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Hazama, Daisuke ; Nakahama, Kenji ; Kodama, Hiroaki ; Miyazaki, Akito ; Azuma, Koichi ; Kawashima, Yosuke ; Sato, Yuki ; Ito, Kentaro ;…

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ORIGINAL ARTICLE

Effectiveness and Safety of Immune Checkpoint Inhibitors Alone or in Combination With Chemotherapy in Pulmonary Sarcomatoid Carcinoma

Daisuke Hazama, MD, PhD,[a] Kenji Nakahama, MD, PhD,[b] Hiroaki Kodama, MD,[c] Akito Miyazaki, MD,[d] Koichi Azuma, MD, PhD,[e] Yosuke Kawashima, MD,[f] Yuki Sato, MD,[g] Kentaro Ito, MD,[h] Yoshimasa Shiraishi, MD,[i] Keita Miura, MD,[j] Takayuki Takahama, MD, PhD,[k] Satoshi Oizumi, MD, PhD,[l] Yoshinobu Namba, MD,[m] Satoshi Ikeda, MD, PhD,[n] Hiroshige Yoshioka, MD, PhD,[o] Asuka Tsuya, MD, PhD,[p] Yuichiro Yasuda, MD, PhD,[q] Yoshiki Negi, MD, PhD,[r] Ayako Hara, MD,[s] Michihito Toda, MD, PhD,[t] Motoko Tachihara, MD, PhD[a,*]

[a]*Division of Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Hyogo, Japan*
[b]*Department of Respiratory Medicine, Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan*
[c]*Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan*
[d]*Department of Thoracic Oncology, National Hospital Organization Osaka Toneyama Medical Center, Osaka, Japan*
[e]*Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Fukuoka, Japan*
[f]*Department of Pulmonary Medicine, Sendai Kousei Hospital, Miyagi, Japan*
[g]*Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Hyogo, Japan*
[h]*Respiratory Center, Matsusaka Municipal Hospital, Mie, Japan*
[i]*Department of Respiratory Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan*
[j]*Department of Respiratory Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan*
[k]*Department of Medical Oncology, Kindai University Faculty of Medicine, Osaka, Japan*
[l]*Department of Respiratory Medicine, National Hospital Organization Hokkaido Cancer Center, Hokkaido, Japan*

*Corresponding author.

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Address for correspondence: Motoko Tachihara, PhD, Division of Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-1, Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan. E-mail: mt0318@med.kobe-u.ac.jp

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[m]Department of Respiratory Medicine and Medical Oncology, Takarazuka City Hospital, Hyogo, Japan
[n]Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, Kanagawa, Japan
[o]Department of Thoracic Oncology, Kansai Medical University, Osaka, Japan
[p]Department of Medical Oncology, Izumi City General Hospital, Osaka, Japan
[q]Department of Thoracic Oncology, Hyogo Cancer Center, Hyogo, Japan
[r]Department of Respiratory Medicine and Hematology, Hyogo Medical University, School of Medicine, Hyogo, Japan
[s]Department of Respiratory Medicine, Itami City Hospital, Hyogo, Japan
[t]Department of General Thoracic Surgery, Kansai Rosai Hospital, Hyogo, Japan

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ABSTRACT

Introduction: Pulmonary sarcomatoid carcinoma (PSC) is a rare subtype of lung cancer associated with poor prognosis and resistance to conventional chemotherapy. Immune checkpoint inhibitors (ICIs), alone or in combination with chemotherapy, were found to have clinical benefits in PSC in recent studies. Nevertheless, because these studies included a small number of patients owing to disease rarity, larger studies are needed to evaluate the effectiveness and safety of ICI-based therapy for PSC.

Methods: This multicenter retrospective study evaluated patients with ICI-naive advanced or metastatic PSC who were treated with ICI-based therapy at 25 hospitals in Japan.

Results: A total of 124 patients were evaluated. The overall response rate, median progression-free survival (PFS), and median overall survival (OS) were 59.0%, 10.5 months, and 32.8 months, respectively. The PFS and OS rates at 24 months were 35.3% and 51.5%, respectively. Programmed death-ligand 1 expression, concomitant chemotherapy, and the treatment line were not significantly associated with PFS or OS. Immune-related adverse events (irAEs) were observed in 70 patients (56.5%), including 30 (24.2%) with grade 3 to 5 events. Patients with mild irAEs (grades 1–2) had longer PFS and OS than did those with severe (grades 3–5) or no irAEs. In a multivariate analysis, any-grade irAEs and the absence of liver metastases were independently associated with PFS, whereas any-grade irAEs and Eastern Cooperative Oncology Group performance status less than or equal to 1 were independently associated with OS.

Conclusions: ICI-based therapy was found to have promising effectiveness in patients with advanced or metastatic PSC, regardless of programmed death-ligand 1 expression, concomitant chemotherapy, or treatment line.

Keywords: Pulmonary sarcomatoid carcinoma; Immune checkpoint inhibitors; Real-world data; Lung cancer

Introduction

Pulmonary sarcomatoid carcinoma (PSC) is a rare subtype of NSCLC, accounting for only 0.4% of all lung cancers. According to the 2015 WHO classification of lung tumors, there are five histopathologic subtypes, as follows: pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and pulmonary blastoma.[1] Some reports have found a worse prognosis for PSC than for typical NSCLC.[2,3] In five retrospective series of patients with advanced or metastatic PSC who received first-line chemotherapy, the median overall survival (OS) was only 4.3 to 8 months.[3–7] Therefore, novel therapeutic strategies for treating PSC are urgently needed.

Immune checkpoint inhibitors (ICIs) have dramatically improved the prognosis of patients with NSCLC.[8] Several studies have reported that PSC is associated with high programmed death-ligand 1 (PD-L1) expression, immune infiltration, and tumor mutational burden, which are predictive biomarkers for tumor response to ICIs.[9–11] These reports provide a rationale for using ICIs in PSC. A recent study including 37 patients with PSC who received ICI monotherapy as a second- or later-line treatment revealed that the overall response rate (ORR), median progression-free survival (PFS), and median OS were 40.5%, 4.89 months, and 12.7 months, respectively.[12] In a study of 49 patients with PSC treated with ICI monotherapy as a second- or later-line treatment, the ORR, median PFS, and median OS were 49.0%, 7.2 months, and 22.2 months, respectively.[13] In recent years, ICI dual therapy and a combination of chemotherapy with ICIs (chemoimmunotherapy) have become standard first-line treatment options for advanced NSCLC, regardless of PD-L1 expression.[8,14,15] Several studies have been conducted on the use of these therapies in patients with PSC. Kim et al.,[16] in a study of 18 patients with PSC, reported the efficacy of combination therapy with durvalumab and tremelimumab in any line of treatment, with an ORR of 26.7%, median PFS of 5.9 months, and median OS of 15.4 months. In a study by Zhou et al.[17] of 34 patients with PSC treated with first-line chemoimmunotherapy, the ORR was 70.6%, median PFS was 10.3 months, median OS was not reached,

and two-year survival rate was 57.8%. Taken together, these studies have revealed that ICI-based therapy has promising therapeutic potential for treating PSC. Nevertheless, the small number of patients with PSC recruited in each study, owing to disease rarity, limits the generalizability of the results. Moreover, immune-related adverse events (irAEs) in PSC have not been fully studied. Here, we evaluated the effectiveness and safety of ICIs, alone or in combination with chemotherapy, in patients with advanced or metastatic PSC.

Materials and Methods

Study Design and Patients

This multicenter, retrospective study evaluated all consecutive patients with immunotherapy-naive advanced or metastatic PSC who were treated with ICIs alone or in combination with chemotherapy at 25 hospitals in Japan between December 2015 and September 2021. Data were obtained from clinical records. According to the smoking status, patients were categorized as never smokers (smoked <100 cigarettes in their lifetime) and ever smokers (smoked more than 100 cigarettes in their lifetime). We diagnosed PSC according to the WHO classification using samples obtained from surgery or biopsy.[1,18] All tumors were staged using the eighth edition of the TNM staging system for lung cancer.[19] We analyzed PD-L1 expression by immunohistochemistry and evaluated it using the tumor proportion score (TPS). Tumors were assessed according to the Response Evaluation Criteria in Solid Tumors (version 1.1).[20] Safety data were assessed using the Common Terminology Criteria for Adverse Events (version 4.0 or later). We defined irAEs as AEs with a potential immunologic basis that required monitoring and interventions. The irAEs were classified by organ system, as follows: pulmonary; cutaneous; hepatic; endocrine; gastrointestinal; renal; and other irAEs, such as thrombocytopenia, arthritis, and pancreatitis. The study was approved by the Institutional Review Board of each participating institution. The requirement for written informed consent was waived owing to the retrospective nature of the study. Instead, the research content was posted on the hospital websites. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Co-primary outcomes were ORR and PFS, and secondary outcomes were OS and incidence of irAEs. We assessed PFS from the first day of ICI treatment to that of the earliest signs of disease progression or death from any cause. We evaluated OS from the initiation of ICI treatment to the date of death or the last follow-up. Baseline characteristics are summarized using frequencies and percentages for categorical variables and medians and ranges for continuous variables. We compared ORR using Fisher's exact test. Survival curves were calculated using the Kaplan-Meier method, and group comparisons were performed using the log-rank test. Multiple testing was adjusted for using the Bonferroni method. Median follow-up was estimated using the reverse Kaplan-Meier method. The data cutoff date was set to May 17, 2022. Patients without disease progression or those surviving at the data cutoff date were censored at their last clinical visit date. Cox proportional hazards regression was used for univariate and multivariate survival analyses. Statistical analyses were carried out using the EZR software (version 1.51; Saitama Medical Center, Jichi Medical University, Saitama, Japan).[21] A two-sided p value lower than 0.05 was considered statistically significant.

Results

Patient Characteristics

We retrospectively collected demographic and clinical data of 124 patients with advanced or metastatic PSC. The patients' baseline characteristics are listed in Table 1. The median patient age was 69 years (range: 35–84 y). Most patients were men (78.2%), were ever smokers (85.5%), and had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1 (83.1%). Furthermore, 76 of the patients (61.3%) had stages III to IV disease, and 48 (38.7%) had recurrent disease. The final diagnosis of PSC was established by surgery in 66 patients (53.2%) and small biopsy in 58 patients (46.8%). Among the histopathologic subtypes, 92 patients (74.2%) were diagnosed with having pleomorphic carcinoma; 15, carcinosarcoma; nine, spindle cell carcinoma; and one, giant cell carcinoma. The samples of the remaining seven patients were difficult to classify into specific subtypes.

We performed PD-L1 testing in 116 samples (93.5%), and PD-L1 expression was determined using the TPS. The 22C3 assay was used for all but one sample, for which the 28-8 assay was used. The PD-L1 TPS was less than 1%, 1% to 49%, more than or equal to 50%, and unknown in 11 (8.9%), 24 (19.4%), 81 (65.3%), and eight (6.5%) patients, respectively. Furthermore, 40 patients received a first-line combination of ICIs with platinum-based chemotherapy; 56, first-line ICI monotherapy or dual therapy; and 28, ICI monotherapy as a second- or later-line therapy. The treatment regimens are listed in Supplementary Table 1. Supplementary Table 2 reveals the prior and subsequent systemic therapies in each treatment group. The *EGFR*, *ALK*, *ROS1*, *BRAF*, *MET*, *KRAS*, and other driver mutation rates were

Table 1. Patient Characteristics

Characteristics	Patients (N = 124) n	%
Age		
Median	69	
Range	35-84	
Sex		
Male	97	78.2
Female	27	21.8
Smoking history		
Never	18	14.5
Ever	106	85.5
ECOG PS		
0-1	103	83.1
≥2	21	16.9
Clinical stage		
Advanced	76	61.3
Recurrence	48	38.7
Diagnosis method		
Surgery	66	53.2
Others	58	46.8
Histologic subtypes		
Pleomorphic carcinoma	92	74.2
Others	32	25.8
Interstitial pneumonia at baseline	6	4.8
Brain metastases at baseline	33	26.6
Liver metastases at baseline	12	9.7
PD-L1 TPS		
<1%	11	8.9
1%-49%	24	19.4
≥50%	81	65.3
Unknown	8	6.5
Treatment regimens		
First-line ICIs with chemotherapy	40	32.3
First-line ICIs without chemotherapy	56	45.2
Later-line ICI monotherapy	28	22.6

ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICI, immune checkpoint inhibitor; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

Table 2. Tumor Response

Response	n	%	(95% CI)
CR	8	6.8	
PR	61	52.1	
SD	18	15.4	
PD	22	18.8	
NE	8	6.8	
No measurable lesion	7		
ORR		59.0	(49.5-68)

CI, confidence interval; CR, complete response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

1.8% (two of 113), 0% (zero of 111), 0% (zero of 69), 4.7% (two of 43), 7.4% (two of 27), 31.0% (13 of 42), and 0% (zero of 42), respectively (Supplementary Fig. 1). Of the 17 patients with gene mutations, 14 had pleomorphic carcinoma, two had carcinosarcoma, and the remaining patient had unclassified cancer. One patient each had PSC with *EGFR/KRAS* comutation and BRAF/KRAS comutation.

Effectiveness and Safety

The ORR was 59.0% (95% confidence interval [CI]: 49.5%–68%; Table 2). At the median follow-up period of 30.6 months (95% CI: 22.4–36.3 mo), 75 (60.5%) PFS events and 60 (48.4%) OS events were observed. The median PFS was 10.5 months (95% CI: 6.8–15.5 mo; Fig. 1*A*), and the median OS was 32.8 months (95% CI: 17.1 mo–not available; Fig. 1*B*). The PFS and OS rates at 24 months were 35.3% (95% CI: 26.0%–44.6%) and 51.5% (95% CI: 41.4%–60.7%), respectively. The Kaplan-Meier curves for PFS and OS according to the PD-L1 expression levels are found in Figure 2*A*. Our data revealed that PD-L1 expression was not significantly associated with PFS ($p = 0.204$). Although PD-L1 expression was correlated with OS ($p = 0.047$), the association was not significant after adjusting for multiple comparisons. To determine the impact of PD-L1 expression on programmed death-1 (PD-1) or PD-L1 inhibitor monotherapy with or without chemotherapy, we further investigated the relationship between PD-L1 expression and survival after excluding 10 patients treated with ICI dual therapy. Among the 114 patients treated with ICI monotherapy alone or in combination with chemotherapy, PD-L1 expression was not associated with PFS or OS (Supplementary Fig. 2*A* and *B*). We also analyzed the differences in treatment efficacy with or without concomitant chemotherapy and across treatment lines. The ORR in each treatment group was 66.7%, 56.6%, and 53.6%, median PFS was 9.2, 11.2, and 12.0 months, and median OS was 24.9, 20.1, and 44.0 months, respectively (Supplementary Table 3; Fig. 2*B*). No significant differences between the treatment groups were found in the ORR, PFS, or OS ($p = 0.5$, $p = 0.88$, and $p = 0.443$, respectively).

The irAEs are summarized in Supplementary Table 4. Those of any grade were reported in 70 patients (56.5%), including 30 (24.2%) with grade greater than or equal to 3 events. The most common grade greater than or equal to 3 irAEs were pneumonitis (6.5%) and hepatitis (6.5%). Treatment discontinuation due to AEs occurred in 30 patients (24.2%), whereas death due to AEs occurred in four patients (3.2%). Of note, patients with mild irAEs (grades 1–2) had longer PFS and OS than did those with severe (grades 3–5) or no irAEs (Fig. 2*C*).

In univariate analysis, ECOG PS less than or equal to 1, any-grade irAEs, and the absence of liver metastases at baseline had a significant influence on PFS and OS

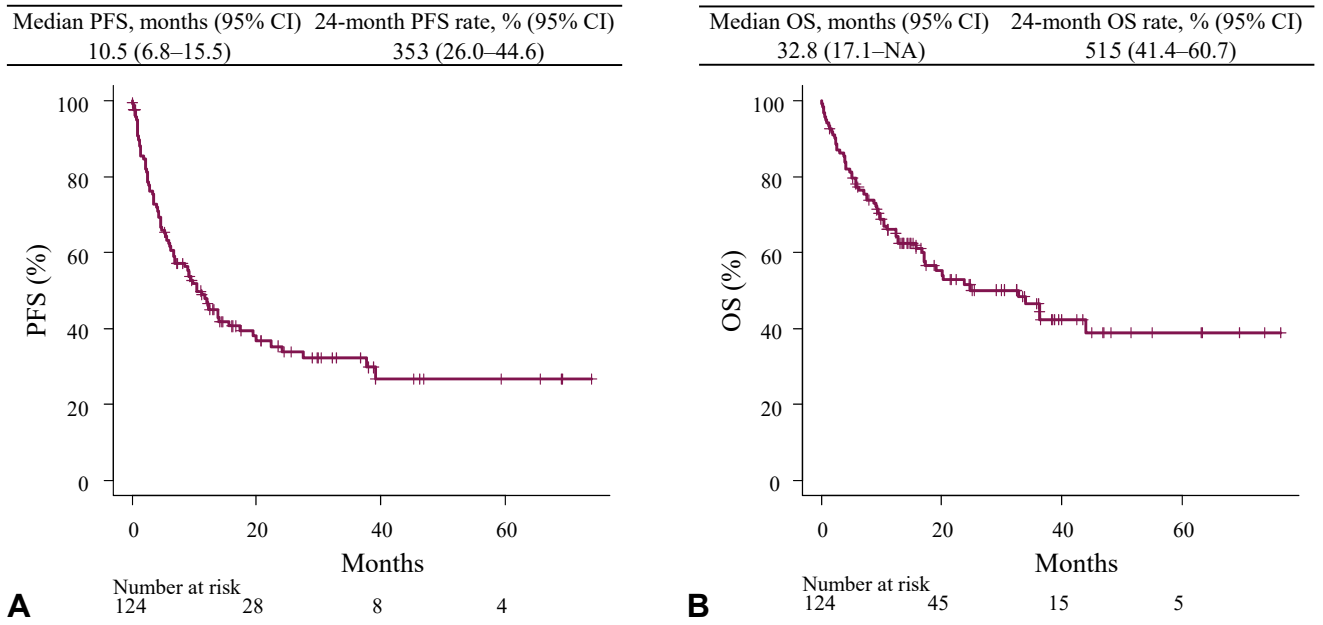

Figure 1. Kaplan-Meier estimates of (*A*) PFS and (*B*) OS. CI, confidence interval; NA, not available; OS, overall survival; PFS, progression-free survival.

(Table 3). Multivariate analysis revealed that any-grade irAEs (hazard ratio [HR] = 0.57; 95% CI: 0.35–0.93; $p = 0.025$) and the absence of liver metastases (HR = 2.58; 95% CI: 1.27–5.27; $p = 0.009$) were significantly associated with longer PFS, whereas ECOG PS less than or equal to 1 (HR = 0.24; 95% CI: 0.12–0.46; $p < 0.001$) and any-grade irAEs (HR = 0.53; 95% CI: 0.31–0.90; $p = 0.020$), with longer OS. Univariate and multivariate analyses of PFS and OS in each treatment group are found in Supplementary Table 5. ECOG PS less than or equal to 1 (HR = 0.32; 95% CI: 0.14–0.71; $p = 0.005$) and any-grade irAEs (HR = 0.44; 95% CI: 0.21–0.93; $p = 0.031$) were significantly associated with OS in patients treated with first-line ICIs without chemotherapy. In patients treated with second- or later-line ICI monotherapy, the absence of liver metastases at baseline (HR = 12.0; 95% CI: 2.52–56.9; $p = 0.002$) was an independent prognostic factor for PFS, whereas ECOG PS less than or equal to 1 (HR = 0.18; 95% CI: 0.05–0.62; $p = 0.006$), for OS.

Discussion

To our knowledge, this is the largest study to date to evaluate the effectiveness and safety of ICI-based treatment in patients with PSC. In the present study, the ORR was 59.0%; median PFS, 10.5 months; and median OS, 32.8 months. The treatment outcomes were comparable with those of a previous study that evaluated first-line ICIs plus chemotherapy in patients with advanced or metastatic PSC[17] and seem to be superior to those reported by previous studies using ICI monotherapy or dual therapy.[12,13,16] Notably, our data revealed that concomitant chemotherapy did not have a survival benefit. Akinboro et al.[22] conducted a pooled analysis using data from 12 randomized controlled trials (RCTs) of patients with NSCLC with PD-L1 TPS greater than or equal to 50% treated with first-line chemo-immunotherapy or immunotherapy alone. They found that chemoimmunotherapy had a significant benefit in PFS but not in OS. They previously reported that PFS and OS improved more with chemoimmunotherapy than with immunotherapy alone in those with a PD-L1 TPS score of 1% to 49%.[23] Perol et al.[24] conducted a real-world retrospective cohort study of patients with non-squamous NSCLC with PD-L1 TPS greater than or equal to 50%. In their study, no significant differences in PFS and OS were observed between patients treated with first-line immunotherapy and those treated with chemoimmunotherapy. Considering the high expression of PD-L1 in PSC, as described subsequently, the addition of platinum-doublet chemotherapy to immunotherapy might provide little improvement in survival in patients with PSC.

Similar to the results of previous studies,[9,10,12,17] we found a high expression of PD-L1 in PSC. Although PD-L1 expression in tumor cells has been reported as a predictive marker for the efficacy of PD-1 or PD-L1 inhibitors in NSCLC,[25] it did not influence PFS or OS in our study. Unlike our findings, some investigators have reported a positive relationship between PD-L1 expression and the effectiveness of ICIs in PSC. Babacan et al.[26] revealed that positive PD-L1 expression (≥1%) is

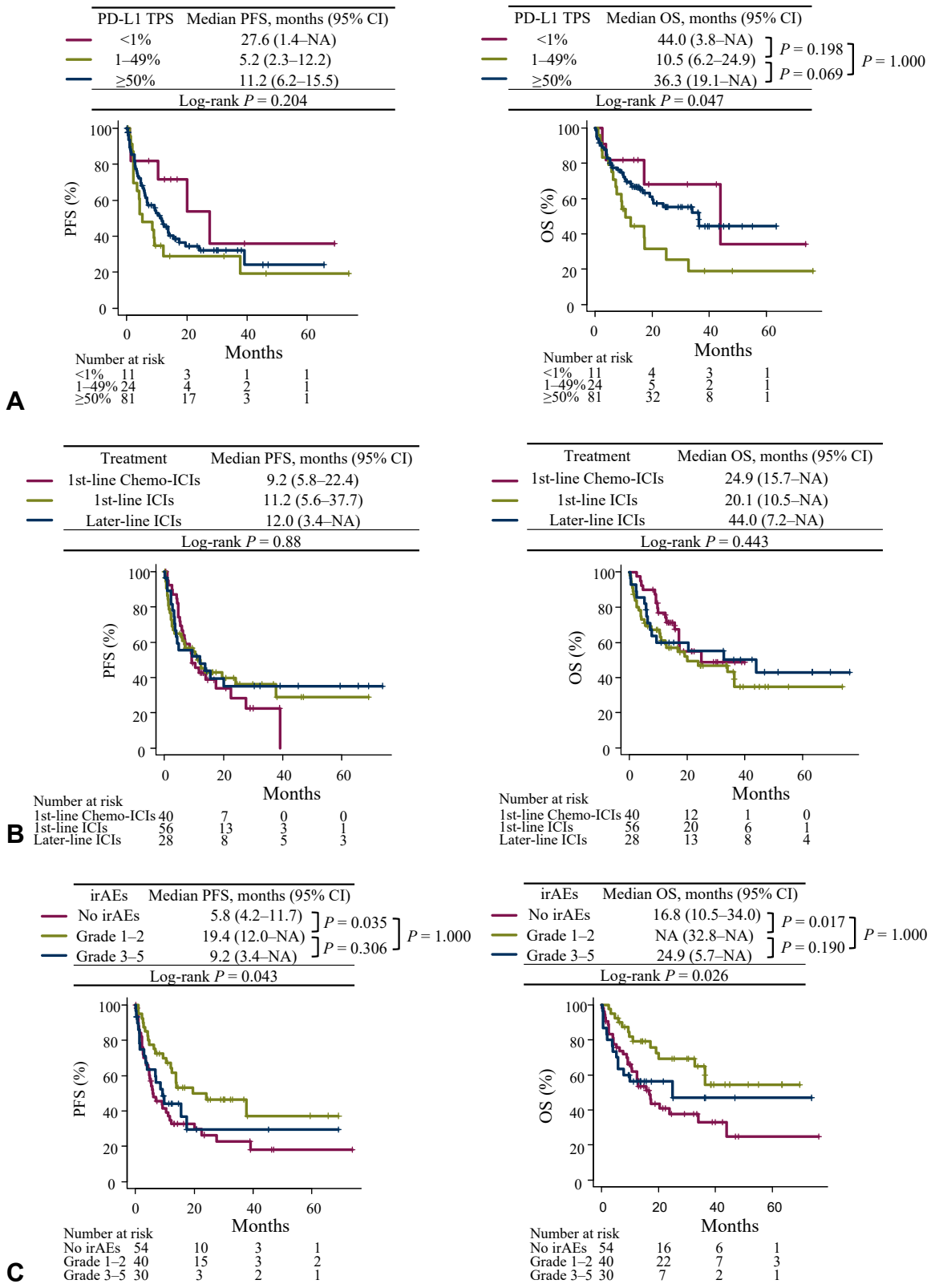

Figure 2. Kaplan-Meier estimates of PFS and OS according to the (*A*) programmed death-ligand 1 expression level, (*B*) treatment, and the (*C*) severity of irAES. Chemo-ICI, immune checkpoint inhibitor with chemotherapy; CI, confidence interval; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; NA, not available; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TPS, tumor proportion score.

Table 3. Univariate and Multivariate Analyses of Factors Associated With PFS and OS

	Univariate		Multivariate	
Variables	HR (95% CI)	*p*	HR (95% CI)	*p*
PFS				
Age (≥75 y vs. <75 y)	0.80 (0.43-1.48)	0.471	0.73 (0.38-1.41)	0.348
Sex (men vs. women)	0.78 (0.46-1.32)	0.356	0.68 (0.39-1.19)	0.177
Smoking history (ever vs. never smoker)	0.64 (0.36-1.15)	0.132		
ECOG PS (0-1 vs. ≥2)	0.51 (0.27-0.95)	0.033	0.52 (0.26-1.04)	0.066
Diagnosis method (surgical vs. small biopsy)	1.18 (0.75-1.86)	0.476		
Histologic subtypes (pleomorphic carcinoma vs. others)	0.91 (0.55-1.51)	0.726		
Interstitial pneumonia at baseline (yes vs. no)	0.72 (0.23-2.30)	0.579		
Brain metastases at baseline (yes vs. no)	1.36 (0.83-2.24)	0.222		
Liver metastases at baseline (yes vs. no)	2.83 (1.43-5.60)	0.003	2.58 (1.27-5.27)	0.009
PD-L1 (<1% vs. ≥1%)	1.91 (0.77-4.76)	0.163	0.42 (0.16-1.05)	0.063
PD-L1 (<50% vs. ≥50%)	0.98 (0.59-1.63)	0.941		
ICIs (with vs. without chemotherapy)	1.11 (0.69-1.79)	0.659		
ICIs (mono- vs. dual therapy)	2.76 (0.68-11.2)	0.158		
Treatment line (first- vs. later-line)	1.11 (0.65-1.93)	0.690		
Any grade irAEs (yes vs. no)	0.62 (0.40-0.98)	0.042	0.57 (0.35-0.93)	0.025
Severe irAEs (yes vs. no)	1.15 (0.67-1.98)	0.611		
OS				
Age (<75 y vs. ≥75 y)	1.47 (0.81-2.69)	0.207	1.71 (0.89-3.26)	0.107
Sex (men vs. women)	1.06 (0.56-2.00)	0.864	0.84 (0.42-1.68)	0.627
Smoking history (ever vs. never smoker)	0.89 (0.44-1.80)	0.740		
ECOG PS (0-1 vs. ≥2)	0.26 (0.14-0.46)	<0.001	0.24 (0.12-0.46)	<0.001
Diagnosis method (surgical vs. small biopsy)	1.19 (0.71-1.99)	0.500		
Histologic subtypes (pleomorphic carcinoma vs. others)	0.95 (0.54-1.67)	0.865		
Interstitial pneumonia (yes vs. no)	0.85 (0.26-2.72)	0.782		
Brain metastases at baseline (yes vs. no)	1.62 (0.95-2.78)	0.079		
Liver metastases at baseline (yes vs. no)	2.19 (1.03-4.64)	0.042	2.04 (0.94-4.41)	0.070
PD-L1 (<1% vs. ≥1%)	0.62 (0.23-1.73)	0.365	0.65 (0.23-1.84)	0.418
PD-L1 (<50% vs. ≥50%)	1.48 (0.86-2.54)	0.160		
ICIs (with vs. without chemotherapy)	0.73 (0.41-1.31)	0.292		
ICIs (mono- vs. dual therapy)	0.83 (0.30-2.29)	0.714		
Treatment line (first- vs. later-line)	1.08 (0.59-1.98)	0.804		
Any grade irAEs (yes vs. no)	0.58 (0.35-0.97)	0.038	0.53 (0.31-0.90)	0.020
Severe irAEs (yes vs. no)	1.23 (0.67-2.24)	0.504		

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

significantly correlated with longer PFS in patients with PSC who received ICI monotherapy. Lee et al.[13] reported that high PD-L1 expression (≥50%) is significantly associated with better OS in patients with pulmonary pleomorphic carcinoma treated with ICI monotherapy. Of note, patients who received ICI dual therapy were also included in our study. Two phase 3 RCTs of ICI dual therapy have revealed that PD-L1 expression is not predictive of survival.[14,15] Similarly, Kim et al.[16] revealed that tumor response is not significantly correlated with PD-L1 expression in patients with PSC who received a combination therapy of durvalumab and tremelimumab. Nevertheless, in the present study, PD-L1 expression was not associated with ORR, PFS, or OS, even after excluding patients treated with ICI dual therapy. The discrepancy may be attributed to intratumoral heterogeneity of PD-L1 expression,[27,28] various cutoff points used to define positive PD-L1 expression, and the presence of multiple testing platforms using different scoring systems.[29,30] Several promising predictive biomarkers for the efficacy of ICI-based therapy, such as tumor mutational burden, tumor-infiltrating leukocytes, and microsatellite instability, have been reported to be high in PSC.[10,31,32] The integration of biomarkers is eagerly anticipated for effectively predicting responses to ICI-based therapy in PSC.

In this study, the incidence of any-grade and grade 3 to 5 irAEs was 56.5% and 24.2%, respectively. Although limited data have been reported to date on the incidence of irAEs in PSC, these proportions seem to be higher than those reported in a meta-analysis of phase 3 RCTs assessing ICIs for lung cancer, which revealed that any-grade irAEs occurred in 37.1% of patients and those of grade greater than or equal to 3 occurred in 18.5%.[33]

This may be due to the high expression of PD-L1, which is reportedly associated with a higher incidence of irAEs.[34,35] Nevertheless, the frequency of irAEs varies in different trials because there are no clear diagnostic criteria for irAEs. Zhao et al.[36] reported that the incidence of irAEs ranged from 17.8% to 67.0% in patients with NSCLC treated with anti–PD-1 antibodies. Moreover, Fujimoto et al.[37] revealed that the incidence and severity of irAEs reported in real-world studies are higher than those in clinical trials. Further studies are needed to elucidate whether patients with PSC experience more frequent and severe irAEs.

We found that patients with mild irAEs had more favorable outcomes than did those with severe or no irAEs. Previous studies have revealed that the occurrence of irAEs is associated with better clinical outcomes in patients with NSCLC treated with ICIs.[36,38] Although the mechanism of irAEs is thought to be mediated by increased T-cell activity and the levels of autoantibodies and inflammatory cytokines,[39] the presence of severe irAEs, compared with mild irAEs, was unfavorable for patient survival in the present study. Similar results have been reported in several studies. Socinski et al.[40] reported that patients with grade 3 to 5 irAEs had shorter OS than did those with grade 1 to 2 or no irAEs in pooled analyses of the IMpower130, IMpower132, and IMpower150 trials, which revealed the efficacy of atezolizumab combined with platinum-based chemotherapy as a first-line treatment for advanced NSCLC. Wang et al.[41] revealed that mild irAEs led to a better prognosis in patients with advanced NSCLC receiving ICI monotherapy, whereas poorer clinical outcomes were associated with severe irAEs. Severe irAEs require systemic steroid therapy and might result in life-threatening conditions. Therefore, early detection and management of irAEs may be important to maximize the therapeutic benefit of ICI-based treatment in PSC.

In our study, multivariate analysis revealed that irAEs and liver metastases were independently associated with PFS, whereas irAEs and ECOG PS were associated with OS. Previous reports have revealed that the ECOG PS is an independent prognostic factor for the survival of patients with NSCLC treated with ICI monotherapy.[37,42] The landmark PFS and OS rates in patients with NSCLC who received first-line immunotherapy are reportedly approximately twice as high in patients with a good PS than in those with a poor PS.[43] Ikeda et al.[44] suggested that the presence of cancer cachexia plays a key role in the response to ICIs in patients with NSCLC and a poor PS. Nevertheless, the relationship between liver metastases and treatment outcomes with ICI-based therapy remains controversial. Although many studies have identified liver metastases as a negative predictive factor for patients with NSCLC treated with ICI monotherapy,[45,46] a recent meta-analysis of RCTs including ICIs alone or in combination with chemotherapy revealed that the presence of liver metastases was not significantly associated with the efficacy of ICI-based therapy.[47] Tumeh et al.[48] revealed that the presence of liver metastases is associated with reduced marginal $CD8^+$ T-cell infiltration in melanoma. Similarly, Qiao et al.[49] revealed that patients with liver metastases from NSCLC tended to have lower $PD\text{-}L1^+$ $CD8^+$ T-cell infiltration than did those without. These results suggest that patients with liver metastases have an immunologically "cold" tumor microenvironment, which may attenuate the efficacy of ICIs. Qiao et al.[49] also reported that ICI-based combination therapy had better treatment outcomes than those of ICI monotherapy in patients with liver metastases. A network meta-analysis of ICI-based therapy for NSCLC indicated that pembrolizumab plus chemotherapy and atezolizumab plus bevacizumab plus chemotherapy were superior to other treatments in terms of PFS and OS in patients with liver metastases.[50] Elucidating the detailed mechanism by which a poor PS or the presence of liver metastases attenuates the effect of ICIs on PSC will help in selecting optimal therapeutic strategies.

Our study had some limitations. First, our study was limited by its retrospective nature. Second, the chemotherapy regimens used in this study were heterogeneous. Third, although diagnosing PSC using small biopsy samples is difficult owing to their heterogeneity, we included such samples in this study to evaluate the effectiveness and safety of ICI-based therapy in the real-world setting. Our data revealed that the diagnostic method used did not significantly affect PFS or OS. Therefore, the diagnosis of PSC by small biopsy might be considered acceptable if samples that fulfill the diagnostic criteria are obtained.

In conclusion, our study revealed that ICI-based therapy has promising effectiveness in patients with advanced or metastatic PSC, regardless of PD-L1 expression, concomitant chemotherapy, or the treatment line.

CRediT Authorship Contribution Statement

Daisuke Hazama: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review and editing.

Motoko Tachihara: Conceptualization, Methodology, Project administration, Supervision, Writing—original draft, Writing—review and editing.

Kenji Nakahama, Hiroaki Kodama, Akito Miyazaki, Koichi Azuma, Yosuke Kawashima, Yuki Sato, Kentaro Ito, Yoshimasa Shiraishi, Keita Miura,

Takayuki Takahama, Satoshi Oizumi, Yoshinobu Namba, Satoshi Ikeda, Hiroshige Yoshioka, Asuka Tsuya, Yuichiro Yasuda, Yoshiki Negi, Ayako Hara, Michihito Toda: Data curation, Investigation, Writing—original draft, Writing—review and editing.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at 10.1016/j.jtocrr.2023.100613.

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