Original Article

Efficacy of first-line immune checkpoint inhibitors in pulmonary sarcomatoid carcinoma

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Background: Pulmonary sarcomatoid carcinomas (PSC) are notorious for their poor prognosis and resistance to chemotherapy. The literature suggests that immunotherapy might be effective against this aggressive tumor. This study aims to evaluate the efficacy of immunotherapy, either alone or combined with chemotherapy, as first-line treatment for PSC patients.

Methods: In a retrospective, multicentric, real-world study conducted between July 2017 and April 2021, patients with stage III (ineligible for surgery or radio-chemotherapy) or stage IV PSC were enrolled. These patients received their first-line treatment with immunotherapy and were categorized into two groups based on their treatment modality: the immuno-chemotherapy (IO CT) group or the immunotherapy-alone (IO) group.

Results: This study analyzed a population of 34 patients from eight different hospital centers. In this cohort, the objective response rate (ORR) was 56%, median duration of response was 20.5 months, median progression-free survival (PFS) was 5.11 months, and median overall survival (OS) 13.9 months. Demographic characteristics remained consistent among the treatment groups except for the age (54.0- and 71.0-year-old in the IO CT and IO group, respectively, P=0.02). The IO CT group demonstrated an ORR

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of 64.0%, a median PFS at 8.72 months, and a median OS of 16.08 months, while the IO group displayed respective values of 52.0%, 3.45 months, and 13.11 months.

Conclusions: This study showed the potential efficacy of immunotherapy as a first-line treatment for PSC. While acknowledging the retrospective nature of the study, our findings suggest a trend favoring the combination of IO CT over IO alone in these patients.

Keywords: Pulmonary sarcomatoid carcinomas (PSC); immunotherapy; immunochemotherapy

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Introduction

Pulmonary sarcomatoid carcinomas (PSC) are rare tumors, accounting for 0.4% of lung malignancies (1). PSC are associated with a shorter overall survival (OS) than conventional non-small cell lung cancer (NSCLC). Prior to the era of immunotherapy, metastatic PSC patients had a median OS ranging from 3.0 to 8.5 months (2-4). This poor prognosis can be attributed, at least in part, to the resistance of these tumors to standard chemotherapies (5). In 2020, our research group published a retrospective study involving 37 patients with PSC who received immunotherapy as a second-line treatment (6). The study reported an encouraging objective response rate (ORR) of 40.5%, a progression-free survival (PFS) of 4.9 months and an OS of 12.7 months. Based on these results, the primary objective of this retrospective study was to comprehensively assess the efficacy of immunotherapy, both as a monotherapy [immunotherapy alone (IO)] and in combination with chemotherapy (IO CT), as a first-line treatment of PSC. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-263/rc).

Highlight box

Key findings

- This manuscript confirms the efficacy of immunotherapy in the first-line treatment of metastatic pulmonary sarcomatoid carcinomas (PSC), as monotherapy or in combination with chemotherapy.

What is known and what is new?

- PSC have a poor prognosis and are associated with resistance to chemotherapy. Immunotherapy appears to be an effective treatment, but its use as monotherapy or in combination with chemotherapy has not been specifically evaluated for this type of tumor as first-line therapy.
- Our findings suggest a trend favoring the combination of immuno-chemotherapy (IO CT) over immunotherapy alone in these patients.

What is the implication, and what should change now?

- First-line treatment for metastatic PSC should incorporate immunotherapy. Further explorations in prospective studies will be necessary to determine the potential superiority of IO CT combinations.

Methods

Patients and study design

All patients with histologically proven, stage III (ineligible for surgery or radio-chemotherapy) or stage IV PSC, and who received a first line of treatment with immunotherapy (either in combination with chemotherapy or other immunotherapy, or as monotherapy) between July 2017 and April 2021 were included in this analysis. Patients who had received chemotherapy as part of curative treatment (surgery or radio-chemotherapy) prior to the metastatic relapse were eligible. Patient data were searched in the archives of the Pneumology, Thoracic Oncology and Medical Oncology departments of 13 hospitals in the Ile-de-France region and collected retrospectively and anonymously from the medical records. The detailed histological reports with programmed cell death 1 ligand 1 (PD-L1) status at diagnosis were retrieved with a centralized reviewing (D.D.). Molecular biology reports were retrieved, with a centralized reviewing (K.L.). The routine panels used have limited sensitivity for detecting STK11 (covering only 30% of anomalies) and do not include KEAP1. Imaging reports at diagnosis and at each evaluation were analyzed [computed tomography (CT) and positron emission tomography-CT (PET-CT)] (G.B.).

Evaluation criteria

Radiological responses were defined in accordance with the Response Evaluation Criteria In Solid Tumors (RECIST), version 1.1 (7). The ORR was defined as the proportion of patients achieving a partial or complete response according to RECIST. The disease control rate (DCR) was defined as the proportion of patients achieving stabilization, partial or complete response according to RECIST. PFS was defined as the interval between the start of a line of therapy to disease progression on that treatment. OS was defined as the time from initiation of treatment to death.

Data were updated 2 years after the last patient was included (April 2023).

Statistical analysis

The patients included were categorized according to their treatment modality into two groups: the IO CT group, comprising patients who received a combination of immunotherapy and chemotherapy, and the IO group, comprising patients who received either immunotherapy monotherapy or dual immunotherapy. Non-parametric tests (χ^2, Fisher and Mann-Whitney) were used to compare these two treatment groups. OS and PFS were estimated using the Kaplan-Meier method. Univariate and multivariate analyses of clinical data were performed to identify prognostic variables. All statistical analyses were conducted using GraphPad Prism version 10.0.3. Univariate analysis was performed with the use of an unpaired Student's *t*-test or fisher's exact test, as appropriate. Multivariate logistic-regression analysis was then performed, with backward stepwise analysis, to identify independent prognostic variables. All comparisons of clinical variables with a P value of less than 0.20 by univariate analysis were entered into the model. A P value of less than 0.05 was considered to indicate statistical significance.

Ethical considerations

The study protocol and the patient information note were reviewed and approved by the "Committee for the Evaluation of Observational Research Protocols" of the "French Respiratory Society (SPLF)" (No. CEPRO 2021-016). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All participating hospitals/institutions were informed and agreed with this study. Patients under care at the investigational centers were informed of the option to withhold their medical data from being used for health research. None of the patients included in the study objected to the utilization of their medical records for research purposes. Patient data were anonymized at the point of collection and retained at Cochin Hospital, APHP, Paris.

Results

Patient characteristics

Thirteen centers agreed to participate in the study, with eight of them collectively enrolling a total of 34 patients (see *Table 1*). They were all non-irradiable stage III or stage IV. Among them, ten patients (29.4%) underwent surgery, and histological diagnosis was available for these patients on complete surgical specimens. For other patients, the diagnosis of PSC was made from small biopsies showing both an epithelial and sarcomatoid component. This diagnosis was supported using pan-cytokeratin (AE1/AE3, CAM5.2), epithelial membrane antigen (EMA), p40, and TTF-1 immunostaining (8). Most tumors (79.4%) were pleomorphic carcinomas. PD-L1 status was assessable for all patients, and all tumors exhibited positive PD-L1 expression (above the 1% threshold), with 31 tumors (91.2%) having a PD-L1 expression equal to or exceeding 50%. The clones used for PD-L1 status were QR1 (n=11), E1L3N (n=12), SP263 (n=1), and 22C3 (n=3) and not specified for seven patients. The mutational status of patients is summarized in Table S1. Next-generation sequencing analysis was available for 32 patients (94.1%). Among them, 20 patients (62.5%) carried at least one *KRAS*, *MET*, or *BRAF* oncogenic mutation. No patient was found to have an *EGFR* mutation, *ALK* or *ROS1* fusion. No co-alterations of KEAP1 or STK11 were identified.

Patients were categorized according to treatment modality. In the IO CT group, patients received immunotherapy with pembrolizumab combined with either paclitaxel (n=4) or pemetrexed (n=7). In the IO group, patients received either pembrolizumab (n=21) or nivolumab-ipilimumab (n=2). The criteria for selecting between ICI monotherapy and ICI combined with chemotherapy were based on the prevailing guidelines at the time of patient treatment. The characteristics of the patients are summarized in *Table 1*.

The clinical characteristics were similar in the two groups, except for age (54.0 years in the IO CT group *vs.* 71.0 years in the IO group, P=0.02). Only three patients

Table 1 Population characteristics by treatment

Characteristics	Total (n=34)	Immunotherapy + chemotherapy (n=11)	Immunotherapy without chemotherapy (n=23)
Sex			
Male	29 (85.3)	10 (90.9)	19 (82.6)
Female	5 (14.7)	1 (9.1)	4 (17.4)
Age (years)	67 [32–86]	54.0 [41–80]	71.0 [32–86]
Smoking status			
Non-smoker	2 (5.9)	0	2 (8.7)
Former smoker	13 (38.2)	6 (54.5)	7 (30.4)
Current smoker	19 (55.9)	5 (45.5)	14 (60.9)
Pack years	35 [0–90]	35 [20–40]	35 [0–80]
Disease stage			
IIIA to IIIC	4 (11.8)	1 (9.1)	3 (13.0)
IVA to IVB	30 (88.2)	10 (90.9)	20 (87.0)
Brain metastasis			
Yes	7 (20.6)	2 (18.2)	5 (21.7)
No	27 (79.4)	9 (81.8)	18 (78.3)
ECOG PS score			
0	16 (47.1)	6 (54.5)	10 (43.5)
1	12 (35.3)	4 (36.4)	8 (34.8)
2	6 (17.6)	1 (9.1)	5 (21.7)
Histologic type of tumor			
Pleomorphic carcinoma	27 (79.4)	9 (81.8)	18 (78.3)
With adenocarcinomatous component	10 (29.4)	3 (27.3)	7 (30.4)
With squamous component	3 (8.8)	1 (9.1)	2 (8.7)
Giant cell carcinoma	2 (5.9)	1 (9.1)	1 (4.3)
Spindle cell carcinoma	5 (14.7)	1 (9.1)	4 (17.4)
Diagnostic technique			
Chest surgery	10 (29.4)	3 (27.3)	7 (30.4)
Transthoracic puncture	18 (52.9)	6 (54.5)	12 (52.2)
Bronchoscopy	1 (2.9)	0	1 (4.3)
Pleuroscopy	2 (5.9)	0	2 (8.7)
Other biopsy	3 (8.8)	2 (18.2)	1 (4.3)
PD-L1 status			
≥75%	14 (41.2)	7 (63.6)	7 (30.4)
≥50%, <75%	17 (50.0)	1 (9.1)	16 (69.6)
≥1%, <50%	3 (8.8)	3 (27.3)	0
<1%	0	0	0

Table 1 *(continued)*

Table 1 *(continued)*

Characteristics	Total (n=34)	Immunotherapy + chemotherapy (n=11)	Immunotherapy without chemotherapy (n=23)
Mutational status			
KRAS mutation	15 (44.1)	5 (45.5)	10 (43.5)
MET ex.14 skipping mutation	5 (14.7)	1 (9.1)	4 (17.4)
BRAF non-V600E	3 (8.8)	2 (18.2)	1 (4.3)
EGFR	0	0	0
TP53	11 (32.4)	5 (45.5)	6 (26.1)

Data are presented as median [range] or n (%). ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death 1 ligand 1.

had PD-L1 expression below the 50% threshold, and all of them were in the IO CT group. Molecular characteristics were comparable in both groups.

Efficiency data—overall population

In the overall population, the ORR was 56% (n=19/34) and the DCR was 68% (n=23/34) (Figure S1). Three patients had a complete response (8.8%), 16 had a partial response (47.1%), 4 were stabilized (11.8%) and 11 had progressive disease (32.4%). The median duration of response was 20.5 months. The median PFS was 5.11 months, and the median OS was 13.9 months (Figure S1). First-line treatment was discontinued in 30 patients (88.2%), mainly due to progression (47.0%), death (17.6%), but also prolonged response exceeding 2 years (11.7%) and less frequently treatment-related toxicity (8.8%). Four patients were on active surveillance following a complete response and five patients were still receiving treatment at the last data update. Among the patients who discontinued first-line treatment, 15 (50%) received a second line. Out of the five patients with *MET* exon 14 skipping mutation, one received targeted therapy as second-line (crizotinib), two died during the first-line treatment, one exhibited a prolonged response for first- and second-line treatment (Table S2). None of the patients with *KRAS* G12C mutations received targeted therapy due to the study's inclusion period, during which no therapy targeting *KRAS* was available.

Efficiency data—according to treatment

Efficacy parameters were subsequently evaluated based on the treatment administered.

As shown in *Figure 1*, there was a trend although not statistically significant for a better ORR (P=0.71) and DCR (P=0.06) in the IO CT group compared to the IO group. A similar trend was noted for PFS (P=0.12) and OS (P=0.33). The median PFS and OS for the IO CT group were 8.72 and 16.08 months, respectively, while those for the IO group were 3.45 and 13.11 months (*Figure 1*).

Factor predictive of treatment efficacy

Univariate and multivariate analyses were carried out to identify prognostic factors in the study population. Univariate analysis on OS showed that performance status (PS) was the sole significant prognostic factor. We did not find any statistical difference PFS between stage III and stage IV patients. The multivariate analysis incorporated clinical variables with a P value of less than 0.20 from the univariate analysis. Inclusion of variables such as presence of cerebral metastasis, PS and high expression of PD-L1 (≥75%) showed that PS remained the sole predictive factor for a better OS (*Figure 2*). High PD-L1 did not exhibit a significant association with improved OS in both univariate and multivariate analyses in this patient cohort.

Discussion

In this cohort of 34 patients with metastatic PSC, first-line immunotherapy with or without chemotherapy was associated with an ORR of 56%, a PFS of 5.11 months and an OS of 13.9 months.

Phase III trials investigating immunotherapy with or without chemotherapy in non-sarcomatoid NSCLC have shown superior PFS and OS compared to our study (9-22)

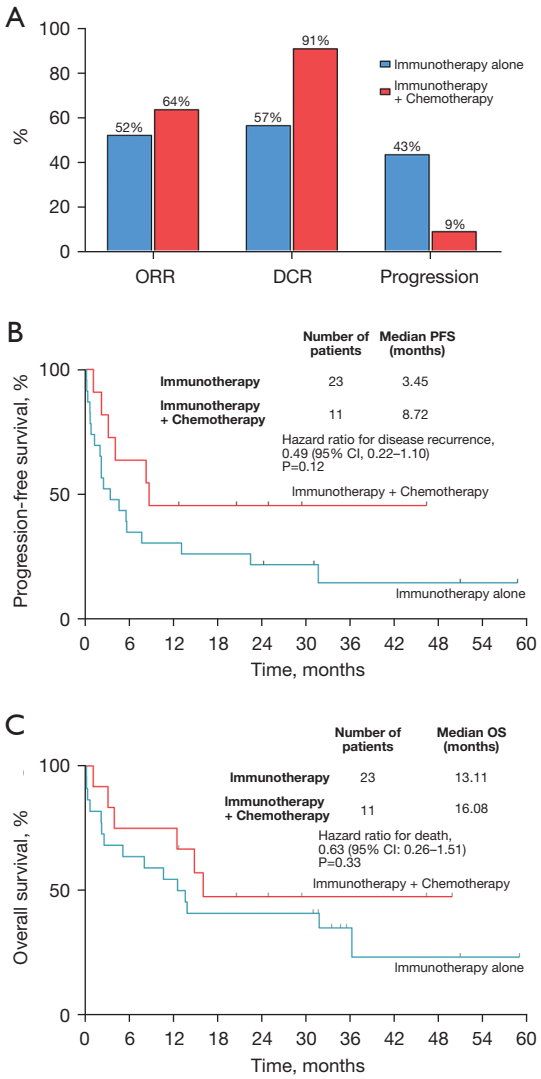

Figure 1 Immunotherapy efficacy according to treatment. (A) ORR, DCR and progression. (B) Kaplan-Meier plot for PFS. (C) Kaplan-Meier plot for OS. ORR, objective response rate; DCR, disease control rate; OS, overall survival; PFS, progression-free survival; CI, confidence interval.

(Table S3). This discrepancy may be partially attributed to the poorer prognosis of PSCs and the more stringent eligibility criteria in phase III trials. Notably, these trials excluded patients with a PS greater than 1, whereas 17.6% of our study participants had a PS of 2. Nevertheless, when juxtaposed with historical data on PSC treatment before the immunotherapy era, where the ORR was below 20%, and OS ranged from 3.0 to 8.5 months, our findings underscore the benefits of immunotherapy for PSC (5,23).

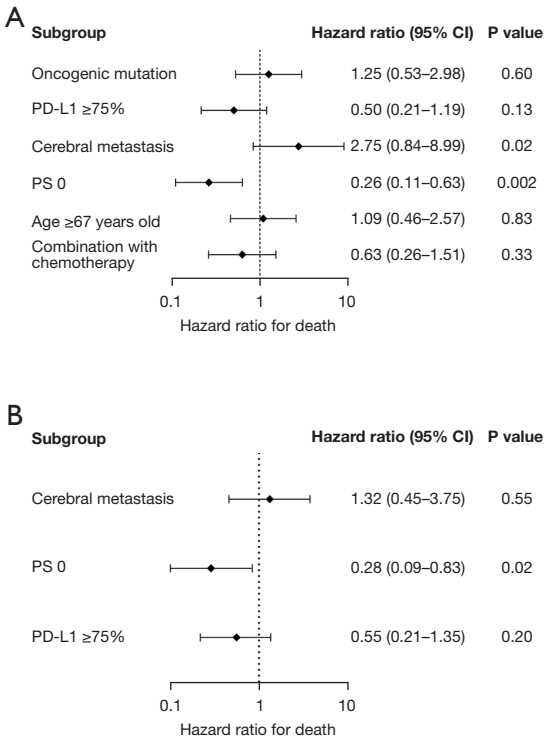

Figure 2 Prognostic factors in patients with pulmonary sarcomatoid carcinoma. (A) Univariate analysis on overall survival. (B) Multivariate analysis on overall survival. PD-L1, programmed cell death 1 ligand 1; PS, performance status; CI, confidence interval.

Comparable findings have been reported by other teams in studies of PSCs treated with immunotherapy, either with or without chemotherapy (24-29) (Table S4). Across these studies, PFS ranged from 4.9 to 10.3 months, while OS ranged from 12.7 to 22.8 months. These studies are also retrospective, with sample sizes similar to our study. However, they differ in terms of treatment-line (first or subsequent), immunotherapy types (anti-PD-1, anti-PD-L1, anti-CTLA4), and whether combined with chemotherapy or anti-angiogenic agents, making direct comparisons challenging.

The choice among the two treatment options—immunotherapy with chemotherapy or immunotherapy alone—is particularly relevant for the management of PSCs, which are frequently associated with high PD-L1 expression on tumor cells (TC) (30): in our series, 91.2% of patients had PD-L1 TC expression greater than or equal to 50%. The limited response rate to conventional chemotherapies and the high PD-L1 TC expression of PSCs suggest that treatment

with immunotherapy in monotherapy might be preferred in this situation. However, the frequent sarcopenia of PSC patients, the high tumor burden and the rapid progression of these cancers (2,5,31-33) could argue in favor of an approach combining immunotherapy and chemotherapy. By grouping patients based on their treatment, a trend emerged in favor of immunotherapy with chemotherapy over immunotherapy alone in terms of ORR, PFS, and OS.

Our study has several limitations, particularly a relatively small sample size and its retrospective nature. These aspects may raise questions about the comparability of patient characteristics between the two groups, notably regarding age. Although other variables such as PS did not exhibit a significant difference between the two groups, it is worth noting that 21.7% of patients in the IO group had a PS of 2, compared to 9.1% in the IO CT group, adding complexity to the interpretation of results.

The frequent occurrence of *KRAS* G12C mutations and *MET* exon 14 skipping in PSC patients emphasizes the need for a clearer understanding of the role of targeted therapies in managing these tumors (34). While studies have shown the effectiveness of immunotherapy for treating metastatic NSCLC with these mutations (35,36), caution is warranted due to increased toxicities observed in patients undergoing sequential immunotherapy followed by targeted therapy (37). In our cohort, 62.5% (n=20/32) had a driver mutation (Table S1), but only one received targeted therapy after immunotherapy, preventing a comprehensive assessment of toxicity in this context. In our cohort, the presence or absence of activating mutations (*KRAS*, *BRAF*, *MET* exon 14) did not predict immunotherapy efficacy. None of the patients had an *EGFR* mutation or *ALK* translocation, typically associated with a poorer prognosis under immunotherapy (38,39).

Conclusions

Our retrospective study of advanced or metastatic PSC patients treated with IO alone or in combination with chemotherapy demonstrated an improvement in clinical outcomes with a trend toward prolonged PFS and OS in patients treated with the combination of IO and chemotherapy. Prospective studies are needed to determine the optimal treatment modality for these patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-263/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-263/dss

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board for AMGEN, AstraZeneca, Bristol Myers Squibb, F. Hoffmann-La Roche, Janssen, MSD Oncology, Lilly and Merck KGaA. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol and the patient information note were reviewed and approved by the "Committee for the Evaluation of Observational Research Protocols" of the "French Respiratory Society (SPLF)" (No. CEPRO 2021-016). All participating hospitals/institutions were informed and agreed with this study. Patients under care at the investigational centers were informed of the option to withhold their medical data from being used for health research. None of the patients included in the study objected to the utilization of their medical records for research purposes.

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Supplementary

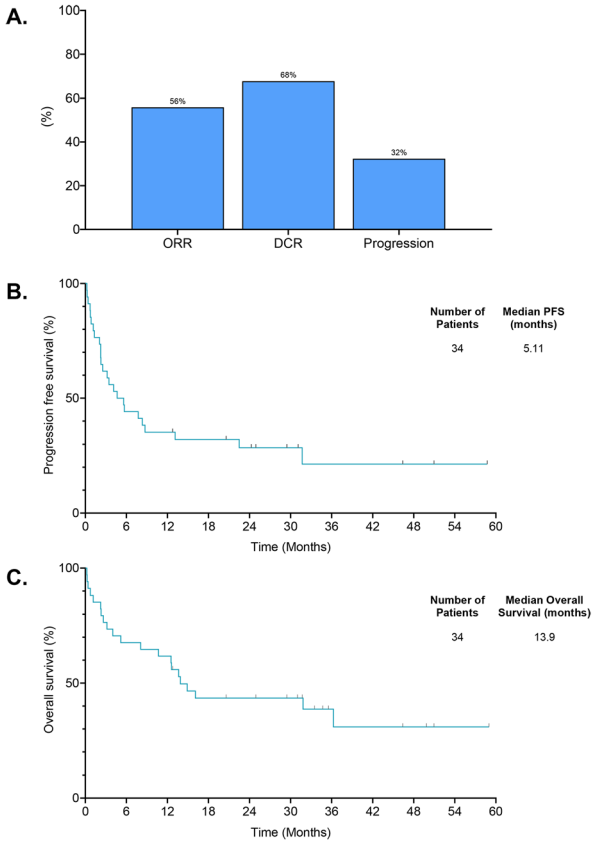

Figure S1 Efficacy of immunotherapy in overall population. (A) ORR, DCR and progression. (B) Kaplan Meier plot for PFS. (C) Kaplan Meier plot for OS. ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival.

Table S1 Mutational status of the population study

Variables	Total (n=34)
NGS, n (%)	
Not performed	2 (5.9)
Oncogenic mutation, n (%)	
Mutated	20 (58.8)
KRAS mutation	15 (44.1)
KRAS G12C	9 (26.5)
KRAS non-G12C	6 (17.6)
MET ex.14 skipping mutation	5 (14.7)
BRAF non-V600E	3 (8.8)
Co-alterations, n (%)	
EGFR	
EGFR amplification	2 (5.9)
KRAS	
KRAS amplification	1 (2.9)
TP53	11 (32.4)
PTEN	2 (5.9)
AKT1	1 (2.9)
MAP2K1	1 (2.9)
CDKN2A	1 (2.9)
TERT	1 (2.9)
PIK3CA	1 (2.9)

NGS, next-generation sequencing.

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Table S2 Characteristics of MET exon 14 mutated patients

No.	Sex	Age at diagnosis (years)	Tabagism [pack years]	Exon 14 mutation (NM_001127500)	Co-mutation	PD-L1 TC (%)	First line treatment	Number of cycles (first line)	Best response (first line)	PFS (first line) (months)	Cause of first-line treatment discontinuation	TKI treatment after first line?[†]	Overall survival (months)
1	Male	78	Former smoker [20]	c.3082G>C; p.?	No	75	Pembrolizumab	43	Partial response	31.7	Progression	No	Alive at the end of follow-up (34.8)
2	Female	71	Non-smoker	c.3028G>A; p.?	No	70	Pembrolizumab	1	Progression	0.7	Progression	No	10.7
3	Male	71	Smoker [50]	c.3028+1G>T; p.?	No	100	Pembrolizumab	2	Progression	0.9	Progression	Yes (crizotinib, partial response, death by peritonitis complicating a perforated ulcer)	2.6
4	Male	69	Smoker [40]	c.3028G>A; p.?	BRAF exon 15: c.1801A>G; p.Lys601Glu	100	Pembrolizumab	5	Stabilisation	3.5	Deceased. Myocarditis, possible imputability to pembrolizumab	No	5.2
5	Male	68	Former smoker [20]	c.2942-19_2961del; p.?	No	10	Pembrolizumab, carboplatin, pemetrexed	4	Stabilisation	2.3	Deceased. Severe SARS-COV2 pneumonia	No	3.2

[†], during the follow-up period, no other therapy targeting MET than crizotinib was available in France (except for clinical trials). PD-L1, programmed cell death 1 ligand 1; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; SARS-COV2, severe acute respiratory syndrome coronavirus 2.

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Table S3 First-line immunotherapy for NSCLC

Study	Treatment	Type	PD-L1 (%)	Groups	ORR (%)	PFS (months)	OS (months)
This study (immunotherapy or immunotherapy + chemotherapy)							
Birsen *et al.*	IO or IO CT	PSC	–	IO	52.0	3.4	13.1
				IO CT	64.0	8.7	16.1
Immunotherapy versus chemotherapy							
Keynote-024 (update)	Pembrolizumab or CT	NSCLC	≥50	IO	46.1	7.7	26.3
				CT	31.1	5.5	13.4
CheckMate-026	Nivolumab or CT	NSCLC	≥5	IO	26.0	4.2	14.4
				CT	33.0	5.9	13.2
Impower-110	Atezolizumab or CT	NSCLC	≥1	IO	40.2	8.2	18.9
				CT	28.6	5.0	14.7
Empower-Lung1	Cemiplimab or CT	NSCLC	≥50	IO	39.0	8.2	NR
				CT	20.0	5.7	14.2
Immunotherapy + chemotherapy versus chemotherapy							
KEYNOTE-189	Pembrolizumab + chemotherapy or CT	Non-squamous NSCLC	–	IO CT	48.3	9.0	22
				CT	19.9	4.9	10.6
IMpower-132	Atezolizumab + chemotherapy or CT	Non-squamous NSCLC	–	IO CT	47.0	7.6	17.5
				CT	32.0	5.2	13.6
ORIENT-11	Sintilimab + CT or CT	Non-squamous NSCLC	–	IO CT	51.9	8.9	NR
				CT	29.8	5.0	NR
RATIONALE-304	Tislelizumab + CT or CT	Non-squamous NSCLC	–	IO CT	57.4	9.7	NR
				CT	36.9	7.6	NR
CameL	Camrelizumab + CT or CT	Non-squamous NSCLC	–	IO CT	55.1	11.0	27.1
				CT	32.9	6.5	19.8
KEYNOTE-407	Pembrolizumab + chemotherapy or CT	Squamous NSCLC	–	IO CT	62.2	8.0	17.2
				CT	38.8	5.1	11.6
IMpower-131	Atezolizumab + chemotherapy or CT	Squamous NSCLC	–	IO CT	49.7	6.3	14.2
				CT	41.0	5.6	13.5
ORIENT-12	Sintilimab + CT or CT	Squamous NSCLC	–	IO CT	44.7	5.5	NR
				CT	35.4	4.9	NR
RATIONALE-307	Tislelizumab + CT or CT	Squamous NSCLC	–	IO CT	72.5	7.6	NR
				CT	49.6	5.5	NR
CameL-sq	Camrelizumab + CT or CT	Squamous NSCLC	–	IO CT	64.8	8.5	NR
				CT	36.7	4.9	14.5
Double immunotherapy versus chemotherapy							
CHECKMATE-9LA	Nivolumab + ipilimumab + CT or CT	NSCLC	–	dIO	38	6.4	15.8
				CT	25	5.3	11.0
CHECKMATE 227	Nivolumab + ipilimumab + CT or nivolumab or CT	NSCLC	≥1	IO	36	5.1	17.1
				dIO	28	4.2	15.7
				CT	30	5.6	14.9

NSCLC, non-small cell lung cancer; PD-L1, programmed cell death 1 ligand 1; ORR, objective response rate; PSC, pulmonary sarcomatoid carcinomas; OS, overall survival; IO, immunotherapy; CT, chemotherapy; dIO, double immunotherapy; NR, non-reached.

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Table S4 Studies investigating the efficacy of immunotherapy in patients with metastatic PSC

Author	Publication year	Treatment line	Type of treatment	Type of study	Number of patients	Median OS (months)	Median PFS (months)	ORR (%)	DCR (%)
Birsen *et al.*	This study	First line	Pembrolizumab alone or pembrolizumab + platinum doublet or nivolumab + ipilimumab	Retrospective	34	13.9	5.11	55.8	67.6
Domblides *et al*.	2020	Second-line or subsequent-line	Nivolumab alone or Pembrolizumab alone or Atezolizumab alone	Retrospective	37	12.7	4.89	29.7	56.8
Inomata *et al*.	2023	First-line (63.6%) or subsequent-line (36.4%)	Nivolumab alone or pembrolizumab alone or platinum doublet + pembrolizumab or platinum doublet + atezolizumab or nivolumab + ipilimumab	Retrospective	22	NR	9.6	NA	NA
Kim *et al*.	2020	First-line	Durvalumab + tremelimumab	Prospective (phase II)	18	15.4	5.9	26.7	60.0
Lee *et al*.	2020	First-line (4.1%) or subsequent-line (95.9%)	Nivolumab alone or pembrolizumab alone or atezolizumab alone	Retrospective	49	22.2	7.2	49.0	NA
Qian *et al*.	2022	First-line	Sintilimab alone or camrelizumab alone or anlotinib + tislelizumab or anlotinib + camrelizumab or anlotinib + sintilimab or anlotinib + pembrolizumab	Retrospective	21	22.8	9.2	57.2	81.0
Zhou *et al*.	2022	First-line (85.7%) or subsequent-line (14.3%)	ICI alone or chemotherapy + ICI or chemotherapy + ICI + bevacizumab	Retrospective	42	NR	10.3	73.8	92.9
Chu *et al*.	2023	First-line	Camrelizumab + famitinib	Prospective	15	18.2	7.8	46.7	86.7

PSC, pulmonary sarcomatoid carcinomas; ICI, immune checkpoint inhibitor; OS, overall survival; PFS, progression-free survival; ORR, overall response rate; DCR, disease control rate; NR, non-reached; NA, non-available.

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