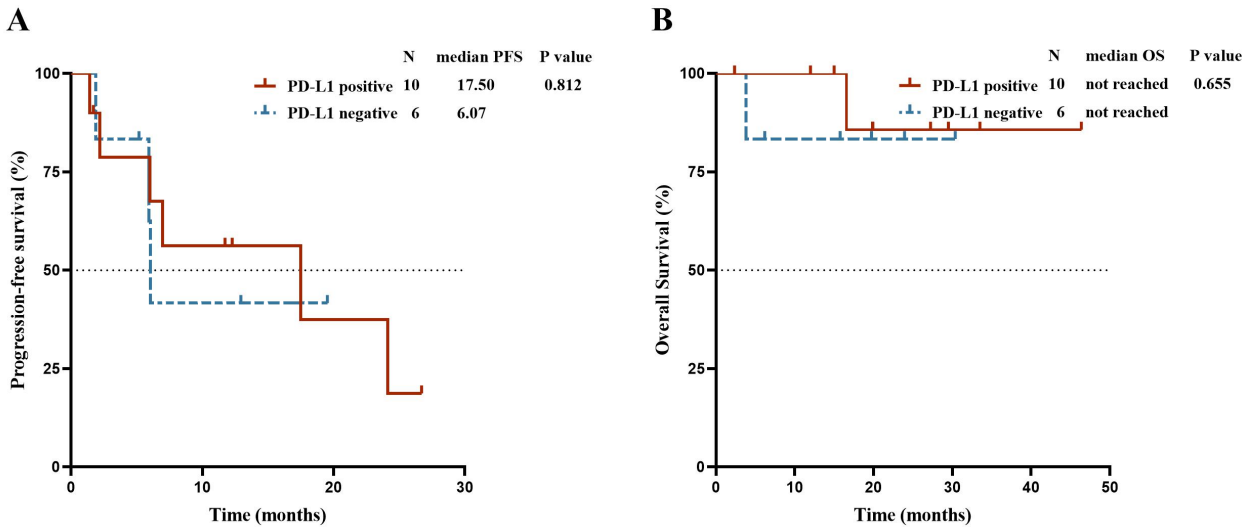

Figure 3. Kaplan-Meier curves of PFS and OS according to the expression of PD-L1. A) PFS of PD-L1-positive vs. -negative patients B) OS of PD-L1-positive vs. -negative patients.

Table 3. Immune-related adverse events of PCS patients.

Immune-related adverse events	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pneumonia	0	1	2	0	0
Skin rash	2	1	0	0	0
Cardiovascular toxicity	0	1		0	1
Elevated LFTs	0	1	0	0	0
Fatigue	0	1	0	0	0
Edema	0	1	0	0	0
Arthralgia	0	1	0	0	0
PCCEP	1	0	0	0	0
Thrombocytopenia	1	0	0	0	0
Hypoadrenia	1	0	0	0	0
Fever	1	0	0	0	0

Abbreviation: RCCEP-reactive cutaneous capillary endothelial proliferation

effect on treatment efficacy. Between the PD-L1-positive and -negative patients, there was no significant difference in ORR (50% vs. 33.3%, respectively, p=0.896) or DCR (90.0% vs. 83.3%, respectively, p=1.000). The median PFS of the PD-L1-positive and -negative patients was 17.50 and 6.07 months (p=0.812), respectively, while the median OS was not reached in either group (p=0.655).

In a previous case report, a patient with pulmonary pleomorphic carcinoma developed necrosis of the lower extremities following treatment with second-line nivolumab [16]. Tozuka et al. [17] reported agranulocytosis, interstitial lung disease, and ocular myasthenia gravis in patients with pulmonary pleomorphic carcinoma after treatment with pembrolizumab. In the present study, irAEs occurred in patients receiving immunotherapy for PSC. However, there have been relatively few reports of irAEs in PSC patients treated with immunotherapy. In the present study, the incidence of irAEs was 48.5% (16/33), the most common were pneumonia (9.1%, 3/33) and skin rash (9.1%, 3/33). Three patients developed pneumonia, which was the main reason for drug withdrawal. Two patients developed cardiovascular toxicity, including one with acute heart failure resulting in death. Notably, the use of combination therapy did not increase the incidence of irAEs. Hence, careful monitoring throughout the treatment period is especially important for the detection and management of irAEs.

There were several limitations to the present study that should be addressed. First, the study cohort was relatively small because of the rarity of PSC. Second, this was a retrospective study and, thus, subject to inherent biases of patient selection and variations in the quality of recorded data. However, as none of the cases were retrieved from prospective clinical studies, the results of this retrospective study should be considered meaningful.

In conclusion, the antitumor activity of ICIs in PSC patients is promising. Lines of immunotherapy and the use of monotherapy vs. combination therapy had little effect on the efficacy of immunotherapy. However, further studies are needed to assess the relevance of PD-L1 expression for PSC patients receiving ICIs. Hence, future studies, especially prospective studies, are warranted to evaluate the efficacy and safety of ICIs for the treatment of PSC.

Supplementary information is available in the online version of the paper.

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References

[1] YENDAMURI S, CATY L, PINE M, ADEM S, BOGNER P et al. Outcomes of sarcomatoid carcinoma of the lung: a surveillance, epidemiology, and end results database analysis. Surgery 2012; 3: 397–402. https://doi.org/10.1016/j.surg.2012.05.007

[2] RAHOUMA M, KAMEL M, NARULA N, NASAR A, HARRISON S et al. Pulmonary sarcomatoid carcinoma: an analysis of a rare cancer from the Surveillance, Epidemiology, and End Results database. Eur J Cardiothorac Surg 2018; 4: 828–834. https://doi.org/10.1093/ejcts/ezx417

[3] NICHOLSON AG, TSAO MS, BEASLEY MB, BORCZUK AC, BRAMBILLA E et al. The 2021 WHO classification of lung tumors: impact of advances since 2015. J Thorac Oncol 2022; 3: 362–387. https://doi.org/10.1016/j.jtho.2021.11.003

[4] DOMBLIDES C, LEROY K, MONNET I, MAZIÈRES J, BARLESI F et al. Efficacy of immune checkpoint inhibitors in lung sarcomatoid carcinoma. J Thorac Oncol 2020; 5: 860–866. https://doi.org/10.1016/j.jtho.2020.01.014

[5] LIU L, ZANG R, SONG P, GAO S. [Current status of diagnosis and treatment of pulmonary sarcomatoid carcinoma.] Zhongguo Fei Ai Za Zhi 2018; 12: 902–906. https://doi.org/10.3779/j.issn.1009-3419.2018.12.07

[6] UNG M, ROUQUETTE I, FILLERON T, TAILLANDY K, BROUCHET L et al. Characteristics and clinical outcomes of sarcomatoid carcinoma of the lung. Clin Lung Cancer 2016; 5: 391–397. https://doi.org/10.1016/j.cllc.2016.03.001

[7] GANDHI L, RODRIGUEZ-ABREU D, GADGEEL S, ESTEBAN E, FELIP E et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018; 22: 2078–2092. https://doi.org/10.1056/NEJMoa1801005

[8] NASSER NJ, GORENBERG M, AGBARYA A. First line immunotherapy for non-small cell lung cancer. Pharmaceuticals (Basel) 2020; 13: 373. https://doi.org/10.3390/ph13110373

[9] LEE J, CHOI Y, JUNG HA, LEE SH, AHN JS et al. Outstanding clinical efficacy of PD-1/PD-L1 inhibitors for pulmonary pleomorphic carcinoma. Eur J Cancer 2020; 132: 150–158. https://doi.org/10.1016/j.ejca.2020.03.029

[10] VIEIRA T, ANTOINE M, HAMARD C, FALLET V, DURUISSEAUX M et al. Sarcomatoid lung carcinomas show high levels of programmed death ligand-1 (PD-L1) and strong immune-cell infiltration by TCD3 cells and macrophages. Lung Cancer 2016; 98: 51–58. https://doi.org/10.1016/j.lungcan.2016.05.013

[11] LOCOCO F, TORRICELLI F, ROSSI G, ALIFANO M, DAMOTTE D et al. Inter-relationship between PD-L1 expression and clinic-pathological features and driver gene mutations in pulmonary sarcomatoid carcinomas. Lung Cancer 2017; 113: 93–101. https://doi.org/10.1016/j.lungcan.2017.09.009

[12] MANEENIL K, XUE Z, LIU M, BOLAND J, WU F et al. Sarcomatoid carcinoma of the lung: The Mayo Clinic experience in 127 patients. Clin Lung Cancer 2018; 3: e323–e333. https://doi.org/10.1016/j.cllc.2017.12.008

[13] VIEIRA T, GIRARD N, UNG M, MONNET I, CAZES A et al. Efficacy of first-line chemotherapy in patients with advanced lung sarcomatoid carcinoma. J Thorac Oncol 2013; 12: 1574–1577. https://doi.org/10.1097/01.JTO.0000437008.00554.90

[14] SUKRITHAN V, SANDLER J, GUCALP R, GRALLA R, HALMOS B. Immune checkpoint blockade is associated with durable responses in pulmonary sarcomatoid carcinoma. Clin Lung Cancer 2019; 3: e242–e246. https://doi.org/10.1016/j.cllc.2018.12.013

[15] HAYASHI K, TOKUI K, INOMATA M, AZECHI K, MIZUSHIMA I et al. Case series of pleomorphic carcinoma of the lung treated with immune checkpoint inhibitors. In Vivo 2021; 3: 1687–1692. https://doi.org/10.21873/invivo.12428

[16] HONJO O, KUBO T, SUGAYA F, NISHIZAKA T, KATO K et al. Severe cytokine release syndrome resulting in purpura fulminans despite successful response to nivolumab therapy in a patient with pleomorphic carcinoma of the lung: a case report. J Immunother Cancer 2019; 1: 97. https://doi.org/10.1186/s40425-019-0582-4

[17] TOZUKA T, SUGANO T, NORO R, TAKANO N, HISAKANE K et al. Pembrolizumab-induced agranulocytosis in a pulmonary pleomorphic carcinoma patient who developed interstitial lung disease and ocular myasthenia gravis. Oxf Med Case Reports 2018; 11: omy094. https://doi.org/10.1093/omcr/omy094

[18] SAKO M, NOKIHARA H, KONDO K, MITSUHASHI A, OZAKI R et al. A case of pulmonary pleomorphic carcinoma with preexisting interstitial pneumonia successfully treated with pembrolizumab. Thorac Cancer 2022; 1: 129–132. https://doi.org/10.1111/1759-7714.14243

[19] XU L, TAO NN, LIANG B, LI DW, LI HC, SU LL. Use of PD-1 inhibitor tislelizumab in the treatment of advanced pulmonary sarcomatoid carcinoma: a case report. Thorac Cancer 2022; 3: 502–505. https://doi.org/10.1111/1759-7714.14290

[20] JIAO Y, LIU M, LUO N, GUO H, LI J. Successful treatment of advanced pulmonary sarcomatoid carcinoma with the PD-1 inhibitor toripalimab: a case report. Oral Oncol 2021; 112: 104992. https://doi.org/10.1016/j.oraloncology.2020.104992

[21] TANIGUCHI H, TAKEMOTO S, OZASA M, HONDA N, SUYAMA T et al. Remarkable response to pembrolizumab with platinum-doublet in PD-L1-low pulmonary sarcomatoid carcinoma: a case report. Thorac Cancer 2021; 7: 1126–1130. https://doi.org/10.1111/1759-7714.13890

[22] YAMASAKI, M, MATSUMOTO, Y, NAKAMOTO, K, HATTORI, N. Pulmonary pleomorphic carcinoma in an elderly patient treated with pembrolizumab shows a marked response. J Cancer Res Ther 2021; 6: 1580–1582. https://doi.org/10.4103/jcrt.JCRT_361_19

[23] HARADA M, MORIKAWA K, KAGOO N, ITO Y, KUBOTA T et al. Argon plasma coagulation with atezolizumab and chemoradiation in lung pleomorphic cancer showed a remarkable response: case report. Medicine (Baltimore) 2021; 21: e26149. https://doi.org/10.1097/MD.0000000000026149

[24] LUO Y, WEI J, ZHANG J, ZENG L, ZENG Z et al. Two different patients with pulmonary pleomorphic carcinoma response to PD-1 inhibitor plus anlotinib. Lung Cancer 2021; 155: 170–174. https://doi.org/10.1016/j.lungcan.2021.03.019

[25] KONG F, WANG W, GONG L, WU W, LIU Y. Anti-PD-1 antibody camrelizumab plus doxorubicin showed durable response in pulmonary sarcomatoid carcinoma: Case report and literature review. J Clin Pharm Ther 2020; 6: 1489–1496. https://doi.org/10.1111/jcpt.13234

[26] OKAUCHI S, SASATANI Y, SHIOZAWA T, YAMADA H, MIYAZAKI K et al. Combination of pembrolizumab with platinum-containing chemotherapy for pleomorphic carcinoma of the lung. In Vivo 2020; 3: 1439–1443. https://doi.org/10.21873/invivo.11926

[27] NISHINO K, KUNIMASA K, KIMURA M, INOUE T, TAMIYA M et al. Favorable response to pembrolizumab after durvalumab failure in a stage III sarcomatoid carcinoma of the lung: a case report. BMC Pharmacol Toxicol 2020; 1: 26. https://doi.org/10.1186/s40360-020-00404-7

[28] YOROZUYA T, TAYA T, YASUDA K, NAGANO Y, SHIOYA M et al. Long-term response with durvalumab after chemoradiotherapy for pulmonary pleomorphic carcinoma: a case report. Thorac Cancer 2020; 4: 1090–1093. https://doi.org/10.1111/1759-7714.13331

[29] BABACAN NA, PINA IB, SIGNORELLI D, PRELAJ A, GARASSINO MC et al. Relationship between programmed death receptor-ligand 1 expression and response to checkpoint inhibitor immunotherapy in pulmonary sarcomatoid carcinoma: a pooled analysis. Clin Lung Cancer 2020; 5: e456–e463. https://doi.org/10.1016/j.cllc.2020.02.022

[30] CHEN Y, ZHANG H, SHI J, WANG T. A partial response of pulmonary pleomorphic carcinoma to camrelizumab (PD1 monoclonal antibody) monotherapy: A case report. Onco Targets Ther 2020; 13: 12471–12476. https://doi.org/10.2147/OTT.S279004

[31] CHEN P, YU M, ZHANG JL, CHEN WY, ZHU L et al. Significant benefits of pembrolizumab in treating refractory advanced pulmonary sarcomatoid carcinoma: A case report. World J Clin Cases 2020; 13: 2876–2884. https://doi.org/10.12998/wjcc.v8.i13.2876

[32] CIMPEANU E, AHMED J, ZAFAR W, DEMARINIS A, BARDAROV SS et al. Pembrolizumab – emerging treatment of pulmonary sarcomatoid carcinoma: a case report. World J Clin Cases 2020; 1: 97–102. https://doi.org/10.12998/wjcc.v8.i1.97

https://doi.org/10.4149/neo_2022_220617N644

The prognostic impact of immune checkpoint inhibitors for the treatment of pulmonary sarcomatoid carcinoma: A multicenter retrospective study

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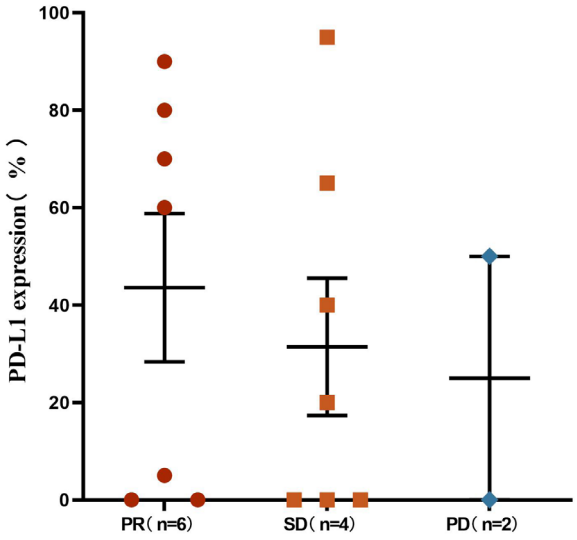
Supplementary Information

Supplementary Table S1. Articles published about immunotherapy in PSC.

First author	Year	Number	Sex (M/F)	Pathological diagnosis	Line (1/2/≥3)	Regimen	CR/PR/SD PD/UK	Median PFS (months)	Median OS (months)	PD-L1 expression (positive/ negative/ unknown)
Sako [18]	2022	1	1/0	PPC	0/1/0	Pembrolizumab [1];	0/1/0/0/0	24+	UK	1/0/0
Xu [19]	2022	1	0/1	PSC	0/1/0	Tislelizumab [1]	0/1/0/0/0	11+	UK	1/0/0
Jiao [20]	2021	1	1/0	PSC	0/1/0	Toripalimab→Toripalimab + Anlotinib→Toripalimab + Anlotinib + Thoracic radiotherapy [1]	0/1/0/0/0	UK	UK	1/0/0
Taniguchi [21]	2021	1	1/0	PSC	1/0/0	Pembrolizumab + Carboplatin + Pemetrexed + left pelvis radiotherapy [1];	0/1/0/0/0	UK	UK	1/0/0
Hayashi [15]	2021	3	3/0	PPC	2/1/0	Pembrolizumab [2]; Pembrolizumab + Carboplatin + Nab-paclitaxel [1];	0/2/0/1/0	4,7+,12+	UK	3/0/0
Yamasaki [22]	2021	1	1/0	PPC	1/0/0	Pembrolizumab [1];	0/1/0/0/0	8	UK	1/0/0
Harada [23]	2021	1	1/0	PPC	1/0/0	Atezolizumab + Carboplatin + Nab-paclitaxel + mediastinal lesion radiotherapy + argon plasma coagulation [1]	1/0/0/0/0	12+	UK	1/0/0
Luo [24]	2021	2	1/1	PPC	2/0/0	Camrelizumab + Anlotinib [2]	0/2/0/0/0	10,8	UK	2/0/0
Kong [25]	2020	1	0/1	PSC	1/0/0	Camrelizumab + Doxorubicin + Cisplatin [1]	0/1/0/0/0	20+	UK	1/0/0
Domblides [4]	2020	37	27/10	PSC	0/20/17	Nivolumab [32]; Pembrolizumab [3]; Atezolizumab [2]	0/15/9/12/1	4.89 [0.3–35.7]	12.7 [0.3–45.7]	18/1/9
Okauchi[26]	2020	1	1/0	PPC	1/0/0	Pembrolizumab + Carboplatin + Paclitaxel [1];	0/1/0/0/0	UK	UK	1/0/0
Nishino [27]	2020	1	1/0	PSC	1/1/0	Pembrolizumab after Durvalumab resistance [1]	1/0/0/0/0	7+	UK	1/0/0
Yorozuya [28]	2020	1	1/0	PPC	0/1/0	Durvalumab	0/0/0/0/1	12	UK	1/0/0
Babacan [29]	2020	5	2/3	PSC	2/3/0	Nivolumab [1]; Pembrolizumab [4]	0/2/1/2/0	3-25+	UK	4/0/1
Lee [9]	2020	49	36/13	PPC	2/38/3	Pembrolizumab [40]; Nivolumab [7]; Atezolizumab [2]	0/24/14/11/0	7.2 (4.9–9.5)	22.2 (7.0–37.3)	45/2/2
Chen [30]	2020	1	1/0	PPC	0/1/0	Camrelizumab [1]	0/1/0/0/0	4+	UK	1/0/0
Chen [31]	2020	1	1/0	PSC	0/0/1	Pembrolizumab [1];	0/1/0/0/0	8	9	1/0/0
Cimpeanu [32]	2020	1	1/0	PSC	1/0/0	Pembrolizumab [1];	0/1/0/0/0	14+	UK	1/0/0

Abbreviations: M-male; F-female; CR-complete response; PR-partial response; SD-stable disease; PD-progressive disease; PFS-progression-free survival; OS-overall survival; UK-unknow



Supplementary Figure S1. PDL expression analysis. Abbreviations: PD-partial response, SD-stable disease, PD-progresive disease