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Cachexia - sarcopenia as a determinant of disease control rate and survival in non-small lung cancer patients receiving immune-checkpoint inhibitors

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ABSTRACT

Purpose: The metabolic changes associated with cachexia – sarcopenia syndrome might down-regulate anti-tumor immunity. We hypothesized that this syndrome reduces efficiency of immune checkpoint inhibitors (ICPI) in non-small cell lung cancer (NSCLC).

Methods: The records of 142 consecutive NSCLC patients receiving first- or second-line anti-Programmed cell death protein 1) ICPI were reviewed. Response evaluation according to Response Evaluation Criteria in Solid Tumors 1.1 was performed at the eighth week of immunotherapy. Pretreatment cachexia was defined as a body-weight loss of 5% or more in the previous 6 months. Sarcopenia was estimated with the third lumbar skeletal muscle mass index (mSMI) and was evaluated before immunotherapy and at the eighth week. A decrease by 5% or more of the mSMI was considered as an evolving sarcopenia. The endpoints were disease control rate (DCR), progression-free (PFS) and overall survival (OS). Logistic regression model and Cox model took into account others covariables known to influence ICPI efficiency, particularly Programmed Death –Ligand 1 tumor cell score, Eastern Cooperative Oncology Group performance status and common somatic mutational status.

Results: In multivariate analysis, cachexia – sarcopenia syndrome reduced the probability of achieving a disease control and were associated with a shorter survival. Patients without cachexia had a better probability to achieve disease control in comparison with those who did not experience cachexia (59.9 % and 41.1 %, respectively; odds ratio 95 % (confidence interval [95 %CI]): 2.60 (1.03–6.58)). Patients with cachexia had a shorter OS when compared with those without cachexia (hazard ratios [HR] (95 %CI): 6.26 (2.23–17.57)). Patients with an evolving sarcopenia had a shorter PFS and OS, with HR (95 %CI): 2.45 (1.09–5.53) and 3.87 (1.60–9.34) respectively.

Conclusion: Cachexia – sarcopenia syndrome negatively influences patients' outcome during anti-PD-1 ICPI therapy.

1. Introduction

Immune checkpoint inhibitors (ICPI) have changed treatment paradigms in many human tumors [1]. Anti-PD-1 (Programmed cell Death protein-1) and anti-PD-L1 (Programmed Death-Ligand 1) have been approved in several settings for treatment of metastatic non-small cell lung cancer (NSCLC) [2–4]. In this disease, the main biological features predicting a high activity of ICPI targeting the PD-1 / PD-L1

complex are a high tumor cell expression of PD-L1 [5], a high tumor mutational burden [6] (TMB) and the presence of tumor infiltrating CD8+ (Cluster of differentiation 8) T-cells [7]. In addition, comutation of *KRAS* (Kirsten rat sarcoma viral oncogene homolog) and *LKB1/STK11* (Liver Kinase B1/Serine Threonine Kinase 11) genes has been shown to predict a poor response to ICPI, independently from PD-L1 tumor expression [8]. So far, among these features, the expression of PD-L1 is the most easily assessable in routine practice and is mandatory

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in some circumstances.

Hitherto, there is weak clinical evidence of a relationship between cachexia and failure of immunotherapy with anti-PD-(L)1 antibodies. Some studies have investigated sarcopenia at diagnosis and its relationship with NSCLC patient outcome during anti-PD-(L)1 [9,10]; Shiroyama et al. suggested that sarcopenic NSCLC patients receiving anti-PD-(L)1 are at higher risk of tumor progression when compared with patients without sarcopenia [9]. Investigating the relationship of pembrolizumab pharmacokinetics and overall survival (OS) in patients with advanced melanoma and NSCLC, Turner et al. demonstrated that association of pembrolizumab clearance with overall survival potentially reflects catabolic activity [10]. Emerging studies in preclinical models of tumors, cachexia is associated with tumor-induced reprogramming of liver metabolism leading to inhibition of many features of antitumor immunity and might explain the link between cachexia and failure of immunotherapy [11]. However, none of the studies published up till now, considered other known predictive factors of sensitivity to anti-PD-(L)1 therapy such as PD-L1 tumor expression. In addition, body weight loss of $\geq 5\%$ during the previous six months, or $\geq 2\%$ if body mass index $< 20 \text{ kg/m}^2$ are paramount criteria for defining cancer cachexia [12,13]. This syndrome is a critical adverse event of cancer. The main feature of cancer cachexia is sarcopenia, defined by a waste of skeletal muscle mass or a loss of lean body weight. Sarcopenia is associated with fatigue, ongoing catabolism, poor tolerance of treatment, and an unfavorable prognosis [12]. Cachexia – sarcopenia syndrome is frequently preceded by Eastern Cooperative Oncology Group (ECOG) performance status (PS) impairment, and associated with several other biological changes such as low serum albumin level or hypophosphatemia. Therefore, evaluating the specific influence of cachexia – sarcopenia during immunotherapy requires the concomitant appraisal of other variables influencing response to immune checkpoint inhibitors.

The herein retrospective study aimed at determining the relationship between cachexia - sarcopenia syndrome and patients' outcome when receiving anti-PD-(L)1 antibody taking into account all other putative parameters of anti-PD-(L)1 including PD-L1 tumor cell expression.

2. Patients and methods

2.1. Data collection

This retrospective study encompassed, consecutive patients with histologically proven, metastatic or recurrent NSCLC, who received anti-PD(L)1 ICPI at our single institution. These patients were either eligible for first line pembrolizumab as having a PD-L1 immuno-histochemical (IHC) score $\geq 50\%$ of tumor cells, or eligible for a subsequent line after having experienced a failure of a first line platinum-based chemotherapy; these latter patients, received pembrolizumab (pending on PD-L1 IHC score $> 1\%$ of tumor cells) or nivolumab (whatever PD-L1 IHC score). The main eligibility criteria were: proven progressive disease ECOG PS 0–2, and measurable disease according to RECIST 1.1 (Response Evaluation Criteria In Solid Tumors). Patients with brain metastases or carcinomatous meningitis were not eligible, as they were also considered not eligible in different anti PD-1 trials in the setting of second line treatment. However, patients with brain metastases upon diagnosis were eligible if they had achieved brain response during first-line therapy, including brain radiotherapy, with a persisting brain tumor response. Other criteria were age ≥ 18 years; baseline neutrophils $\geq 1500/\text{mm}^3$; platelets $\geq 100\ 000/\text{mm}^3$; bilirubin, alkaline phosphatase and transaminase levels $< 1.5 \times$ normal upper limits; sodium $> 125 \text{ mmol/L}$; normal calcium; creatinine clearance $> 40 \text{ mL/min}$; normal electrocardiogram. Patients receiving corticosteroids at a dose higher than 10 mg per day of prednisolone or equivalent for more than 10 days in the month prior to ICPI therapy were not eligible. None of the patients had prior autoimmune disease, human

immunodeficiency virus infection, or chronic hepatitis B or C. Patients suffering of controlled and stable cardiac diseases were eligible. Knowing the potential risk of immune-related cardiac toxic events induced by ICPI, patients with acute cardiac failure and with unstable coronary angina were not eligible. De-identified data were directly extracted from the Montpellier University centralized computing system, saving patients' medical records (DxCare, Medasys, Gif sur Yvette, France) by one of us (SJB) and subsequently verified by JLP and BR. The database encompassed 8 variables characterizing disease and demography, 4 characterizing sarcopenia, 4 informing the immunotherapy schedule, and 6 describing survival. Response evaluation was done on computed tomography (CT)-scan of the target lesions and classified according to RECIST 1.1 [14]. The first response evaluation took place during the eighth week of treatment. Subsequent tumor measurements were performed every 8 weeks. The Montpellier Academic Hospital institutional review board approved this retrospective single center study (IRB N°: 2019_IRB-MTP_09-05).

For all patients, specimens of tumor biopsies were tested for tumor cell PD-L1 expression by mean of quantitative score on formalin-fixed paraffin-embedded tumor tissue stained by IHC with E1L3N® (Cell Signaling Technology). The PD-L1 IHC score ranged between $< 1\%$ and 100 % of stained tumor cells.

2.2. Sarcopenia evaluation

In this study we used the third lumbar vertebra (L3) skeletal muscle mass index (L3 mSMI) as an estimator of sarcopenia: the recommended calculation of L3 mSMI was extracted by one operator (EP), under the supervision of SB using skeletal muscle area measurement on axial Computed Tomography (CT) sections (cm^2 of muscle tissue) at the level of the upper edge of L3 [15]. The muscles in the L3 region, containing psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis, were analyzed using AW Volume Share 7software (General Electric), which enables specific tissue demarcation using Hounsfield unit (HU) thresholding. The muscle area at L3 vertebra level, divided by the squared patient height, was then calculated in cm^2/m^2 and the thresholds were 52.4 cm^2/m^2 and 38.5 cm^2/m^2 for men and women respectively [15]. The sarcopenia estimation was performed on both the pre-immunotherapy CT and on the eighth week CT. An evolving sarcopenia was defined as a decrease in L3 mSMI of 5% or more during the first eight weeks of immune-checkpoint inhibitor therapy. In this study, the arbitrarily defined 5% threshold was a priori chosen as an *evolving sarcopenia* estimator congruent with the accepted definition of cachexia (body-weight loss of 5% or more).

2.3. Statistics

Quantitative variables were described by their mean, and median. The qualitative variables were described by their size (n), percentage (%). Disease control rate (DCR) was defined as the sum of proportion of complete or partial responder patients and proportion of patients who achieved a stable disease at the first tumor measurement. Overall survival (OS), was defined as the time from first administration of ICPI therapy to death due to any cause and progression-free survival (PFS) was defined as the time from first administration of ICPI to either RECIST 1.1 disease progression or death from any cause, whichever occurred first.

Probabilities and odds ratios (OR) of a change in the categorically-dependent variable, namely disease control versus progressive disease at the eighth week, conditional on the values of independent covariables were analyzed in a logistic regression model. Survival analyses were processed as follows: the cutoff date for the entire population was November 6, 2018. The non-parametric Kaplan-Meier estimates were used to calculate probabilities and plot survival curves. Survival distribution of groups defined by the different states of a covariable was

Table 1
Patients' demography and disease characteristics.

		N	%
Age (mean ± SD)	63.54 ± 10.58		
Gender	men	93	65.49
Performance status	0 - 1	94	66.20
	> 1	48	33.80
Body weight loss %	< 5%	58	41.13
	[5–10%[40	28.37
	≥ 10 %	43	30.50
	MD	1	
Weight loss % 2 classes	< 5%	58	41.13
	≥ 5%	83	58.87
	MD	1	0.01
PD-L1 IHC score	< 1%	29	20.42
	[1–20%[19	13.38
	[20–50%[22	15.49
	≥ 50 %	56	39.44
	MD	16	11.27
Histology	ADC	114	80.28
	Non ADC	28	19.72
Smoking	Missing data	4	2.82
	Current smoker	35	24.65
	Never smoker	7	4.93
	Past smoker (more than one year)	96	67.61
Smoker yes/no	MD	4	2.82
	Non smoker	7	4.93
	Smoker	131	92.25
Somatic genotype	BRAF mutation	5	3.52
	EGFR HER2 ALK ROS1 ^a	13	9.15
	KRASmutation	45	31.69
	None	79	55.63
Body-mass index	Underweighted (< 18.5)	18	12.68
	Normal (18.5–24.9)	76	53.52
	Overweighted (25–29.9)	38	26.76
	Obese (> 30)	10	7.04
Serum albumin (g/L)	< 32	26	20.16
	≥ 32	103	79.84
Phosphoremia (mmol/L)	< 1.2	111	86.72
	≥ 1.2	17	13.28
mSMI (cm ² /m ²)	Sarcopenia (M < 52.4/F < 38.5)	92	65.71
	No sarcopenia (M > = 52.4/F > = 38.5)	48	34.29
Evolving sarcopenia	No (< 5% mSMI (cm ² /m ²))	74	65.49
	Yes (≥ 5% mSMI (cm ² /m ²))	39	34.51

Abbreviations used: SD: standard deviation ; PD-L1 IHC: Programmed Death-Ligand 1 immunohistochemistry; ADC: adenocarcinoma; MD: missing data ; mSMI: skeletal muscle mass index.

^a EGFR or HER2 mutation / ALK or ROS1 translocation.

compared using the log-rank test. Covariates related to the occurrence of the survival event with a $p < 0.20$ were included in a multivariate Cox hazard proportional model. However, the variable L3 mSMI was included in the model regardless of the log-rank test in order to search for a L3 mSMI effect. The proportional hazard assumption was tested graphically [function LOG (-LOG (S (t)))] and, where needed, by a time-dependent Cox model. Where covariates did not meet the proportional hazard assumption, a stratified Cox model was applied. Stepwise, backward and forward variable selections were tested. The variables with an alpha risk of 5% were selected in the final model. Statistical Analysis System version 9.4 was used.

3. Results

3.1. Patient population

The cohort of this study consisted of 142 patients treated at our single institution from July 2015 to February 2017 for metastatic NSCLC and receiving anti-PD-(L)1 antibodies (Table 1). Among them, 19 (13.4 %) received pembrolizumab as first-line systemic therapy and 123 (86.6 %) received pembrolizumab or nivolumab after failure of platinum-based regimen. The median number of received infusions was 4 (range: 1–43). On Table 1, patients' demography and disease characteristics are shown. A majority of patients had an adenocarcinoma ($n = 114$; 80.3 %). At the pre-immunotherapy evaluation, 92 patients (65.7 %) were sarcopenic as defined by a L3 mSMI below the reference threshold. In addition, during the first eight weeks, 39 patients (34.5 %) experienced an evolving sarcopenia at the 5% threshold of decrease in L3 mSMI. At the eighth week, according to RECIST 1.1, one patient achieved a complete response (0.7 %), 22 patients achieved a partial response (15.5 %), and 41 had a stable disease (28.9 %), resulting in a 45.1 % DCR. Forty nine patients experienced disease progression (34.5 %) and 29 patients did not reach the eighth week evaluation due to death or drop-out for safety reasons before the first evaluation. Five patients among the group who experienced a progressive disease at the eighth week, five patients further continued the anti-PD-1 immunotherapy beyond the sixth cycle insofar as a pseudo-progression was observed. At the cutoff date (November 6, 2018), 107 patients had experienced a progression of their disease (75.4 %) and 76 had died (53.5 %). Median follow-up was 5.5 months (0–32.9).

3.2. Determinants of disease control rate

In the univariate analyses (Table 2), patients with a poor PS, patients with cachexia (body-weight loss of 5% or more (Fig. 1a)), and those with an evolving sarcopenia (Fig. 2a) had a significantly lower probability of achieving a disease control when compared with patients presenting with the opposite features of each variable. A high PD-L1 IHC score was associated with a high probability of achieving a disease control, inasmuch as the higher the score, the better the probability of disease control, albeit this trend did not reach statistical significance.

As a first step, the logistic regression model was run with all variables related to the occurrence of a disease control with a $p < 0.20$. Body weight loss and PD-L1 IHC score were the two determinants of achieving a disease control at the eighth week. As neither L3 mSMI at diagnosis, nor evolving sarcopenia during the first eight weeks were determinants of disease control, and as there is missing data regarding the latter variable, the model was run again without these two variables. In the final logistic regression model the three significant determinants of a disease control were: no occurrence of cachexia at immunotherapy start (less than 5% of body weight loss), an ECOG PS 0, and a PD-L1 IHC score > 50 % with a respective OR and 95 % confidence interval (95 %CI) : 2.60 (1.03–6.58), 3.7 (1.23–11.22) and 2.95 (1.10–7.93).

3.3. Determinants of progression-free survival

In univariate analyses (Table 3), patients with a poor PS, patients with cachexia (Fig. 1b), patients with a serum albumin level < 32 g/L, patients affected by a non-adenocarcinoma NSCLC and those with an evolving sarcopenia (Fig. 2b) had a significantly shorter PFS in comparison with patients presenting with the opposite features of each variables. Patients with sarcopenia at the beginning of immunotherapy had a numerically shorter median PFS when compared with patients without sarcopenia (Fig. 3a). A high IHC PD-L1 score was associated with a longer PFS insofar as the highest PD-L1 IHC score, the longest the PFS, albeit this trend did not reach a statistical significance.

The function LOG (-LOG (S (t))) demonstrated that some variables,

Table 2

Univariate analyses of disease control rate determinants at the eighth week in patients receiving immune check point inhibitors.

Variable	Status	Nb 1	% 1	p_value
Age (y)	< 64	28	51%	0.23
	≥ 64	36	62%	.
Gender	Male	39	53%	0.25
	Female	25	64%	.
Performance status	0 - 1	54	64%	< 0.01
	> 1	10	34%	.
Body -weight loss	< 5%	38	72%	< 0.01
	≥ 5% ; < 10 %	15	47%	.
	≥ 10 %	10	37%	.
PD-L1 IHC score	< 1%	10	45%	0.14
	≥ 1% ; < 20 %	6	43%	.
	≥ 20 % et < 50 %	11	69%	.
	≥ 50 %	32	68%	.
Histology	ADC	55	59%	0.25
	Non ADC	9	45%	.
Smoking status	Current smoker	17	59%	1.00
	Never smoker	3	60%	.
	Former smoker	43	57%	.
Somatic genotype	BRAF mutation	3	75%	0.75
	EGFR HER2 ALK ROS1 ^a	4	44%	.
	KRAS mutation	19	54%	.
	None	38	58%	.
body mass index	Underweighted (< 18.5)	10	77%	0.09
	Normal weight (18.5–24.9)	27	46%	.
	Overweighted (25–29.9)	20	65%	.
	Obese (> 30)	7	70%	.
Serum albumin	< 32 g/L	7	54%	0.74
	> = 32 g/L	51	59%	.
Phosphoremia	< 1.2 mmol/L	48	56%	0.29
	≥ 1.2 mmol/L	10	71%	.
Line number	First line	8	53%	0.78
	Subsequent line	56	57%	.
mSMI (cm ² /m ²)	Sarcopenia (H < 52.4/F < 38.5)	38	54%	0.36
	No sarcopenia (H > = 52.4/F > = 38.5)	25	63%	.
Evolving sarcopenia	No (< 5% mSMI)	46	67%	0.02
	Yes (≥ 5% mSMI)	15	43%	.

Abbreviations used: SD : standard deviation ; PD-L1 IHC: Programmed Death-Ligand 1 immunohistochemistry; ADC: adenocarcinoma; MD: missing data; mSMI : Skeletal muscle mass index. NR: not reached.

^a EGFR or HER2 mutation / ALK or ROS1 translocation.

although affecting PFS with a $p < 0.20$ in the univariate analyses, did not satisfy the proportional hazard assumption: these variables were the body mass index (BMI), the PD-L1 IHC score, the serum albumin level and the somatic genotype. Therefore the Cox model was stratified on these four variables. Patients with an ECOG PS > 1, patients with a serum albumin level < 32 g/L, patient with sarcopenia (low pretreatment L3 mSMI) and patients with evolving sarcopenia proved to have a shorter PFS when compared with the opposite features of each variable with hazard ratios (HR) (95 %CI): 5.72 (1.96–16.67), 7.11 (2.06–24.55), 3.83 (1.21–12.12), and 2.45 (1.09–5.53) respectively.

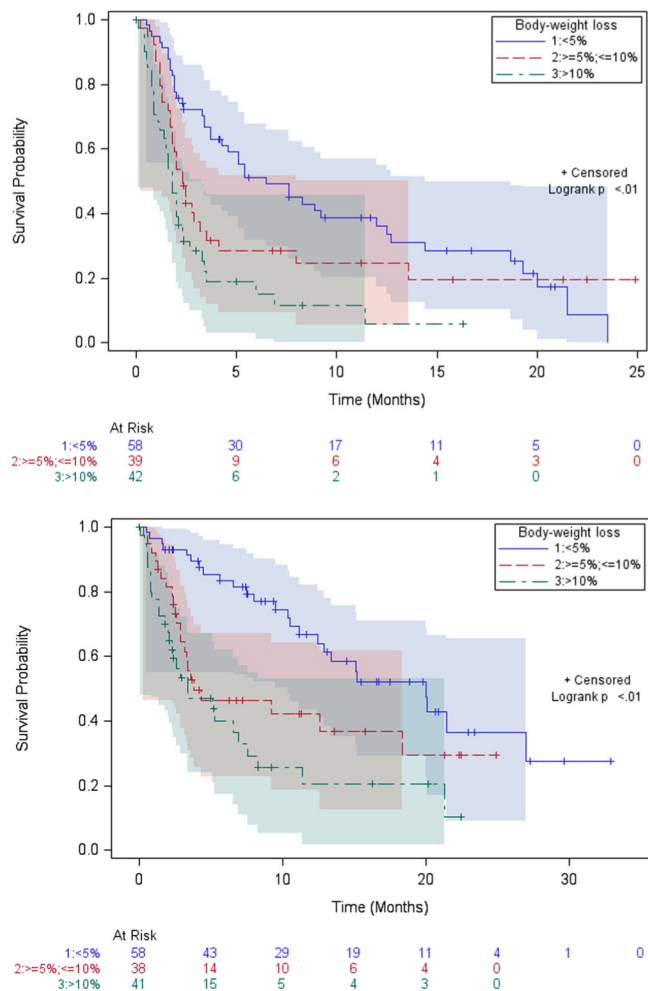


Fig. 1. Kaplan-Meier estimates of survival of non-small cell lung patients receiving anti-PD-1 immune-checkpoint inhibitors, according to body-weight loss in the three previous months; a: progression-free survival; b: overall survival.

3.4. Overall survival

In univariate analyses (Table 3), patients with a poor PS, patients with cachexia (Fig. 1b), patients with a serum albumin level < 32 g/L and active or former smoker patients had a significantly shorter OS in comparison with patients presenting with the opposite features of each variable. Patients with sarcopenia at the beginning of immunotherapy and patients with an evolving sarcopenia at the eighth week had a numerically shorter median OS when compared with patients without sarcopenia and those without evolving sarcopenia (Figs. 2b and 3 b). In addition, patients EGFR- or HER2mutant or ALK- or ROS1-translocated adenocarcinoma had a shorter median OS when compared with any other alteration of somatic genotype. There was a statistical trend towards an increased risk of death for patients who presented with sarcopenia at time of immunotherapy induction ($p = 0.08$) and for those who presented with an evolving sarcopenia ($p = 0.07$).

The function LOG (-LOG (S (t))) demonstrated that some variables, albeit affecting OS at a p level < 0.20 in the univariate analyses, did not satisfy the proportional hazard assumption: these variables were the BMI and the somatic genotype. Therefore the Cox model was stratified on these two variables. Patients with cachexia, serum albumin level < 32 g/L, and an evolving sarcopenia along the first eight weeks proved to have a shorter OS when compared with patients with opposite features of each variables with HR (95 % CI) : 6.26 (2.23–17.57), 2.80 (1.10–7.13), and 3.87 (1.60–9.34) respectively.

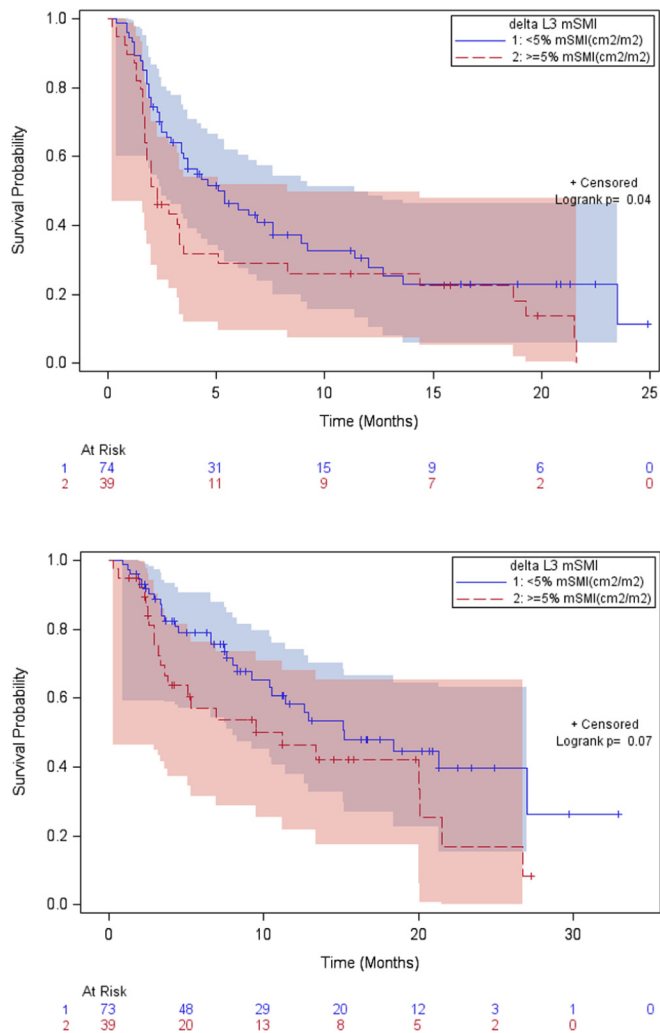


Fig. 2. Kaplan-Meier estimates of survival of non-small cell lung patients receiving anti-PD-1 immune-checkpoint inhibitors comparing patients with evolving sarcopenia defined as a decrease of 5% or more of third lumbar skeletal muscle mass index (L3 mSMI) during the first eight weeks of immunotherapy and patients with stable mSMI; a: progression-free survival; b: overall survival.

4. Discussion

In this study, we evaluated cachexia – sarcopenia syndrome along with other putative determinants of DCR and survival in patients receiving anti-PD-1 ICPI. This study took into account other known variables influencing patients outcome such as tumor PD-L1 IHC score, histology, age, PS, and basic somatic genotype. Prognosis of patients in the herein cohort depend on known features of weak activity of immunotherapy, namely a poor PS, an EGFR- mutant or ALK-rearranged adenocarcinoma [16], a PD-L1 IHC score < 1%. Cachexia, in its currently accepted definition, proved to be an important factor of outcome in patients receiving ICPI, insofar as it was a significant determinant of both DCR and OS. Previous studies suggested that the sarcopenia, as estimated by L3 mSMI, is a predictive determinant of immunotherapy failure but, in our study, it appeared to be mainly a determinant of long term prognosis affecting OS and influencing neither DCR nor PFS. The dynamic change in L3 mSMI during the first eight weeks appeared as a stronger determinant than sarcopenia at start of immunotherapy: a decrease of 5% or more of the L3 mSMI was a prognostic determinant of both poor PFS and OS. One can hypothesize that this dynamic changes reflect an ongoing metabolic modification towards catabolism. As many preclinical clues suggest that the catabolism reduces immune response [11], evolving sarcopenia as defined in the herein study, might be

regarded as a more reliable marker of ongoing metabolic processes with detrimental effect on immunotherapy efficacy. This is in accordance with similar reports in the setting of stage III NSCLC patients receiving chemoradiotherapy. Sanders et al. have reported a study which aimed at determining whether weight loss occurring during the first two months of chemoradiotherapy is a prognostic determinant in patients with stage IIIA or IIIB NSCLC [17]. Patients who did not have cachexia at the time of diagnosis and who completed the complete protocol were retrospectively analyzed. Among them, patients who had lost more than 5% of their body weight during the two first months of therapy had a shorter survival than did patients whose body-weight remained stable. Therefore, more than the crude pretreatment evaluation of cachexia – sarcopenia syndrome, the dynamic body-weight loss as measured in the Sanders’ study, or the evolving sarcopenia as measured during the first eight weeks in the herein study, are associated with a poor outcome during systemic therapy. We hypothesized that evolving sarcopenia is an important determinant of DCR and survival by reflecting an ongoing catabolic process leading to inhibition of many features of antitumor immunity immune response, including CD8+ T-cell stringent spatial exclusion from the tumor microenvironment [18]. On the opposite, DCR and survival of underweighted patients did not significantly differ when compared with survival of any other groups. One can hypothesize that BMI might reflect other features than cachexia - sarcopenia syndrome and does not systematically indicates an ongoing process.

As immunotherapy using ICPI might induce sustained control of the disease, but does so in a subpopulation of patients only, active search attempts at describing criteria able to discriminate patients expected to achieve a benefit and those for whom we have to spare futile toxicity [19]. In this perspective, the three disease characteristics having been investigated in NSCLC are the tumor PD-L1 score, the tumor mutational burden and the presence of CD8+ T-cells in the tumor microenvironment. Among them the former is considered as important in the setting of NSCLC as, for instance, first-line pembrolizumab is only approved with a PD-L1 IHC score over 50 % of tumor cells [3], and durvalumab consolidative therapy for chemoradiotherapy controlled patients with stage III unresectable NSCLC is approved by the European Medical Agency pending of a positive score [20]. Even if nivolumab is approved whatever the PD-L1 IHC score in patients with NSCLC progressing after a platinum-based first line of therapy, this score greatly influence nivolumab benefit [2]. Despite numerous weaknesses of the PD-L1 IHC score due to heterogeneity of PD-L1 expression in a single tumor, or between primary tumor and metastases, and the possible changes occurring along treatment time, this score is a reliable indication and a putative factor of stratification in randomized studies of immunotherapy in NSCLC [21]. The relationship between TMB and response to ICPI has been suggested in some studies [6] but this TMB – response relationship is not uniformly reported probably because there is no universally accepted definition of a high TMB [22]. Up till now, TMB assessment on tumor tissue or in plasma remains limited by its high cost and its clinical accessibility, particularly for whole exome sequencing. Consequently, TMB cannot yet be used in clinical practice. More specific knowledge on somatic mutations or comutations able to predict sensitivity, such as comutation of *TP53* (Tumor Protein 53) and *KRAS* genes, or resistance, such as comutation of *LKB1/STK11* and *KRAS* genes, of NSCLC to ICPI might be easier to apply in daily practice [8]. The analysis of tumor infiltrating immune cells is a promising marker of sensitivity to immunotherapy, as it has been deeply evaluated in a study of neoadjuvant immunotherapy [7]. After two infusions of neoadjuvant nivolumab, the resected tumor specimen was infiltrated by liquid containing CD8+ T-cells and PD-1 positive immune cells. Some of the infiltrating immune cells express PD-L1, which is consistent with an adaptive immune resistance mechanism. This elegant demonstration of CD8+ T-cell activation in the tumor microenvironment should be difficult to assess on smaller (non-surgical) specimens. Another promising method developed in order to predict tumor sensitivity to ICPI is positron emission tomography (PET) imaging with antibodies to PD-L1.

Table 3

Univariate analysis of progression-free and overall survival determinants in patients receiving immune check point inhibitors.

Variable		Progression free survival			Overall survival		
		median	95 %CI	Log-rank	median	95 %CI	Log-rank
Age (y)	< 64	2.5	1.8 – 3.5	0.42	9.5	4.3 – 18.4	0.40
	≥ 64	3.5	2 – 5.4		12.9	6.6 – 21.5	
Gender	Male	2.4	1.9 – 3.7	0.41	10.5	5.6 – 20.1	0.83
	Female	3.5	2.3 – 5.4		12.6	4.2 – 20	
Performance status	0 - 1	4.6	3.3 – 7.6	< 0.01	18.4	11.2 - 26.7	< 0.01
	> 1	1.6	1.1 - 2		2.5	1.5 – 3.4	
Body weight loss	< 5%	6.5	3.7 – 12	< 0.01	20	12.5 – 27	< 0.01
	5-10 %	2.3	1.7 – 3.2		3.8	2.9 – 18.4	
	> = 10 %	1.8	1.2 – 2.3		3.4	2.1 – 6.9	
PD-L1 IHC score	< 1%	2.3	1.6 – 3.3	0.06	8.3	3.3 - 20.1	0.46
	≥ 1 et < 20 %	2.8	1.7 - 5.1		6.6	3.2 – 12.6	
	≥ 20 et < 50 %	3.4	1.7 - 8.9		12.9	1.9 – NR*	
	≥ 50 %	4.6	2.3 - 12		15.11	3.4 – NR*	
Histology	ADC	3.4	2.3 - 5.4	< 0.01	10.4	5.6 – 20.1	0.22
	Non ADC	1.8	1.4 - 5.4		10.5	3.6 – 15.1	
Smoking status	Yes	3.3	2.3 - 4.6	0.09	12.5	7.5 – 20	0.03
	No	2.9	0.4 - 3.4		3.8	0.4 – 12.9	
Somatic genotype	BRAF	7.6	0.8 – NR*	0.10	NR*	NR*	< 0.01
	EGFR HER2 ALK ROS1 ^a	1.9	0.9 - 3.2		2.9	0.9 – 11.4	
	KRAS	2.8	1.9 – 7.6		8	3.6 – 21.5	
	None	3.4	2 – 5.1		12.6	7.6 – 20.1	
Immunotherapy sequence	First line	3.4	1.8 – 21.5	0.74	21.5	2.3 – NR*	0.78
	Subsequent line	2.9	2 – 4.1		10.5	6.9 – 15.2	
Body mass index	Underweighted (< 18.5)	19.3	1.2 – NR*	0.18	20	2.3 – NR*	0.04
	Normal (18.5–24.9)	2.5	2 – 3.4		6.6	3.3 – 15.2	
	Overweighted (25–29.9)	3.7	1.8 – 6.5		12.6	6.9 – 15.1	
	Obese (> 30)	7.6	1 – 18.7		NR*	1.5 – NR*	
Serum albumin (g/L)	< 32 g/L	1.15	0.6 – 2.3	< 0.01	1.9	0.8 – 2.9	< 0.01
	≥ 32 g/L	3.4	2.4 – 6.9		15.1	9.5 – 26.7	
Phosphoremia (mmol/L)	< 1,2	2.9	2 – 5.4	0.99	11.2	6.6 – 21.3	0.91
	> = 1,2	3.3	1.2 – 8		11.4	2 – NR*	
	Sarcopenia (H < 52.4/F < 38.05)	2.3	1.9 - 3.4		0.56	7.6	
mSMI (cm ² /m ²)	No sarcopenia (H > = 52.4/F > = 38.05)	4.1	2.8 – 7.6		12.6	9.2 – NR*	
	Yes (< 5% loss in mSMI)	5.1	3.4 – 7.6	0.04	15.2	10.4 –NR*	0.07
Evolving sarcopenia	No (< 5% loss in mSMI)	5.1	3.4 – 7.6		15.2	10.4 –NR*	
	Yes (≥ 5% loss in mSMI)	2.3	1.7 – 3.3		11.2	3.6 – 20.1	

Abbreviations used: SD : standard deviation ; PD-L1 IHC: programmed death-ligand 1 immunohistochemistry; ADC: adenocarcinoma; MD: missing data; mSMI : Skeletal muscle mass index. NR: not reached.

^a EGFR or HER2 mutation / ALK or ROS1 translocation.

For instance, ⁸⁹Zirconium-atezolizumab imaging was recently reported to allow pretreatment evaluation of primary tumors and their metastases in various malignancies including NSCLC [23]. In addition, clinical responses to atezolizumab therapy were better correlated with pretreatment PET signal rather than with immunohistochemistry- or RNA-sequencing based predictive biomarkers.

These different ways of improving the detection of patients who will benefit most from ICPI might need time before being applicable in daily clinical practice. Consequently, the negative correlation of cachexia – sarcopenia with response to immunotherapy cannot be neglected. Two others studies also suggest that cachexia might be a determinant of poor outcome of immunotherapy in NSCLC but they did not evaluate PD-L1 score, and other important covariables such as PS [9,10]. The herein study, allows an evaluation of cachexia - sarcopenia syndrome relatively to other important variables such a PD-L1 IHC score.

The relationship between weight loss and prognosis of patients undergoing ICPI therapy as observed in our study deserves further investigations aimed at determining whether an early intervention designed to reverse or slow down cachexia might improve a patient's outcome. In the past, studies evaluating progestational drugs or corticosteroids have failed to correct cancer cachexia, although these classical drugs might alleviate anorexia and increase weight [24]. There was actually no correction of cancer cachexia insofar as these drugs altered body composition by increasing fluid retention but decreased skeletal muscle mass. Recently, Temel et al. reported two simultaneous phase 3 studies comparing anamorelin versus placebo in lung cancer patients with cachexia [25]. Anamorelin is a high-affinity, selective

ghrelin-receptor agonist and thus acts through the insulin-like growth factor pathway. These two studies demonstrated that this agonist significantly increased lean body weight (as assessed at weeks 6 and 12 by dual-energy x-ray absorptiometry) but failed to modify muscle strength, a co-primary endpoint. Survival did not differ significantly between anamorelin and placebo groups, but various treatments were delivered in these large studies and a significant proportion of patients received best supportive care only. Therefore, there is still a case for investigating anamorelin in other settings such as immunotherapy of lung cancer.

There are limitations to our study: the first one is its retrospective nature. However, our institution has a long experience of recording for all patients the complete demography and disease characteristics covariables. In addition, the PD-L1 IHC score has been implemented at the very beginning of immunotherapy era. One can hypothesize that cachexia – sarcopenia syndrome is more a general marker of a poor prognosis rather than a predictive marker of therapy efficiency. Although we cannot rule out a predominant prognostic effect of cachexia – sarcopenia, as it is observed in other settings of NSCLC [24] and in other malignancies, the correlation of cachexia - sarcopenia with a low disease DCR at the eighth week in our study, suggests a possible interaction of cachexia – sarcopenia syndrome with failure of patient's immunity as putative explanation of this negative effect. The French Cooperative Thoracic Intergroup recently reported a real world study of nivolumab in NSCLC patients who experienced disease progression after chemotherapy in over 900 patients [26]. We project to validate the results of the present study in this larger cohort.

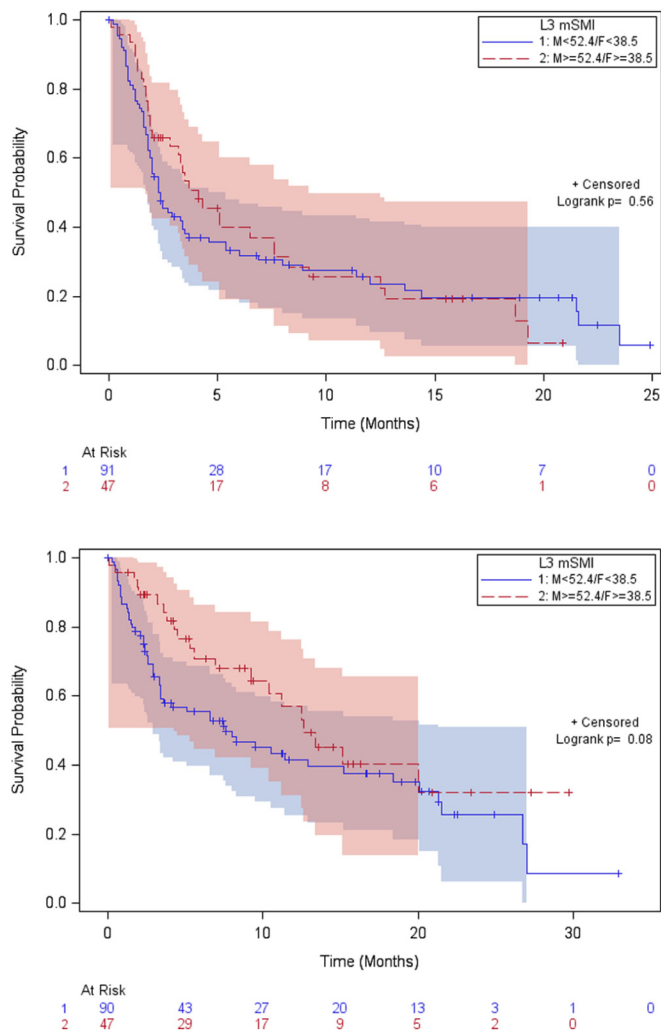


Fig. 3. Kaplan-Meier estimates of survival of non-small cell lung patients receiving anti-PD-1 immune-checkpoint inhibitors according to third lumbar skeletal muscle mass index (L3 mSMI) at time of immunotherapy induction; a: progression-free survival; b: overall survival.

In conclusion, NSCLC patients who have a cachexia – sarcopenia syndrome at the beginning of immunotherapy, and patients who experience a rapidly evolving sarcopenia have a lower probability of DCR and a shorter survival when compared with patients without this syndrome. Early evaluation of sarcopenic patients should be considered.

CRedit authorship contribution statement

Benoit Roch: Conceptualization, Data curation, Supervision, Validation, Writing - original draft, Writing - review & editing. **Amandine Coffy:** Conceptualization, Data curation, Formal analysis, Writing - review & editing. **Sandy Jean-Baptiste:** Data curation, Formal analysis, Investigation, Writing - review & editing. **Estelle Palaysi:** Conceptualization, Data curation, Formal analysis, Writing - review & editing. **Jean-Pierre Daures:** Conceptualization, Formal analysis, Methodology, Writing - original draft, Writing - review & editing. **Jean-Louis Pujol:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Writing - original draft, Writing - review & editing. **Sébastien Bommart:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

None for the current work.

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