ORIGINAL ARTICLE

Phase II study of durvalumab and tremelimumab in pulmonary sarcomatoid carcinoma: KCSG-LU16-07

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Abstract

Background: Pulmonary sarcomatoid carcinoma (PSC) is rare with a poor outcome and is resistant to conventional cytotoxic chemotherapy. The efficacy and safety of durvalumab and tremelimumab for treating recurrent or metastatic PSCs were assessed by a nonrandomized, open-label, phase II study.

Methods: A total of 18 patients with recurrent or metastatic PSC received 1500 mg of durvalumab and 75 mg of tremelimumab every four weeks, followed by 750 mg of durvalumab every two weeks until the disease progressed, or an unacceptable toxicity level was reached. The primary endpoint was the objective response rate (ORR). The secondary endpoints were progression-free survival (PFS), overall survival (OS), and toxicity. Genomic profiling of PSC by next-generation sequencing (NGS) and determination of peripheral blood lymphocyte subsets using flow cytometry were performed for exploratory analysis.

Results: A total of 15 out of 18 patients were evaluated for the analysis of the primary endpoint. At the data cutoff point, the ORR of 26.7% (95% confidence interval [CI]: 7.8–55.1) was achieved with the median follow-up duration of 12.0 months (range, 8.4–16.1). Median PFS and OS were 5.9 months (95% CI: 1.1–11.9) and 15.4 months (95% CI: 11.1-not reached), respectively. Treatment-related adverse events (AEs) of any grade were reported in 16 patients; the most common AEs were pruritus ($n = 5$), pneumonitis ($n = 4$), and rash ($n = 4$). Treatment was discontinued in two patients due to AEs of grade ≥ 3.

Conclusions: Durvalumab and tremelimumab demonstrated clinical benefit with a prolonged survival and manageable toxicity profile in patients with recurrent or metastatic PSC.

Introduction

Pulmonary sarcomatoid carcinoma (PSC) is a rare type of lung malignancy with poorly differentiated characteristics, accounting for less than 1% of all lung cancers.[1, 2] It occurs mainly in elderly men and is associated with a heavy smoking history.[3–5] Its clinical course is aggressive and a poor prognosis is observed, even in the early phases of the disease.[6] These tumors are also highly resistant to conventional cytotoxic chemotherapy.[7] It has been previously reported that the response rate of conventional cytotoxic chemotherapy used for non–small cell lung cancer (NSCLC) was 0%–16.5% in PSC and the median overall survival (OS) was only 5–6.3 months.[7, 8] Thus, novel therapeutic strategies are desperately needed.

Immunotherapy has risen to the forefront as the most rapidly evolving treatment strategy in oncology. Immune checkpoint inhibitors (ICIs) have shown notable success in several clinical trials involving multiple tumor types including NSCLC.[9–11] Durvalumab (MEDI4736) is a selective human immunoglobulin (Ig) G1 monoclonal antibody (mAb) against programmed death ligand 1 (PD-L1). Tremelimumab is a selective human IgG2 mAb binding to cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4). An early phase study reported the clinical efficacy of durvalumab plus tremelimumab treatment with its safety profile manageable regardless of PD-L1 expression level.[12]

Given that PSC shows high positivity rate of PD-L1 up to 90.2% and exhibits strong immune-cell infiltration,[13–15] it is reasonable to apply ICIs in PSC. However, ICIs have not been explored prospectively in PSC. Here, we performed a phase II study (NCT03022500) to investigate the efficacy and safety of the combined treatment of durvalumab plus tremelimumab in patients with recurrent or metastatic PSC.

Methods

Study design and patients

This was an open-label and multicenter single-arm phase II study in patients with recurrent or metastatic PSC. The histology of PSC was classified as sarcomatoid carcinoma, spindle cell carcinoma, giant cell carcinoma, pleomorphic carcinoma, carcinosarcoma, and pulmonary blastoma on the basis of the World Health Organization classification.[16] Patients with recurrent or metastatic PSC were eligible if the following criteria were met: ≥ 20 years of age; patients had not received any, or prior lines of chemotherapy or targeted therapies; had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1; and had a minimum of one measureable lesion using the Response Evaluation Criteria in Solid Tumor (RECIST)

version 1.1. Patients with brain metastases were eligible if they had no symptoms or were neurologically stable without administration of steroids after surgery or radiotherapy. Patients were not eligible if they had a history of carcinomatous meningitis, had an active autoimmune disease for the last two years, were receiving systemic steroid therapy or other form of immunosuppressive treatment, or had been on anti-PD-1, –PD-L1, or –CTLA-4 mAb treatments. This study received the approval of the Institutional Review Board of each participating center and was performed in compliance with the protocol, good clinical practice guidelines, and the Declaration of Helsinki. Informed consents were acquired from patients prior to study entry.

Treatments and assessments

Patients received 1500 mg of durvalumab and 75 mg of tremelimumab; both were administered intravenously every four weeks for up to four cycles, followed by 750 mg of durvalumab every two weeks. Treatment was continued until investigator-assessed and confirmed progression, intolerable toxicities, withdrawal of consent, or a total of 18 cycles had been reached.

The modified RECIST version 1.1 [17] was used to evaluate tumor response every eight weeks. Once radiological progression was initially identified, the study treatment was continued on patients who were clinically stable until the confirmation of progression which was a minimum of four weeks later. Patients administered at least one cycle of study treatment were eligible for safety evaluation. Adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Immunohistochemistry of PD-L1

Immunohistochemistry analysis of PD-L1 was done on pretreatment formalin-fixed paraffin-embedded tumor tissues using the SP263 assay (Ventana Medical Systems, Tucson, AZ, United States) or the 22C3 pharmDx assay (Dako, Carpinteria, CA, United States) according to the manufacturer's recommendations. The expression of PD-L1 was evaluated by the percentage of tumor cells with membranous staining of PD-L1[18] and assessed by pathologists in a blinded fashion.

Fluorescence-activated cell sorting (FACS)

Freshly collected whole blood was labeled at room temperature for 15 minutes with the following fluorescence-conjugated mAbs: BD Multitest CD3 FITC/CD8 PE/CD45 PerCP/CD4 APC and BD Multitest CD3 FITC/CD16

+ CD56 PE/CD45 PerCP/CD19 APC (BD Biosciences, San Jose, CA, United States). To remove red blood cells, FACS lysis solution (BD Biosciences, San Jose, CA, United States) was added and incubated at room temperature for 15 minutes. A FACSCalibur flow cytometer and CellQuest software (BD Biosciences, San Jose, CA, United States) was used to acquire and analyze the data.

Next-generation sequencing

Formalin-fixed paraffin-embedded (FFPE) tumor tissues from 12 patients were deeply sequenced with a next-generation sequencing (NGS) panel developed by Seoul National University Hospital (SNUH) FIRST Lung Cancer Panel (LCP), which comprised 64 lung cancer-related target genes.[19]

Statistical analysis

Overall response rate (ORR) by investigator review was the primary endpoint. All patients receiving any study treatment were eligible to be evaluated for a response. A null hypothesis of 5% ORR and alternative hypothesis of 30% ORR were established. To prove the hypothesis, Simon optimal 2-stage design was used with a one-sided type I error of 5% and power of 80%. If one or more responses occurred in the first five patients in the first stage, then the study would proceed to the second stage. At the end of the study, it was considered positive if at least three responses were observed out of 18 patients. OS, progression-free survival (PFS), safety, and biomarker analysis were secondary endpoints. PFS and OS were estimated using the Kaplan-Meier method.

Results

Patient characteristics

A total of 18 patients with a diagnosis of PSC were enrolled between May 2017 and February 2018. Baseline characteristics are described in Table 1. The median age of 12 men and six women was 61.5 years (range, 44–78) and nearly 60% of patients had a smoking history. The PD-L1 expression was evaluated in 14 patients. Nine of 14 patients (64.3%) included had ≥50% PD-L1 expression. A total of 12 patients (67%) had received prior cytotoxic chemotherapy for PSC; nine (50%) of 18 patients had received only one line of prior cytotoxic chemotherapy; and two patients (11.1%) had received two lines of prior cytotoxic chemotherapy.

Table 1 Baseline characteristics of the patients (N = 18)

Characteristics		No. of patients (%)
Median age, years (range)		62 (44–78)
Sex	Male	12 (66.7)
	Female	6 (33.3)
ECOG performance status	0	9 (50.0)
	1	9 (50.0)
PD-L1 expression[†]	High (≥ 50%)	9 (64.3)
	Low (< 50%)	5 (35.6)
Brain metastases	Yes	3 (16.7)
	No	15 (83.3)
Smoking status	Current smoker	1 (5.6)
	Former smoker	10 (55.6)
	Never smoker	7 (38.9)
Type of prior therapy[‡]	Surgery	10 (55.6)
	Radiotherapy	4 (22.2)
	Chemotherapy	12 (66.7)
Lines of prior chemotherapy[§]	0	7 (38.9)
	1	8 (44.4)
	2	3 (17.7)

[†]PD-L1 data were not available for four patients due to lack of tumor tissues. [‡]Includes adjuvant treatment. [§]Only given in advanced diseases. ECOG, Eastern Cooperative Oncology Group.

**Table 2** Efficacy results (investigator-assessed) in the total population

Efficacy	No. of patients (%)
Best overall response	
Complete response	0 (0.0)
Partial response	4 (26.7)
Stable disease	5 (33.3)
Progressive disease	6 (40.0)
Not evaluable	3 (16.7)
Median PFS, months (95% CI)	5.9 (1.1–11.9)
Median OS, months (95% CI)	15.4 (11.1–not reached)

OS, overall survival; PFS, progression-free survival.

Response and survival outcome

All 18 patients who had received at least one cycle of study treatment were eligible for the efficacy and safety analyses. Three patients did not undergo tumor response assessment. While partial responses were achieved in four patients, no complete response occurred. Thus the primary endpoint of the study was met. The ORR was 26.7% (95% confidence interval [CI]: 7.8–55.1) with the disease control rate of 60.0% (95% CI: 32.3–83.7) (Table 2). The amount of tumor shrinkage of the target lesion from baseline for individual patients is shown in Fig 1a,b. Tumor response was not significantly correlated with the PD-L1 expression. The median duration of response was 10.3 months (95% CI: 7.8–10.3). The responses were durable and two patients still showed ongoing responses at the data analysis point (Fig 1c).

Figure 1 Response to durvalumab plus tremelimumab and treatment duration. (**a**) Waterfall plot of maximum percent change in tumor size from baseline as assessed by the investigators. (**b**) Spider plot of change in tumor size from baseline over time. (**c**) Swimmer's plot of time from start of treatment to time of last treatment. ■, Partial response; ■, Stable disease; ■, Progressive disease; ●, PD-L1 ≥ 50%; ●, PD-L1 < 50%; ■, PR; ■, SD/PD; ▲, Response start; ●, Response end; ——, Partial Response.
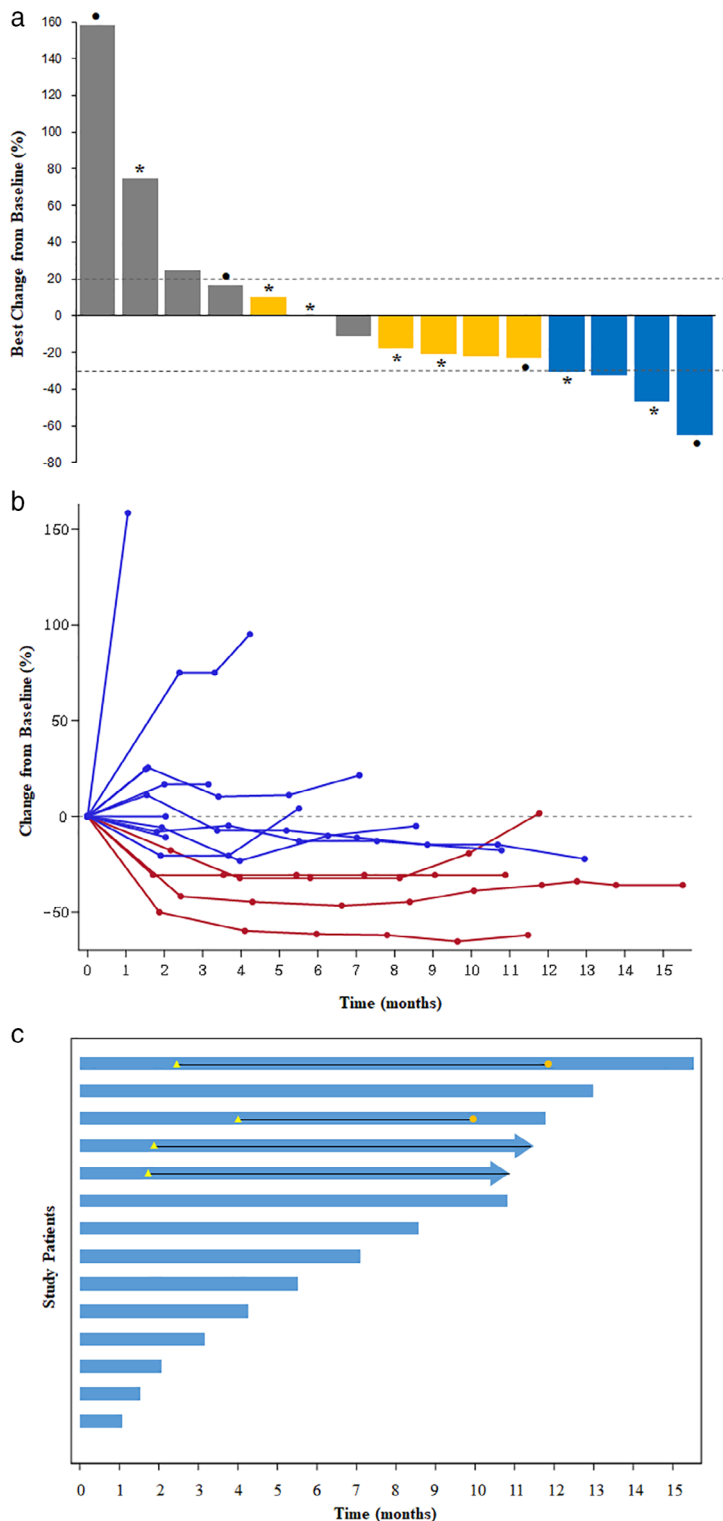
At the data cutoff of 27 February 2019, the median follow-up duration was 12.0 months (95% CI: 8.4–16.1). Median PFS and OS were 5.9 months (95% CI: 1.1–11.9) and 15.4 months (95% CI: 11.1-not reached), respectively (Table 2). The Kaplan-Meier curves of PFS and OS of the evaluated patients are shown in Fig 2a,b, respectively.
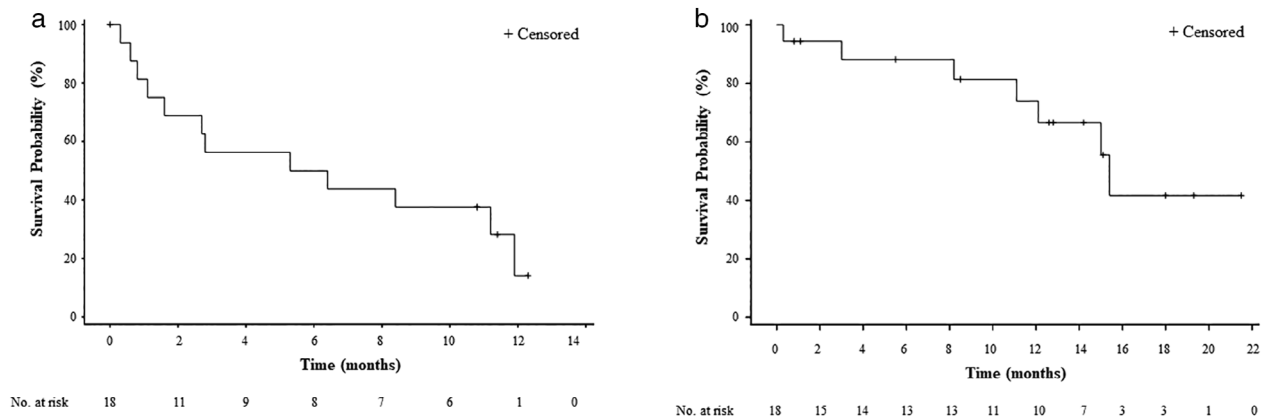
Figure 2 Kaplan-Meier curve for progression-free survival (**a**) and overall survival (**b**).

Table 3 Treatment-related adverse events (*N* = 18)

Adverse event	Any grade	Grade ≥ 3
	No. of patients (%)	
Anemia	1 (5.6)	0
Arthralgia	1 (5.6)	0
Nausea	1 (5.6)	0
Diarrhea	1 (5.6)	0
Amylase increased	3 (16.7)	1 (5.6)
Lipase increased	2 (11.1)	1 (5.6)
AST increased	1 (5.6)	0
Hyperthyroidism	1 (5.6)	0
Hypothyroidism	1 (5.6)	0
Dyspnea	1 (5.6)	0
Pneumonitis	3 (16.7)	1 (5.6)
Pruritus	4 (22.2)	1 (5.6)
Rash	4 (22.2)	0

Safety

AEs of any grade, regardless of attribution, were reported in 16 patients with 84 AEs and one serious AE. The worst grades of treatment-related AEs (TEAEs) per patient are shown in Table 3. The most frequently occurring TEAEs of any grade were pruritus (*n* = 4), rash (*n* = 4), pneumonitis (*n* = 3), and amylase elevation (*n* = 3). TEAEs of grade 3 or higher occurred in two patients. One patient had grade 4 of lipase and grade 3 of amylase elevation, respectively. This led to discontinuation of durvalumab and tremelimumab treatment. The other patient experienced grade 3 pneumonitis and grade 3 pruritus, which also led to study treatment discontinuation. Overall, grade 3 and 4 AEs were managed using the standard guidelines and the patients fully recovered. Seven deaths were reported during the study. However, none were related to the treatment, and occurred as a result of disease progression.

Genomic profiling

At the data analysis point, pretreatment tumor tissues (archival or prior to first dosing) were obtained from 12 patients that were eligible for exploring the potential molecular biomarkers via NGS. The mutational analysis results are summarized in Fig 3. The most commonly occurring genetic mutations occurred in the genetic loci such as *TP53*, *KRAS*, and *PIK3CA* in eight, three, and three patients, respectively. The *MET* exon 14 skipping mutation and *BRAF* K601E mutation were also observed in a single case each. However, no single cases of *EGFR* mutations or *ALK* translocation were detected in this study. Notably, this mutational analysis also identified a single case of *JAK2* A597fs mutation known to affect the downstream signaling of the interferon gamma receptor pathway, which interrupts PD-L1 expression and leads to primary resistance to ICIs. The patient with the *JAK2* inactivating mutation showed no tumor response with very rapid disease progression.

Circulating lymphocyte subsets

Whole blood from 14 patients with and without clinical benefit was analyzed to compare the composition of circulating lymphocyte subsets. Clinical benefit was defined as partial response or stable disease of more than six months. Patients with clinical benefit (*n* = 7) had higher proportions of circulating CD8$^+$ T cells (28.4% vs. 19.0%, *P* = 0.051) and lower CD4$^+$ to CD8$^+$ T-cell ratio (1.6 vs. 2.6, *P* = 0.116) in pretreatment blood than the ones without clinical benefit (*n* = 7) (Fig S1).

Discussion

In this study, durvalumab and tremelimumab demonstrated antitumor activity in recurrent or metastatic PSC
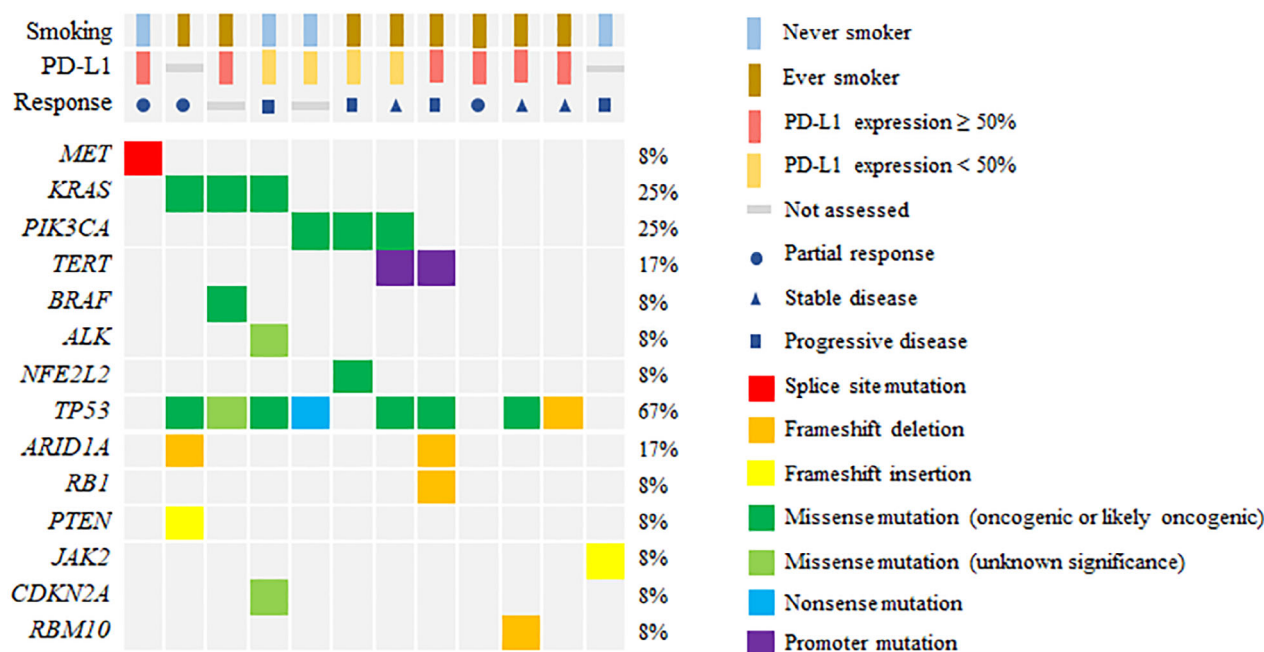
Figure 3 Integrated clinical and genomic profiling data (*N* = 12). Each column represents one patient.

and met the primary endpoint of the prespecified ORR. To the best of our knowledge, this is the first prospective trial of PSC and the first positive trial of PSC. Although a retrospective study of 39 patients with PSC demonstrating an ORR of 38.5% with ICI alone has been previously reported,[20] ICI combinations have not been explored in PSC. The combined treatment of durvalumab and tremelimumab was effective with an ORR of 26.7%. The median PFS and OS of the durvalumab and tremelimumab regimen in previous studies were reported to be much longer than those of cytotoxic chemotherapy in this clinical setting.[8, 21] Furthermore, the median duration of response was 10.3 months with the durable response of two patients still having an ongoing response at the data cutoff point. This is in contrast with the relatively short duration of response observed with cytotoxic chemotherapies. Thus, the clinical benefit achieved with this regimen is greater than that of conventional chemoagents obtained in patients with PSC.

The safety profile of durvalumab and tremelimumab reported in this study was as expected based on the known data about AEs reported from ICIs with no new safety signals identified. All AEs were manageable and consistent with those previously reported in other tumor types.[12, 22, 23] The discontinuation rate due to AEs was low with only two patients reported during the study.

High immune-cell infiltration has been described in PSC, which indicates the existence of strong antitumor immune responses.[15] However, this malignancy has a poor

outcome compared with other histological subtypes. Enhanced PD-L1 level might explain this conflict. In agreement with this, our data demonstrated that 64% of patients expressed a high level of PD-L1 (≥50% positivity). This approximately corresponds to the range of 53% to 90.2% in PSC as previously reported in other studies.[13–15] The therapeutic resistance of PSC might be also explained by other immune inhibitory mechanisms including inhibitory immune cells (regulatory T cells and myeloid-derived suppressor cells), cytokines, and expression of other immune checkpoint molecules. Further study is needed to delineate the underlying mechanisms of therapeutic resistance in this type of malignancy.

In contrast to common subtypes of lung cancer extensively studied for the presence of targetable genetic alterations, little data is available on PSC. A total of 12 cases of PSC in our study were tested for genetic-alterations in 64 genes. Of these, 11 out of 12 cases had at least one genetic alteration. Consistent with a previous study,[24] the majority of cases (eight cases, 66.7%) had *TP53* mutations and three cases (25%) had *KRAS* and *PIK3CA* mutations. One patient harbored a *MET* exon 14 skipping mutation and another patient with a *KRAS* hotspot mutation harbored a concurrent non-V600E *BRAF* mutation, as reported previously.[25, 26] Therefore, our NGS analysis for these patients suggests that PSC has a similar genotype to that of high-grade adenocarcinoma found in smokers. Of note, A *JAK2* inactivating mutation was identified in the tumor of a patient who did not respond to durvalumab

and showed progressive disease. When the *JAK2* is inactivated, PD-L1 expression is inhibited through interruption of downstream signaling of the interferon gamma receptor pathway.[27, 28] This implies that *JAK2* inactivation might be associated with primary resistance to anti-PD-1/PD-L1 inhibitors.

PD-L1 expression and circulating lymphocyte sets were analyzed to find biomarkers for treatment prediction, but there was no statistically significant finding. This could be due to an insufficient number of patients being analyzed. Appropriate selection of patients with validated biomarkers remains the key to success.

This study has several limitations. First, this trial enrolled a heterogeneous patient population with different types of previous therapies and a range of previous lines of chemotherapy. Second, as this was not a randomized trial, direct comparisons of durvalumab and tremelimumab with conventional chemotherapy or anti-PD-1/PD-L1 inhibitor monotherapy were not possible. Third, sample size was relatively small due to the rare incidence of PSC. However, this study was the first prospective trial of PSC and met the prespecified ORR primary endpoint.

In conclusion, durvalumab and tremelimumab combination therapy has demonstrated promising efficacy with a favorable toxicity profile in the treatment of PSC. Given this antitumor activity in this patient population, further randomized studies with durvalumab plus tremelimumab should be considered for patients with PSC.

Acknowledgments

Disclosure

References

1 Brambilla E, Travis WD, Colby TV, Corrin B, Shimosato Y. The new World Health Organization classification of lung tumours. *Eur Respir J* 2001; **18** (6): 1059–68.

2 Travis WD. Sarcomatoid neoplasms of the lung and pleura. *Arch Pathol Lab Med* 2010; **134** (11): 1645–58.

3 Mochizuki T, Ishii G, Nagai K *et al.* Pleomorphic carcinoma of the lung: Clinicopathologic characteristics of 70 cases. *Am J Surg Pathol* 2008; **32** (11): 1727–35.

4 Rossi G, Cavazza A, Sturm N *et al.* Pulmonary carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements: A clinicopathologic and immunohistochemical study of 75 cases. *Am J Surg Pathol* 2003; **27** (3): 311–24.

5 Ung M, Rouquette I, Filleron T *et al.* Characteristics and clinical outcomes of sarcomatoid carcinoma of the lung. *Clin Lung Cancer* 2016; **17** (5): 391–7.

6 Yendamuri S, Caty L, Pine M *et al.* Outcomes of sarcomatoid carcinoma of the lung: A surveillance, epidemiology, and end results database analysis. *Surgery* 2012; **152** (3): 397–402.

7 Bae HM, Min HS, Lee SH *et al.* Palliative chemotherapy for pulmonary pleomorphic carcinoma. *Lung Cancer* 2007; **58** (1): 112–5.

8 Lee J, Jung HA, Kim Y *et al.* Efficacy of mesna, doxorubicin, ifosfamide, and dacarbazine (MAID) in patients with advanced pulmonary pleomorphic carcinoma. *Lung Cancer* 2018; **122**: 160–4.

9 Brahmer J, Reckamp KL, Baas P *et al.* Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015; **373** (2): 123–35.

10 Herbst RS, Baas P, Kim DW *et al.* Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. *Lancet* 2016; **387** (10027): 1540–50.

11 Reck M, Rodriguez-Abreu D, Robinson AG *et al.* Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 2016; **375** (19): 1823–33.

12 Antonia S, Goldberg SB, Balmanoukian A *et al.* Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: A multicentre, phase 1b study. *Lancet Oncol* 2016; **17** (3): 299–308.

13 Kim S, Kim MY, Koh J *et al.* Programmed death-1 ligand 1 and 2 are highly expressed in pleomorphic carcinomas of the lung: Comparison of sarcomatous and carcinomatous areas. *Eur J Cancer* 2015; **51** (17): 2698–707.

14 Velcheti V, Rimm DL, Schalper KA. Sarcomatoid lung carcinomas show high levels of programmed death ligand-1 (PD-L1). *J Thorac Oncol* 2013; **8** (6): 803–5.

15 Vieira T, Antoine M, Hamard C *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**: 51–8.

16 Travis WD, Brambilla E, Nicholson AG *et al.* The 2015 World Health Organization classification of lung tumors: Impact of genetic, clinical and radiologic advances since the 2004 classification. *J Thorac Oncol* 2015; **10** (9): 1243–60.

17 Topalian SL, Hodi FS, Brahmer JR *et al.* Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012; **366** (26): 2443–54.

18 Hendry S, Byrne DJ, Wright GM *et al.* Comparison of four PD-L1 immunohistochemical assays in lung cancer. *J Thorac Oncol* 2018; **13** (3): 367–76.

19 Im SW, Chae J, Jang SS *et al.* A newly developed capture-based sequencing panel for genomic assay of lung cancer. *Genes Genomics* 2020; **42**: 751–9.

20 Domblides C, Monnet I, Mazieres J *et al.* Efficacy of immune checkpoint inhibitors in lung sarcomatoid carcinoma: Data from a French multicentric cohort. *Ann Oncol* 2018; **29** (suppl_8): viii400–41. https://doi.org/10.1093/annonc/mdy1288.

21 Vieira T, Girard N, Ung M *et al.* Efficacy of first-line chemotherapy in patients with advanced lung sarcomatoid carcinoma. *J Thorac Oncol* 2013; **8** (12): 1574–7.

22 Bondarenko I, Juan-Vidal O, Pajkos G *et al.* Preliminary efficacy of durvalumab plus tremelimumab in platinum-refractory/resistant ED-SCLC from arm a of the phase II BALTIC study. *Ann Oncol* 2018; **29** (Suppl 8): viii596–602. https://doi.org/10.1093/annonc/mdy1298.

23 Siu LL, Even C, Mesia R *et al.* Safety and efficacy of durvalumab with or without tremelimumab in patients with PD-L1-low/negative recurrent or metastatic HNSCC: The phase 2 CONDOR randomized clinical trial. *JAMA Oncol* 2019; **5** (2): 195–203.

24 Terra SB, Jang JS, Bi L *et al.* Molecular characterization of pulmonary sarcomatoid carcinoma: Analysis of 33 cases. *Mod Pathol* 2016; **29** (8): 824–31.

25 Kwon D, Koh J, Kim S *et al.* MET exon 14 skipping mutation in triple-negative pulmonary adenocarcinomas and pleomorphic carcinomas: An analysis of intratumoral MET status heterogeneity and clinicopathological characteristics. *Lung Cancer* 2017; **106**: 131–7.

26 Tissot C, Couraud S, Tanguy R, Bringuier PP, Girard N, Souquet PJ. Clinical characteristics and outcome of patients with lung cancer harboring BRAF mutations. *Lung Cancer* 2016; **91**: 23–8.

27 Neubauer H, Cumano A, Muller M, Wu H, Huffstadt U, Pfeffer K. Jak2 deficiency defines an essential developmental checkpoint in definitive hematopoiesis. *Cell* 1998; **93** (3): 397–409.

28 Perner F, Perner C, Ernst T, Heidel FH. Roles of JAK2 in aging, inflammation, hematopoiesis and malignant transformation. *Cell* 2019; **8** (8): 854.

Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

Figure S1. Comparison of pretreatment lymphocyte subsets in blood between patients with clinical benefit (*n* = 7) and those without clinical benefit (*n* = 7). Clinical benefit was defined as partial response or stable disease of more than six months. Error bars represent standard deviation of the mean value.