



HAL
open science

Efficacy of Immune Checkpoint Inhibitors in Lung Sarcomatoid Carcinoma

Charlotte Domblides, Karen Leroy, Isabelle Monnet, Julien Mazières, Fabrice Barlesi, Valérie Gounant, Simon Baldacci, Bertrand Mennequier, Anne-Claire Toffart, Clarisse Audigier-Valette, et al.

► **To cite this version:**

Charlotte Domblides, Karen Leroy, Isabelle Monnet, Julien Mazières, Fabrice Barlesi, et al.. Efficacy of Immune Checkpoint Inhibitors in Lung Sarcomatoid Carcinoma. Congrès de pneumologie de langue française, Jan 2019, Marseille, France. pp.860-866, 10.1016/j.jtho.2020.01.014 . hal-02633843

HAL Id: hal-02633843

<https://hal.science/hal-02633843v1>

Submitted on 22 Aug 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Efficacy of Immune Checkpoint Inhibitors in Lung Sarcomatoid Carcinoma

Charlotte Domblides, MD^{1,2}, Karen Leroy, MD, PhD³, Isabelle Monnet, MD⁴, Julien Mazières, MD, PhD⁵, Fabrice Barlesi, MD, PhD⁶, Valérie Gounant, MD⁷, Simon Baldacci, MD⁸, Bertrand Mennequier, MD⁹, Anne-Claire Toffart, MD¹⁰, Clarisse Audigier-Valette, MD¹¹, Ludovic Doucet, MD¹², Etienne Giroux-Leprieur, MD¹³, Florian Guisier, MD¹⁴, Charles Ricordel, MD, PhD¹⁵, Olivier Molinier, MD¹⁶, Maurice Perol, MD¹⁷, Eric Pichon, MD¹⁸, Gilles Robinet, MD¹⁹, Dorine Templement-Grangerat, MD²⁰, Anne-Marie Ruppert, MD^{21,22}, Nathalie Rabbe^{23,24}, Martine Antoine, MD²⁵, and Marie Wislez, MD, PhD^{23,24}

¹Department of Medical Oncology, Hôpital Saint-André, Bordeaux University Hospital-CHU Bordeaux, France

²ImmunoConcEpt, CNRS UMR 5164, University of Bordeaux, Bordeaux, France; Bordeaux University, Bordeaux 33076, France

³AP-HP, Groupe Hospitalier HUPC, Hôpital Cochin, Service de Génétique et Biologie Moléculaires, F-75014, Paris, France

⁴Service Pneumologie, CHI de Créteil, Créteil, France

⁵Service Pneumologie, Hôpital Larrey, Université Paul Sabatier, Toulouse, France

⁶Aix Marseille University, CNRS, INSERM, CRCM, APHM, Multidisciplinary Oncology & Therapeutic Innovations dpt, Marseille, France

⁷Service Oncologie Thoracique, Hôpital Bichat, Paris, France

⁸Thoracic Oncology Department, Lille University Hospital, Lille, France

⁹Service Pneumologie, Hôpital Civil, Strasbourg, France

¹⁰Service Hospitalo-Universitaire de Pneumologie et Physiologie, CHU Grenoble Alpes, France

¹¹Service Pneumologie, CH Sainte Musse, Toulon, France

¹²Service Oncologie, Hôpital Saint-Louis, Paris, France

¹³Service Pneumologie, Hôpital Ambroise Paré, Paris, France

¹⁴Service Pneumologie, Hôpital Charles Nicolle, Rouen, France

¹⁵Service Pneumologie, CHU Rennes, France

¹⁶Service Pneumologie, Hôpital du Mans, France

¹⁷Département de Cancérologie Médicale, Centre Léon Bérard, Lyon, France

¹⁸Service Pneumologie, CHRU Bretonneau, Tours, France

¹⁹Service Pneumologie, CHRU Morvan, Brest, France

²⁰Service Pneumologie, CH Annecy-Genevois, Saint-Julien-en-Genevois, France

²¹ Sorbonne Université, GRC n°04, Theranoscan, F-75252, Paris, France

²²AP-HP, Groupe Hospitalier HUEP, Hôpital Tenon, Service de Pneumologie, F-75970, Paris, France

²³AP-HP, Groupe Hospitalier HUPC, Hôpital Cochin, Unité d'Oncologie Thoracique, Service de Pneumologie, F-75014, Paris, France

²⁴Centre de Recherche des Cordeliers, Université Paris Descartes, UMRS1138 « Complement, Inflammation and Cancer », F-75006 Paris, France

²⁵AP-HP, Groupe Hospitalier HUEP, Hôpital Tenon, Service de Cytologie et Anatomie Pathologique, F-75970, Paris, France

Correspondence: Marie Wislez, MD, PhD, Hôpital Cochin, Unité d'Oncologie Thoracique, Service de Pneumologie, 75014, Paris, France. E-mail: marie.wislez@aphp.fr.

This work was supported by Bristol-Myers Squibb Foundation for Research in Immuno-Oncology 2016 Award; Fonds de Recherche en Santé Respiratoire under the high patronage of Fondation du Souffle 2016 Award.

Abstract (239 words)

Background: Immune checkpoint inhibitors (ICI) have improved cancer prognosis, but have not been evaluated specifically in sarcomatoid carcinoma (SC), a rare lung cancer subtype with poor prognosis. As such, our study sought to retrospectively assess the ICI efficacy in SC.

Methods: All consecutive patients with centrally confirmed SC treated in \geq second-line between 2011 and 2017 were enrolled. PD-L1 tumor expression was assessed using immunohistochemistry (SP263 clone), and the tumor mutational burden (TMB) with the Foundation One panel. TMB was considered high if ≥ 10 mutations/megabase (MMb).

Results: Overall, 37 SC patients were evaluated, predominantly men (73%), median age of 63.2 years (36.8-79.7), current or former smokers (94.6%). Immunotherapy (Nivolumab 86.5% of cases) was given in second-line in 54% patients and third-line or beyond in 46%. The ORR was 40.5% and DCR 64.8%, regardless of PD-L1 status. Median OS was 12.7 months [range: 0.3-45.7]. One-third of patients exhibited early progression. The median PD-L1 expression was 70% [0-100]. There was a trend toward higher PD-L1 expression in responsive diseases, with an ORR of 58.8% in PD-L1+ patients and 0% in the single PD-L1- patient ($p=0.44$). The median TMB was 18 [4-39] MMb, 87.5% of cases displaying a high TMB. There was a trend towards higher TMB in responders versus stable or progressive diseases ($p=0.2$).

Conclusions: SC patients exhibited high response rates and prolonged OS under ICI treatment. These data support the prospective investigation of ICI in SC patients in first-line treatment.

Keywords: Pulmonary sarcomatoid carcinoma, Immune Check Point Inhibitor, PD-L1, Tumor Mutational Burden

Introduction

Pulmonary sarcomatoid carcinoma (SC) is a rare non-small cell lung cancer (NSCLC) subtype characterized by poorly differentiated tumors containing sarcoma or sarcoma-like elements, rapid tumor growth, high level of blood-vessel invasion, and epithelial to mesenchymal transition (EMT).¹ Its prognosis is poor (overall survival [OS] of 7 months), due to early metastasis occurrence and a high level of chemo-resistance to platinum-based standard regimens.² There is thus a crucial need to identify new therapeutic targets.

Immune checkpoint inhibitors (ICI) improve the outcomes of NSCLC patients. These treatments have not been evaluated in SC, though there is a strong rationale for using them in this indication. SC is highly related to tobacco use (80% of patients), with high mutation rates, including *KRAS* mutations^{3,4} We previously showed that PD-L1 was more commonly expressed in 75 SCs compared to non-SCs.⁵ Furthermore, SCs appear to be “hot tumors”, since we reported higher immune and inflammatory cell infiltration compared to non-SC.⁵ However, the loss of E-cadherin observed in EMT could explain why SC does not necessarily respond to the blockage of anti-PD-1/PD-L1. One explanation for this could be that the interaction between T-CD8-CD103 lymphocytes would not be optimal, thus leading to a lack of functionality among these resident memory T lymphocytes. This lack of interaction could also influence T lymphocyte retention at the tumor site.⁶ This study thus sought to assess the ICI efficacy in this specific NSCLC subtype.

Patients and methods

All consecutive patients from 42 French centers with stage III/IV SC treated by ICI in second-line or beyond between 2011 and 2017 were included. Clinical characteristics were collected from patient medical charts, and the histological type was reviewed by an expert pathologist (M.A.). We assessed tumor response according to the RECIST criteria, OS, and duration of ICI treatment. Early progression was defined as progression occurring prior to the first evaluation at 2 months.

PD-L1 expression was centrally stained and assessed again using immunohistochemistry with clone SP263 from Ventana (Roche). The tumor proportion score (TPS) (*i.e.*, the percentage of positive tumor cells) was considered positive if $\geq 5\%$. Genome profiling by Foundation Medicine from samples was performed in available surgical biopsies (n=9). The tumor mutational burden (TMB) was assessed, and it was considered high if ≥ 10 MMb (Mutation/Megabase).

Results

Clinical characteristics

Overall, 42 centers participated in the study, 27 of them including a total of 37 patients. The patient clinical characteristics were provided in Table 1. Before ICI treatment, all patients received a platinum-based chemotherapy regimen, with a median number of platinum cycles of 4 [range: 1-6]. The objective response rate (ORR) under chemotherapy was 29.7% (11/37), and the disease control rate (DCR) 56.8% (21/37), without any complete responses.

ICI treatment

Immunotherapy characteristics, with nivolumab as the main drug, have been summarized in Table 2. The median cycle number was 10 [range: 1-32]. The ORR was 40.5% (n=15/37), the DCR 64.8% (n=24/37), and the progression 32.4% (n=12/37). The median PFS under ICI was 4.89 months [range: 0.3-35.7] with a 1-year PFS rate of 15%. The median OS under ICI was 12.7 months [range: 0.3-45.7], and the 1-year survival rate 51.3%. Because 62% of patients were PS 0-1, ORR, PFS and OS were analyzed according to PS. There was a trend to higher efficacy and survivals according to PS but it did not reach significance (Supplementary Figure 1).

PD-L1 status was assessed for the 19 samples (51.3%) available. The median PD-L1 expression was 70% [range: 0-100], with only 1 PD-L1- negative sample (Table 2 and Figure 1A). Overall, 12 patients (32.4%) exhibited early progression, prior to the first assessment at 2 months. Their characteristics were presented in Table 3. Of these patients, five died without any further treatment, with a median 0.62-month [range: 0.33-2.98] treatment duration. In these patients, the PD-L1 TPS was 0%, 50%, and 90%, being undetermined for the remaining two. Two patients harbored a *KRAS* mutation (one p.Gly12Ala and one p.Gly12Cys) and one an *EGFR* mutation (exon 18).

Six patients with early progression received a subsequent treatment line (Table 3), stopping immunotherapy after a median 1.38-month [range: 0.92-2.46] duration. The median OS from ICI initiation was 4.2 months [range: 3.25-18.52].

The last early progressor exhibited an isolated brain progression. He received whole brain radiotherapy and continued ICI for another 13.2 months, until a new progression was detected. He then received a new treatment line, with an 18.5-month survival since ICI initiation.

Toxicities were reported in six patients (16.2%), three of whom stopped ICI because of an immune undesirable event: one patient displayed Grade 2 autoimmune hepatitis and Grade 2 diarrhea at 12.5 months; another patient exhibited interstitial pneumonia and thyroiditis, both of Grade 2, at 3.2 months; of note, this patient was still alive without any treatment after a 45.7-month follow-up; the third patient suffered from interstitial pneumonia at 1.7 months and died a few days thereafter.

Treatments received at early progression are specified in Table 3, and in Supplementary Table 2 for the subgroup without progression.

PD-L1 expression

The tumor with no PD-L1 overexpression was from a non-smoker with a low TMB (4 MMB) and an exon 18 *EGFR* mutation. This patient displayed early progression with an OS of 1.84 months (Figure 1A). Conversely, the 18 tumors that expressed PD-L1 originated from current or former smokers, with nine patients harboring a *KRAS* mutation (one with a *MET* exon 14 co-mutation) (Figure 1A).

PD-L1 expression tended to be higher in responsive diseases, yet without statistical significance (Supplementary Figure 2). The ORR was 58.8% in PD-L1+ patients and 0% in the single PD-L1- one with the same trend observed for DCR (76.5% in PD-L1+ vs. 0% in PD-L1-). There was a trend towards higher median OS in PD-L1+ subgroup vs. PD-L1-, without statistical significance (Figure 2A).

TMB status

The TMB was assessed in eight (21.6%) tumors (Figure 1B). The median TMB was 18 [range: 4-39] MMb, with 7/8 (87.5%) tumors harboring a TMB >10MMb and only one with a TMB <10MMb.

The tumor with a low TMB was from the *EGFR*-mutated patient with a PD-L1- expression, early progression, and death after ICI initiation (Figure 1B and Supplementary Table 1).

All high TMB tumors had a PD-L1 expression >10 % (median 70% [range: 10-100]), and all tumors had a *TP53* mutation, with three of them (42.8%) displaying *TP53/KRAS* co-mutations (Figure 1B). There was a trend towards a higher TMB in responders vs. stable or progressive diseases (Supplementary Figure 2), with median TMBs of 32, 14.5, and 14 MMb, respectively. A higher TMB was associated with a trend towards higher survival, with a median 18-months OS in high TMB populations vs. 1.84-month OS in low (Figure 2B).

Discussion

Based on our data, immunotherapy was found effective in SC, with a 40.5% ORR and 12.7-month OS. These results appear to be superior to those observed with chemotherapy. For the latter, the OS data reported in the literature were between 5 and 7.7 months, and the ORR data between 0% and 16.5%.^{2,7} Therefore, SC patients are likely to be very good candidates for ICI therapy. Even compared to patients without SC, the response rates in our study were twice as high as those usually reported in this case (20% in non-SC vs. 40.5% in SC),⁸ along with a similar PFS than squamous (median PFS 3.5 months) and slightly higher than non-squamous (median PFS 2.3 months). Furthermore, there was a slightly higher OS (SC: median OS 9.2 months [7.3-13.3]; non-SC: median OS 12.2 months [9.7-15]). A few case reports have previously shown good ICI responses in this setting.^{9,10} There was a trend to higher efficacy and survivals according to PS but it did not reach significance. A limitation of our work is the small number of patients enrolled due to the disease's rarity, despite all ICI-treated patients from the 27 centers being consecutively included. On the other hand, all cases were histologically and centrally confirmed by an expert pathologist.

SC is associated with tobacco use, resulting in a high mutation rate, with probably numerous neoantigens¹¹ rendering patients highly immunogenic and, thus, good candidates for ICI. As shown, SC harbors a high PD-L1 overexpression with significant immune infiltration, especially CD4+ T lymphocytes and macrophages.⁵ Chen J. et al. demonstrated almost 50% of SCs to be highly infiltrated with CD8+ T cells, which are among the main effectors of antitumor immune response.¹¹

Using a 5% cut-off, we observed that all patients except one had a positive PD-L1 expression. Our rates were higher than those from the SC literature (between 53% in a Caucasian and 90% in a Korean series), probably due to PD-L1 assay differences (antibodies, cut-off), high SC tumor heterogeneity and the small number of cases studied.^{3,5,13-15} Almost two-thirds of our patients had >50% PD-L1 expression on initial tumor samples; they could thus be eligible for first-line immunotherapy.

Despite favorable overall response and survival rates, one-third of patients experienced early progression, and almost half of them died without any further treatment. We did not find any specific clinical or pathological characteristics predictive of early progression but we cannot ignore the almost 40% of patients with a PS \geq 2 at ICI initiation. PD-L1 was not predictive, with expression ranging from 0% to 100% in this subgroup. One patient harbored an exon 18 *EGFR* mutation with a negative PD-L1

expression and low TMB, confirming the observation that patients with *EGFR* mutations derive, even in SC, a low benefit from ICIs. In the early progression subgroup, three patients were *TP53* and *KRAS* co-mutated, meaning that patient selection could not be based on these mutations. One of these three patients was co-mutated *TP53/KRAS/STK11*. The inactivating *STK11* mutation was previously reported to be associated with “cold tumors”, reflected by low CD8+ T cell infiltration and ICI-resistance.^{16,17}

To conclude, SC patients were shown to display high response rates and prolonged OS under ICI. However, one-third of patients experienced early progression. We were unable to identify any characteristics predicting these early progressions. The specific place of ICI as first-line treatment, combined with chemotherapy for patients with PD-L1 expression <50%, must be further assessed.

Bibliography

1. Vieira T, Antoine M, Ruppert A-M, et al. Blood vessel invasion is a major feature and a factor of poor prognosis in sarcomatoid carcinoma of the lung. *Lung Cancer Amst Neth.* 2014;85(2):276-281. doi:10.1016/j.lungcan.2014.06.004
2. 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):1574-1577. doi:10.1097/01.JTO.0000437008.00554.90
3. Pécuchet N, Vieira T, Rabbe N, et al. Molecular classification of pulmonary sarcomatoid carcinomas suggests new therapeutic opportunities. *Ann Oncol Off J Eur Soc Med Oncol.* 2017;28(7):1597-1604. doi:10.1093/annonc/mdx162
4. Saffroy R, Fallet V, Girard N, et al. MET exon 14 mutations as targets in routine molecular analysis of primary sarcomatoid carcinoma of the lung. *Oncotarget.* 2017;8(26):42428-42437. doi:10.18632/oncotarget.16403
5. 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 Amst Neth.* 2016;98:51-58. doi:10.1016/j.lungcan.2016.05.013
6. Mami-Chouaib F, Blanc C, Cognac S, et al. Resident memory T cells, critical components in tumor immunology. *J Immunother Cancer.* 2018;6(1):87. doi:10.1186/s40425-018-0399-6
7. Maneenil K, Xue Z, Liu M, et al. Sarcomatoid Carcinoma of the Lung: The Mayo Clinic Experience in 127 Patients. *Clin Lung Cancer.* 2018;19(3):e323-e333. doi:10.1016/j.clc.2017.12.008
8. Horn L, Spigel DR, Vokes EE, et al. Nivolumab Versus Docetaxel in Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer: Two-Year Outcomes From Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057). *J Clin Oncol Off J Am Soc Clin Oncol.* 2017;35(35):3924-3933. doi:10.1200/JCO.2017.74.3062
9. Roesel C, Kambartel K, Kopeika U, Berzins A, Voshaar T, Krbek T. Lazarus-type tumour response to therapy with nivolumab for sarcomatoid carcinomas of the lung. *Curr Oncol Tor Ont.* 2019;26(2):e270-e273. doi:10.3747/co.26.4377
10. Kotlowska MP, Rueda AG, Olmedo ME, et al. Efficacy of immunotherapy in sarcomatoid lung cancer, a case report and literature review. *Respir Med Case Rep.* 2019;26:310-314. doi:10.1016/j.rmcr.2019.02.017
11. Fallet V, Saffroy R, Girard N, et al. High-throughput somatic mutation profiling in pulmonary sarcomatoid carcinomas using the LungCarta™ Panel: exploring therapeutic targets. *Ann Oncol Off J Eur Soc Med Oncol.* 2015;26(8):1748-1753. doi:10.1093/annonc/mdv232
12. Chen J, He Q, Liu J, et al. CD8+ tumor-infiltrating lymphocytes as a novel prognostic biomarker in lung sarcomatoid carcinoma, a rare subtype of lung cancer. *Cancer Manag Res.* 2018;10:3505-3511. doi:10.2147/CMAR.S169074
13. Velcheti V, Rimm DL, Schalper KA. Sarcomatoid lung carcinomas show high levels of programmed death ligand-1 (PD-L1). *J Thorac Oncol Off Publ Int Assoc Study Lung Cancer.* 2013;8(6):803-805. doi:10.1097/JTO.0b013e318292be18

14. Lococo F, Torricelli F, Rossi G, et al. Inter-relationship between PD-L1 expression and clinic-pathological features and driver gene mutations in pulmonary sarcomatoid carcinomas. *Lung Cancer Amst Neth.* 2017;113:93-101. doi:10.1016/j.lungcan.2017.09.009
15. Yvarel V, Patoir A, Casteillo F, et al. PD-L1 expression in pleomorphic, spindle cell and giant cell carcinoma of the lung is related to TTF-1, p40 expression and might indicate a worse prognosis. *PloS One.* 2017;12(7):e0180346. doi:10.1371/journal.pone.0180346
16. Biton J, Mansuet-Lupo A, Pécuchet N, et al. TP53, STK11, and EGFR Mutations Predict Tumor Immune Profile and the Response to Anti-PD-1 in Lung Adenocarcinoma. *Clin Cancer Res Off J Am Assoc Cancer Res.* 2018;24(22):5710-5723. doi:10.1158/1078-0432.CCR-18-0163
17. Skoulidis F, Goldberg ME, Greenawalt DM, et al. STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in KRAS-Mutant Lung Adenocarcinoma. *Cancer Discov.* 2018;8(7):822-835. doi:10.1158/2159-8290.CD-18-0099

Figure legends

Figure 1: Swimming plots of treatment duration for each patients according to PD-L1 (A) or TMB (B) status.

Each line corresponds to one patient, with specified mutational status between brackets and reasons for treatment discontinuation (death, progression, toxicity).

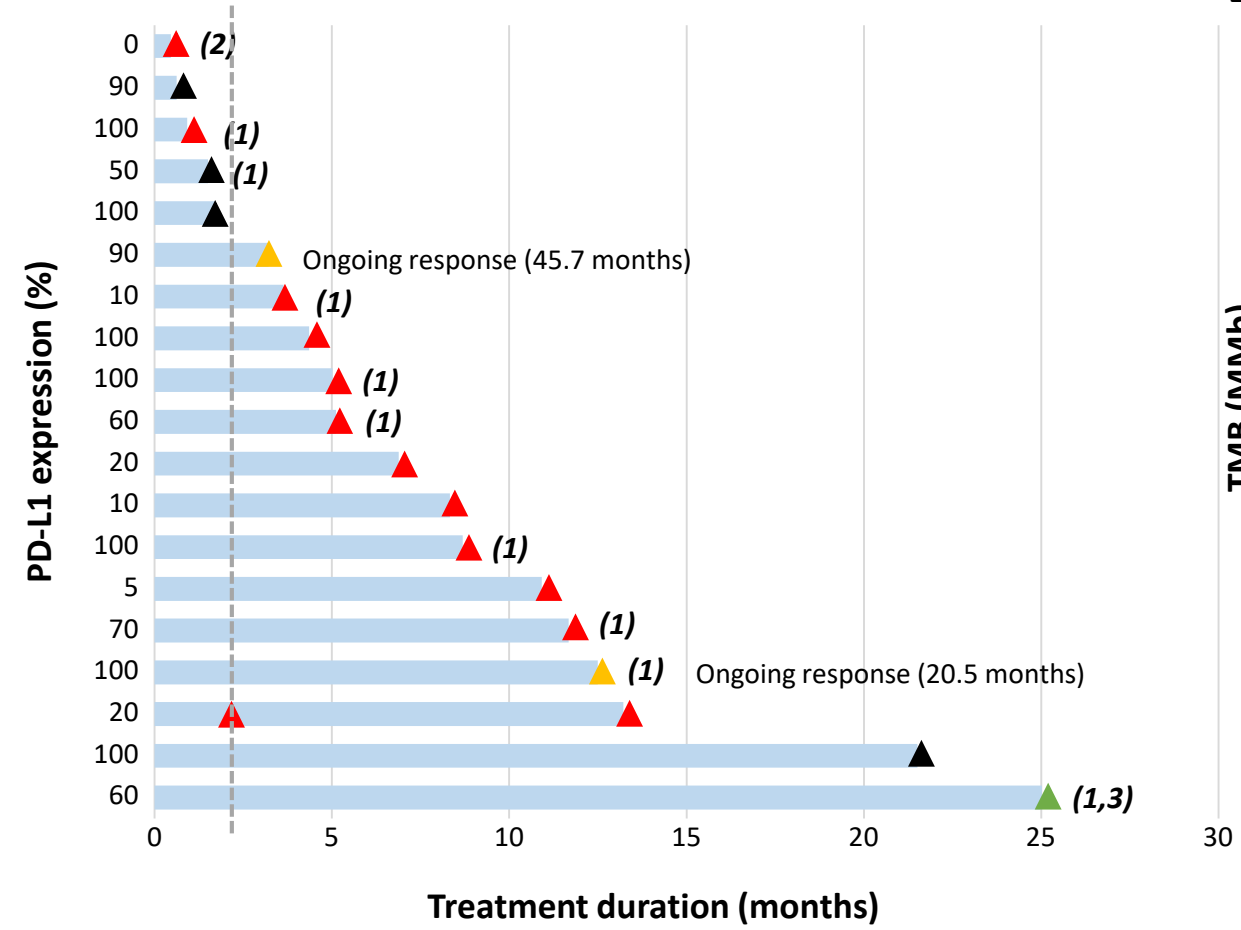
Figure 2: OS according to PD-L1 expression (A) and TMB status (B).

A: Overall survival from ICI initiation. Median (mo.): PD-L1 positive: 16.1 [0.62-45.7] vs. PD-L1 negative: 1.8 (HR 0.22 [0.0005-1.7]; P=0.1).

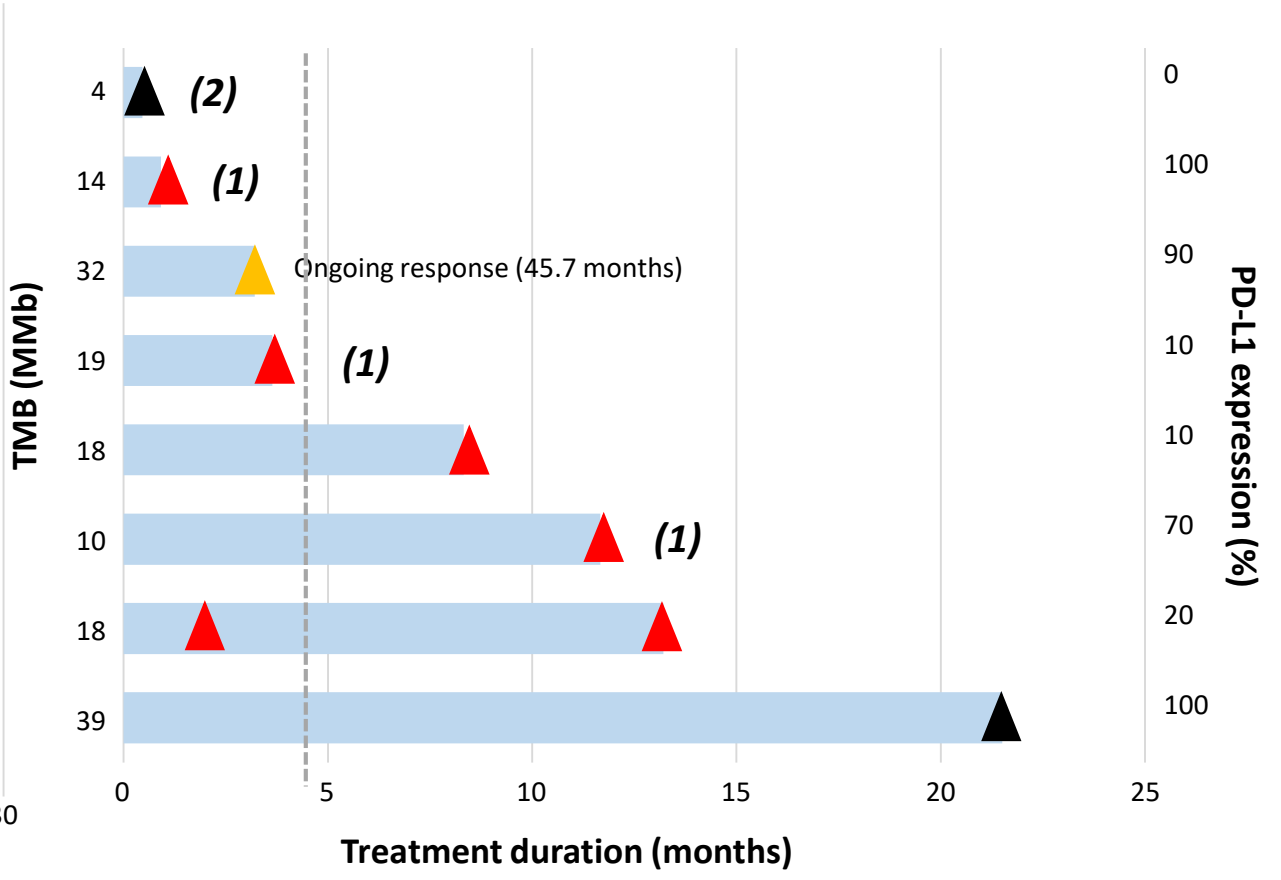
B: Overall survival from ICI initiation according to tumor mutational burden (TMB) assessment (n=8). TMB high: more than 10 mutations/megabase, and TMB low: less than 10 mutations/megabase. Median (months): 18 (4.2-45.7) vs. 1.84 (HR 0.1 [0.01-0.85]; P= 0.0082).

Figure 1

A



B



- ▲ Ongoing treatment
 - ▲ Progression
 - ▲ Death
 - ▲ Toxicity
- 1: KRAS mutation
2: EGFR mutation
3: Met exon 14

Figure 2

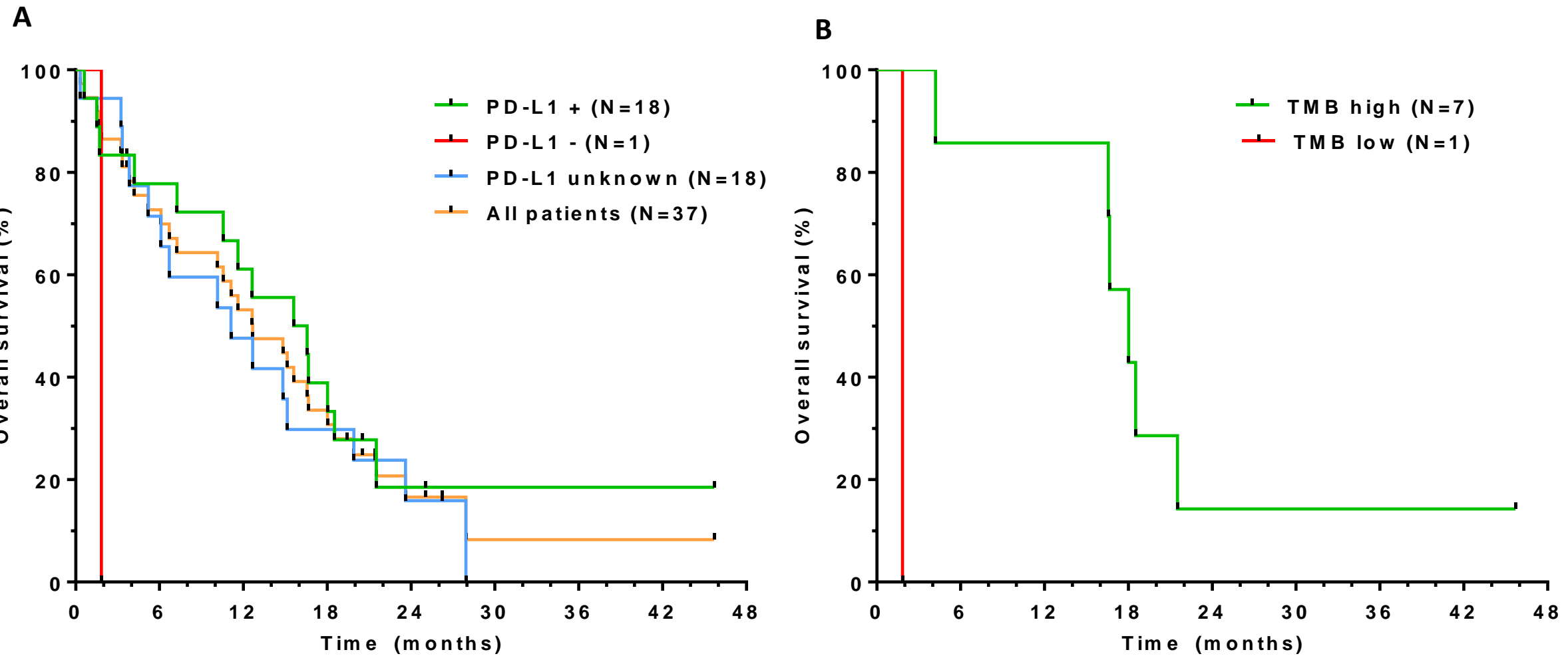


Table 1: Demographics (n=37)

Characteristics	n (%)
Gender	
Male	27 (73)
Female	10 (27)
Median age (years, range)	63.2 (36.8-79.7)
Smoking status	
Current smokers	15 (40.5)
Former smokers	20 (54.1)
Never smokers	2 (5.4)
Median tobacco consumption (range)	35 (0-70)
Packs of cigarettes per year	
PS at diagnosis	
0-1	27 (73)
2-3	9 (24.3)
Unknown	1 (2.7)
TNM staging	
II	4 (10.8)
III	12 (32.4)
IV	17 (45.9)
Unknown	4 (10.8)
Diagnosis method	
Percutaneous lung biopsy	22 (59.5)
Surgery*	5 (13.5)
Bronchial biopsy	3 (8.1)
Node biopsy	3 (8.1)
Pleural biopsy	2 (5.4)
Cytology	2 (5.4)
Mutation status	
<i>EGFR</i> mutation	1 (2.7)
<i>KRAS</i> mutation	14 (37.8)
<i>MET</i> exon 14 mutation	3 (8.1)
No mutations	17 (45.9)
Co-mutations	2 (5.4)
Unknown	4 (10.8)
First-line chemotherapy	
Cisplatin-containing	18 (48.7)
Carboplatin-containing	17 (45.9)
Taxane	15 (40.6)
Pemetrexed	14 (37.8)
Vinorelbine	6 (16.2)
Gemcitabine	2 (5.4)

*: Pneumonectomy n=3 and lobectomy n=2

Table 2: Characteristics of ICI treatment (n=37).

Characteristics	n (%)
PS at ICI initiation	
0-1	23 (62.2)
2-3	13 (35.1)
Unknown	1 (2.7)
Line of ICI treatment	
2 nd line	20 (54)
3 rd or more	17 (46)
Type of ICI treatment	
Nivolumab	32 (86.5)
Pembrolizumab	3 (8.1)
Atezolizumab	2 (5.4)
Median PD-L1 score (range)	70% (0-100)
PD-L1 status (cut-off 5%)	N = 19
Positive	18 (94.7)
Negative	1 (5.3)
Median number of cycles (range)	10 (1-32)
Best response under ICI treatment	
Partial response	15 (40.5)
Stable disease	9 (24.3)
Progression	12 (32.4)
Unknown	1 (2.7)
PFS (months, range)	4.89 (0.3-35.7)
1-year PFS rate	10.8%
Reason for ICI discontinuation	
Progression	27 (73)
Toxicity	3 (8.1)
Death	4 (10.8)
Ongoing	2 (5.4)
Unknown	1 (2.7)
Median OS (months, range)	12.7 (0.3-45.7)

Table 3: Characteristics of patients with early progression**PS: performance status; ICI: immune checkpoint inhibitor; OS: overall survival; M: male; F: female; WT: wild type**

Gender	Age (year)	PS at ICI initiation	Smoking status	EGFR status	KRAS status	ALK status	ROS1 status	MET exon 14 status	PD-L1 status	TMB (mutations/megabase)	STK11 status	TP53 status	ICI duration (mo.)	OS from ICI initiation	Outcome
M	73.8	3	Active	WT	WT	WT	WT	WT	Unknown	Unknown	Unknown	Unknown	0.3	0.3	Death
M	54.7	1	Non smoker	Exon 18	WT	WT	Unknown	Unknown	0	4	WT	Mutated	0.4	1.8	Death
M	62.1	3	Active	WT	WT	WT	WT	Unknown	90	Unknown	Unknown	Unknown	0.6	0.6	Death
F	49.9	1	Former	Unknown	G12A	Unknown	Unknown	Unknown	50	Unknown	Unknown	Unknown	1.5	1.5	Death
M	79.7	2	Former	WT	G12C	WT	Unknown	WT	Unknown	Unknown	Unknown	Unknown	2.9	10.1	Death
F	49.5	2	Active	WT	G13C	WT	WT	Unknown	100	14	Mutated	Mutated	0.9	4.2	New line: erlotinib
F	59.2	1	Former	WT	WT	WT	WT	Unknown	Unknown	Unknown	Unknown	Unknown	1.3	3.2	New line : gemcitabine
M	68.1	1	Former	WT	WT	WT	WT	Mutated	Unknown	Unknown	Unknown	Unknown	1.3	12.6	New line : crizotinib
F	56.6	1	Active	WT	WT	WT	WT	WT	Unknown	Unknown	Unknown	Unknown	1.3	3.3	New line : navelbine
F	64.0	2	Non smoker	WT	WT	WT	WT	WT	Unknown	Unknown	Unknown	Unknown	2.4	5.2	New line : gemcitabine
M	62.4	1	Former	WT	Unknown	WT	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	3.6	New line : gemcitabine
F	50.5	1	Active	WT	WT	WT	WT	WT	20	18	WT	Mutated	13.2	18.5	Continuation beyond progression