The Impact of Body Composition Parameters on Severe Toxicity of Nivolumab

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Abstract

Background: The occurrence of severe, acute limiting toxicity in patients receiving anti-PD-1 monoclonal antibodies, such as nivolumab, is largely unpredictable. Sarcopenia was found associated with anti-CTLA4 acute toxicity. We explore the clinical and pharmacological parameters influencing nivolumab toxicity, including body composition.

Methods: From June 2015 to January 2017, all consecutive patients treated with nivolumab in our institution were prospectively included. We studied the relationship between muscle mass assessed by computed tomography, nivolumab trough level (C_{min}) at day 14 assessed using ELISA method, and the occurrence of immune grade 3 or 4 toxicity or any toxicity leading to treatment discontinuation (irALT).

Results: In our population (n=92) with a majority of lung cancer (72%), forty-five (51.7%) patients were sarcopenic. Median plasma nivolumab C_{min} at day 14 was 15.4 µg/mL (IQR=11.8-21.0). In multivariate analysis, hypoalbuminemia (<35g/L) was independently associated with low nivolumab C_{min} on day 14 (OR=0.09; 95%CI = 0.01-0.59, p=0.01) and overweight/obesity with high nivolumab C_{min} on day 14 (OR=5.94; 95%CI=1.25-28.29, p=0.03). We observed 22 irALT in 19 patients (21%). The most frequent irALT were respiratory (6.5%) disorders and gastrointestinal (4.3%) disorders. Patients with sarcopenia were at significantly increased risk of experiencing an irALT (OR = 3.84; 95%CI= 1.02-14.46, p=0.047). No association was found between toxicity and nivolumab plasma C_{min} at day 14.

Conclusions: Our results highlight the importance of assessing body composition, and suggest that sarcopenia could predict severe immune-related toxicity of nivolumab in real life.

Key words: lung cancer; nivolumab; pharmacology; body composition; toxicity

1. Introduction

Over the last years, immune checkpoint inhibitors (ICI) such as nivolumab have become a cornerstone treatment of various malignancies [1–3]. Nivolumab is a fully human monoclonal immunoglobulin G4 (IgG4) that targets programmed cell death receptor-1 (PD-1), providing improved overall survival with durable responses in solid tumor patients. On the other side, nivolumab and ICI have a specific toxicity profile, designated as immune-related adverse events (irAEs) [4]. IrAEs result from an activation of immune response against normal tissues. Severe irAEs occurred in about 10-20% of patients treated with anti-PD-1 monoclonal antibodies with a large interindividual variability [1–3]. Currently, predictors of nivolumab toxicity are still lacking for daily clinical practice.

During the last decade, body composition has been identified as a predictive factor of toxicity for various anticancer treatments. Sarcopenia (low muscle mass) is associated with increased toxicity [5], both for standard chemotherapy such as capecitabine in metastatic breast cancer patient [6], 5-fluoro-uracile in colorectal cancer [7] and tyrosine kinase inhibitors such as sunitinib in renal cancer patient [8] and sorafenib in hepatocellular carcinoma [9]. Regarding immunotherapy, patients with sarcopenia and low muscle attenuation are more likely to experience severe treatment-related toxicity with ipilimumab treatment [10]. For anti-PD-1 antibodies, sarcopenia and high body mass index (BMI) association has been identified as a risk factor for early toxicities in melanoma patients [11].

Sarcopenia could predict drugs over-exposure and thus, the occurrence of dose-dependent toxicities [9]. In the case of monoclonal antibodies, body composition participates in the inter-subject variability in drug exposure [12,13]. Moreover, anti-PD-1 antibodies exhibit a moderate to large interindividual variability in their pharmacokinetics [14]. As far as we know, the relationship between nivolumab toxicity, body composition and nivolumab exposure has not yet been investigated.

The aims of the present study were (a) to explore the influence of sarcopenia on the onset of immune-related acute limiting toxicity (irALT) in patients with advanced solid tumors and treated with nivolumab, (b) to investigate the relationship between body composition and nivolumab plasma exposure.

2. Materials and Methods

2.1 Participants

We performed a prospective medical record review of all consecutive adult patients treated with nivolumab for a metastatic solid tumor in the CERTIM cohort (Immunomodulatory Therapies Multidisciplinary Study group) of our institution from June 2015 to January 2017.

2.2 Ethics

The study was approved by the local ethics board (Cochin local ethical committee, number 5231487) according to good clinical practice and applicable laws, and the declaration of Helsinki. All patients gave their written informed consent to participate in the study.

2.3 Treatment

All patients received the recommended dose of nivolumab (3mg/kg intravenously every 2 weeks). Nivolumab was continued until disease progression or unacceptable toxicity.

2.4 Clinical and toxicity assessments

Clinical and biological assessments were performed before nivolumab treatment, including information on patient demographics, tumor type and stage, the extent of metastatic disease, prior oncological treatment and biochemistry results. Baseline thyroid disorder was collected and included hypo or hyperthyroidism. Toxicities were recorded at each cycle. Adverse events (AEs) severity was graded according to the National Cancer Institute Common Terminology Criteria for AE (CTCAE), version 4.0. irALT was defined as grade 3-4 toxicity or any toxicity leading to treatment discontinuation. irALT was associated with exposure to nivolumab and was consistent with a potential immunologic basis. This irALT could require: frequent monitoring until resolution, hospitalization, immune suppression, or endocrine replacement therapy. In our prospective study, investigators specified whether an AE was considered to be treatment related and/or immune related.

2.5 Pharmacokinetic analysis

Nivolumab trough plasma concentrations (C_{min}) were determined at day 14 using a validated in-house enzyme-linked immunosorbent assay (ELISA) [15]. The calibration range for nivolumab assay was 5-100 μg/mL with a limit of detection at 3 μg/mL. Within- and between-

day imprecision for internal quality controls (5, 20 and 75 µg/mL) were less than 5% and 12%, respectively. All plasma samples were analyzed within the month after blood collection.

2.6 Anthropometry and body composition

Weight closest to the first administration of nivolumab was measured with a medical balance beam scale and height was measured with a stadiometer. Body mass index (BMI) was calculated (weight (kg) / height (m^2)) and the World Health Organization (WHO) categories were used: underweight (BMI<18.5); normal (18.5<BMI<24.9); overweight (25<BMI<29.9), obesity (BMI>30) [16].

Body composition was evaluated by assessing muscle tissue areas on CT-scan images, as previously described [17]. CT scan closest to treatment initiation was used. CT scans had been performed within no more than two months before initiation of nivolumab. CT images parameters included: contrast enhanced or unenhanced and 3-mm slice thickness. The third lumbar vertebrae (L3) was chosen as a standard landmark, as previously described [17] and two consecutive transverse CT images where both transverse processes were clearly apparent were analyzed using ImageJ software v1.50i (National Institutes of Health, USA, http://rsb.info.nih.gov/ij). Muscles were identified based on their anatomic features. The structure of those specific muscles was analyzed based on pre-established thresholds of skeletal muscle tissue (-29 to +150 Hounsfield units). Cross-sectional areas (cm^2) of the sum of all of these muscles were computed and the mean value for the two consecutive images was calculated for each patient. These values were normalized for height and expressed in units of cm^2/m^2. Gender- and BMI-specific cut-points previously determined in cancer patients were used to define sarcopenia [18].

2.7 Statistical analysis

Continuous data are expressed as median (interquartile range), and categorical data are given as percentages. Cumulative incidence of irALT was assessed in the whole cohort. Log-rank test was used to compare survival between groups of patients. In patients with lung cancer, survival was measured from cohort entry until the date of progression or censored date for Progression Free Survival (PFS) and until the date of death or censored date for Overall Survival (OS). Logistic regression analyses were used to identify parameters associated with irALT and C_{min} (dichotomized based on median value), and odds ratios (OR) with 95% confidence intervals (95%IC) were estimated. Variables that had significance of p≤0.20 on univariate analysis were

eligible for inclusion in multivariate analysis. We considered differences to be statistically significant in multivariate analysis when the p value was <0.05.

Analyses were performed using SAS (version 9.4) statistical software (SAS Institute).

3. Results

3.1 Patients' characteristics

From June 2015 to January 2017, 92 patients received nivolumab in the CERTIM cohort in our institution. Among them, 87 met the criteria for the analysis of anthropometric parameters associated with irALT (5 patients lacked an evaluable CT image). Baseline characteristics of the study cohort (n=92) are presented in Table 1. Among 92 patients, 63% were male with a median age for the whole cohort of 64.6 years (IQR 56.3-69.8 years). A majority of patients had lung cancer (71.7%).

3.2 Anthropometry and body composition

A total of 38 (41.3%) patients had a BMI $\geq$ 25 kg/m^2 and 13 (14.1%) over 30, while 21 (24.1%) had both sarcopenia and a BMI $\geq$ 25 kg/m^2. Forty-five patients (51.7%) were sarcopenic according to Martin cut-points [16]. Only two patients (2.2%) were clinically underweight by WHO standards. Twenty-two patients (23.9%) had serum albumin < 35 g/L. All nutritional characteristics are shown in Table 2.

3.3 Factors influencing nivolumab plasma trough level

The median dose of nivolumab was 210 mg (range 130-370). Nivolumab plasma C_{min} was assayed in 87 patients on day 14 after treatment start and median nivolumab plasma C_{min} was 15.4 µg/mL (IQR=11.8-21.0). In multivariate analysis, hypoalbuminemia (<35g/L) was independently associated with low nivolumab plasma C_{min} (OR=0.09; 95%CI = 0.01-0.59, p=0.01) and overweight/obesity with high nivolumab plasma C_{min} (OR=5.94; 95%CI=1.25-28.29, p=0.03) (Table 3). No significant association was observed between plasma nivolumab C_{min} and sarcopenia.

3.4 The incidence of irALT

Among 825 nivolumab infusions, we observed 22 irALT in 19 (21%) patients. Patients received a median number of 6 nivolumab infusions (IQR=3-12) and half of all irALT occurred within

the first six infusions (Figure 1). The latest irALT was observed during the twenty-fifth cycle. The most frequent irALT were respiratory (6.5%) disorders such as pneumonitis and gastrointestinal (4.3%) disorders such as colitis.

The irALT also included musculoskeletal disorders (3.3%) such as arthralgia and myositis, two acute renal failures (2.2%), endocrine disorders with one hypophysitis (1.1%) and one diabetic ketoacidosis (1.1%), and others toxicities including one grade 3 thrombocytopenia (1.1%), one grade 4 myasthenia (1.1%), one grade 3 nervous system disorder (1.1%) and one grade 3 rash (1.1%). One death due to toxicity (1.1%) occurred, related to pulmonary hypertension.

3.5 Predictive factors of irALT: impact of body composition parameters

Patients with sarcopenia experienced more irALT compared with non-sarcopenic patients. Among the patients who experienced irALT, 76.5% were sarcopenic versus 45.7% in patients with no irALT (OR = 3.86; 95%CI= 1.14-13.01, p=0.03). The risk of irALT was also increased in female patients (OR = 4.28; 95%CI= 1.40-13.10, p=0.01). There was no significant association between overweight sarcopenic patients and irALT. On multivariate logistic regression analysis (Table 4) including age, gender, BMI, CRP, PS, tumor type and sarcopenia, sarcopenia was the single parameter independently associated with increased risk of experiencing an irALT (OR = 3.84; 95%CI= 1.02-14.46, p=0.047). There was no significant association between plasma nivolumab C_{min} and irALT. No association between irALT and efficacy data (OS and PFS) was found in patients with lung cancer (p=0.72 and p=0.34, respectively). In irALT group, 3 patients had a response to nivolumab (27.3%) versus 14 patients (25%) in no irALT group.

4. Discussion

This is the first study to examine the potential association between nivolumab toxicity, body composition and C_{min} of nivolumab at day 14. We have shown in this study that sarcopenic patients experienced significantly more immune-related acute limiting toxicities with no relationship with C_{min} of nivolumab.

In phase 3 studies, the incidence of immune acute limiting toxicity was between 10-20% [1–3]. In this real life study, the incidence was 21%, as might be expected in non-selected patients. Immune-related toxicity spectrum was close to those usually found with nivolumab. In our cohort, 51.7% of patients were sarcopenic based on CT-scan images before treatment initiation. The prevalence of sarcopenia in our study is in accordance with those reported previously in patients with renal cell carcinoma or NSCLC [8,19]. We reported that sarcopenic patients experienced significantly more irALT (OR = 3.84; 95%CI= 1.02-14.46, p=0,047). Previous studies reported a link between sarcopenia and increased toxicity of chemotherapy [6,20–22] or tyrosine kinase inhibitors [8,9]. This association has been observed in patients treated with anticancer drugs based on body surface area as well as flat-dosed targeted therapies. In the immunotherapy field, a study has reported an increased risk of high-grade ipilimumab AEs in sarcopenic patients [10]. An association between muscle attenuation (MA), which refers to a poor quality skeletal muscle, and serious irAEs was also reported [10]. In melanoma patients, sarcopenic overweight females seem to experiment more anti-PD1-related early adverse limiting toxicity [11]. Daly and al. also reported an association between BMI > 25 $kg.m^{-2}$ and toxicity, but patients with BMI > 25 $kg.m^{-2}$ had lower MA compared with patients with a normal BMI, and the increased risk of toxicity could most likely be attributed to the low MA [10]. A higher incidence of irAEs of any grade and a better clinical outcome were reported in overweight/obese patients treated with ICI [23]. A nonlinear relationship between BMI and ICI efficacy was found and might rather suggest a relationship between muscle loss and survival [24]. Sarcopenia is associated with worse survival in lung cancer patients treated with ICI in several retrospective studies [25–27]. However, sarcopenia was associated with more irAEs of any grade in patients with non-low skeletal muscle mass. When considering any grade and any toxicity, irAEs correlate with the efficacy of ICI [28]. Here, we studied the association between severe acute limiting toxicity and body composition. Severe acute toxicity did not appear as a predictive parameter for efficacy in the main subgroup of lung cancer patients, possibly because

of lack of power but also because limiting acute toxicities are not the best surrogate to analyze relationship between toxicity and efficacy.

Several hypotheses may be considered to explain the increased toxicity in sarcopenic patients. Altered body composition may influence pharmacokinetic parameters of anti-cancer drugs at any level: absorption, distribution, metabolism or clearance [29]. These alterations could result in an increased risk of toxicity, especially in drugs with narrow therapeutic index. However, different pharmacokinetic/pharmacodynamic studies argue for a large therapeutic index for nivolumab. In our study, we found neither association between plasma nivolumab C_{min} at day 14 and toxicity nor sarcopenia. These results suggest that the increased risk of irALT in sarcopenic patients would not be related to increased nivolumab plasma exposure. As a possible alternative to pharmacokinetic explanation, either malnutrition or systemic inflammation cause sarcopenia and may increase toxicity. Regarding inflammation, we found no association between irALT and CRP. However, proinflammatory cytokines such as IL1a, IL2 and IFNα2 were significantly upregulated in patients with severe immune-related toxicities at baseline and during treatment [30]. Cytokines such as IL-1 also play a pivotal role in promoting skeletal muscle atrophy and sarcopenia [5]. Systemic inflammation could underlie both irALT and sarcopenia. The association between sarcopenia and irALT could be based on Ubiquitin Proteasome system (UPS) as well. Sarcopenia is promoted by UPS [5]. UPS also contributes to the development of autoimmune disease; and some proteasome inhibitors such as bortezomib have demonstrated efficacy in autoimmune disease [31,32].Thus UPS could promote both sarcopenia and auto-immunity. Finally, sarcopenia is often considered as a sign of multifactorial frailty (including simultaneously malnutrition and inflammation), and thus could explain a lower treatment tolerance [33].

In our study, the interindividual variability in nivolumab C_{min} (CV=37%) was moderate, which is in accordance with the literature [14]. Albumin level below 35 g/L was identified as an independent predictor of lower nivolumab plasma C_{min}. This association was also reported for other monoclonal antibodies [34,35]. In a model-based population pharmacokinetic analysis, nivolumab clearance was greater in patients with lower albumin levels [36]. Hypoalbuminemia could be a sign of liver disease, hypercatabolism or low neonatal Fc receptor (FcRn) expression level or activity [37]. The recycling of albumin and monoclonal antibody such as nivolumab are both mediated by the same mechanism using FcRn and therefore albumin level may reflect the abundance and efficiency of FcRn [38]. In our study, nivolumab plasma C_{min} at day 14 is

also positively associated with BMI. Due to their high molecular weight, monoclonal antibodies are mainly distributed in vascular compartment, with a consequently low volume of distribution [12]. But a small proportion passes through or between cell membranes via transcellular or paracellular mechanisms towards peripheral compartments [39]. In pediatric patients, known for having higher interstitial fluid volume, monoclonal antibodies volume of distribution is higher [40]. Considering that nivolumab volume of distribution is around 8.0 liters, which is greater than human total blood volume, we can hypothesize that nivolumab could diffuse in peripheral compartment. Overweight patients are also characterized by a higher fluid volume [41]. This could explain a higher volume of distribution, responsible for a lengthened half-life and thus increased nivolumab plasma C_{min}. Overall, even if serum albumin and BMI were identified as variability factors of nivolumab plasma C_{min}, at day 14, the variations in plasma exposure related to these parameters were not clinically meaningful because of large therapeutic index of nivolumab [14].

The main limitations of our study are the relatively small number of patients included and the few biological and CT-scan missing data despite prospective data collection, decreasing the statistical power of some analyses.

Facing the increasing use of anti-PD1 and immunotherapy combinations, without toxicity biomarkers identified yet, our results highlight the importance of assessing body composition, and suggest that sarcopenia could predict severe immune-related toxicity of nivolumab. Our findings have potentially direct bedside implications, as evaluating sarcopenia on CT scan is feasible in daily practice due to opportunistic use of pre-existing CT scans , and more accurate than other methods for assessing body composition. This would enable enhanced follow-up of patients at risk for better management of immune related toxicities. As immune related toxicities could occur at any time of nivolumab treatment, strengthened surveillance could be necessary all along patient care. The importance of body composition in the field of immunotherapy is worth investigating further.

References

[1] Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:1627–39. https://doi.org/10.1056/NEJMoa1507643.

[2] Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 2015;373:1803–13. https://doi.org/10.1056/NEJMoa1510665.

[3] Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015;372:320–30. https://doi.org/10.1056/NEJMoa1412082.

[4] Champiat S, Lambotte O, Barreau E, Belkhir R, Berdelou A, Carbonnel F, et al. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. Ann Oncol 2016;27:559–74. https://doi.org/10.1093/annonc/mdv623.

[5] Bozzetti F. Forcing the vicious circle: sarcopenia increases toxicity, decreases response to chemotherapy and worsens with chemotherapy. Ann Oncol 2017;28:2107–18. https://doi.org/10.1093/annonc/mdx271.

[6] Prado CMM, Baracos VE, McCargar LJ, Reiman T, Mourtzakis M, Tonkin K, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res 2009;15:2920–6. https://doi.org/10.1158/1078-0432.CCR-08-2242.

[7] Prado CMM, Baracos VE, McCargar LJ, Mourtzakis M, Mulder KE, Reiman T, et al. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. Clin Cancer Res 2007;13:3264–8. https://doi.org/10.1158/1078-0432.CCR-06-3067.

[8] Huillard O, Mir O, Peyromaure M, Tlemsani C, Giroux J, Boudou-Rouquette P, et al. Sarcopenia and body mass index predict sunitinib-induced early dose-limiting toxicities in renal cancer patients. Br J Cancer 2013;108:1034–41. https://doi.org/10.1038/bjc.2013.58.

[9] Mir O, Coriat R, Blanchet B, Durand J-P, Boudou-Rouquette P, Michels J, et al. Sarcopenia predicts early dose-limiting toxicities and pharmacokinetics of sorafenib in patients with hepatocellular carcinoma. PLoS ONE 2012;7:e37563. https://doi.org/10.1371/journal.pone.0037563.

[10] Daly LE, Power DG, O'Reilly Á, Donnellan P, Cushen SJ, O'Sullivan K, et al. The impact of body composition parameters on ipilimumab toxicity and survival in patients with metastatic melanoma. Br J Cancer 2017;116:310–7. https://doi.org/10.1038/bjc.2016.431.

[11] Heidelberger V, Goldwasser F, Kramkimel N, Jouinot A, Huillard O, Boudou-Rouquette P, et al. Sarcopenic overweight is associated with early acute limiting toxicity of anti-PD1 checkpoint inhibitors in melanoma patients. Invest New Drugs 2017. https://doi.org/10.1007/s10637-017-0464-x.

[12] Dirks NL, Meibohm B. Population pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokinet 2010;49:633–59. https://doi.org/10.2165/11535960-000000000-00000.

[13] Keizer RJ, Huitema ADR, Schellens JHM, Beijnen JH. Clinical pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokinet 2010;49:493–507. https://doi.org/10.2165/11531280-000000000-00000.

[14] Sheng J, Srivastava S, Sanghavi K, Lu Z, Schmidt BJ, Bello A, et al. Clinical Pharmacology Considerations for the Development of Immune Checkpoint Inhibitors. J Clin Pharmacol 2017;57 Suppl 10:S26–42. https://doi.org/10.1002/jcph.990.

[15] Puszkiel A, Noé G, Boudou-Rouquette P, Cossec CL-, Arrondeau J, Giraud J-S, et al. Development and validation of an ELISA method for the quantification of nivolumab in plasma from non-small-cell lung cancer patients. Journal of Pharmaceutical and Biomedical Analysis 2017;139:30–6. https://doi.org/10.1016/j.jpba.2017.02.041.

[16] Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser 2000;894:i–xii, 1–253.

[17] Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab 2008;33:997–1006. https://doi.org/10.1139/H08-075.

[18] Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol 2013;31:1539–47. https://doi.org/10.1200/JCO.2012.45.2722.

[19] Baracos VE, Reiman T, Mourtzakis M, Gioulbasanis I, Antoun S. Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. Am J Clin Nutr 2010;91:1133S-1137S. https://doi.org/10.3945/ajcn.2010.28608C.

[20] Barret M, Antoun S, Dalban C, Malka D, Mansourbakht T, Zaanan A, et al. Sarcopenia is linked to treatment toxicity in patients with metastatic colorectal cancer. Nutr Cancer 2014;66:583–9. https://doi.org/10.1080/01635581.2014.894103.

[21] Prado CMM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol 2008;9:629–35. https://doi.org/10.1016/S1470-2045(08)70153-0.

[22] Tan BHL, Birdsell LA, Martin L, Baracos VE, Fearon KCH. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clin Cancer Res 2009;15:6973–9. https://doi.org/10.1158/1078-0432.CCR-09-1525.

[23] Cortellini A, Bersanelli M, Buti S, Cannita K, Santini D, Perrone F, et al. A multicenter study of body mass index in cancer patients treated with anti-PD-1/PD-L1 immune checkpoint inhibitors: when overweight becomes favorable. J Immunother Cancer 2019;7:57. https://doi.org/10.1186/s40425-019-0527-y.

[24] Naik GS, Waikar SS, Johnson AEW, Buchbinder EI, Haq R, Hodi FS, et al. Complex inter-relationship of body mass index, gender and serum creatinine on survival: exploring the obesity paradox in melanoma patients treated with checkpoint inhibition. J Immunother Cancer 2019;7:89. https://doi.org/10.1186/s40425-019-0512-5.

[25] Nishioka N, Uchino J, Hirai S, Katayama Y, Yoshimura A, Okura N, et al. Association of Sarcopenia with and Efficacy of Anti-PD-1/PD-L1 Therapy in Non-Small-Cell Lung Cancer. J Clin Med 2019;8. https://doi.org/10.3390/jcm8040450.

[26] Shiroyama T, Nagatomo I, Koyama S, Hirata H, Nishida S, Miyake K, et al. Impact of sarcopenia in patients with advanced non-small cell lung cancer treated with PD-1 inhibitors: A preliminary retrospective study. Sci Rep 2019;9:2447. https://doi.org/10.1038/s41598-019-39120-6.

[27] Cortellini A, Verna L, Porzio G, Bozzetti F, Palumbo P, Masciocchi C, et al. Predictive value of skeletal muscle mass for immunotherapy with nivolumab in non-small cell lung cancer patients: A "hypothesis-generator" preliminary report. Thorac Cancer 2019;10:347–51. https://doi.org/10.1111/1759-7714.12965.

[28] Haratani K, Hayashi H, Chiba Y, Kudo K, Yonesaka K, Kato R, et al. Association of Immune-Related Adverse Events With Nivolumab Efficacy in Non-Small-Cell Lung Cancer. JAMA Oncol 2018;4:374–8. https://doi.org/10.1001/jamaoncol.2017.2925.

[29] Trobec K, Kerec Kos M, von Haehling S, Springer J, Anker SD, Lainscak M. Pharmacokinetics of drugs in cachectic patients: a systematic review. PLoS ONE 2013;8:e79603. https://doi.org/10.1371/journal.pone.0079603.

[30] Lim SY, Lee JH, Gide TN, Menzies AM, Guminski A, Carlino MS, et al. Circulating Cytokines Predict Immune-Related Toxicity in Melanoma Patients Receiving Anti-PD-1-Based Immunotherapy. Clin Cancer Res 2019;25:1557–63. https://doi.org/10.1158/1078-0432.CCR-18-2795.

[31] Verbrugge SE, Scheper RJ, Lems WF, de Gruijl TD, Jansen G. Proteasome inhibitors as experimental therapeutics of autoimmune diseases. Arthritis Res Ther 2015;17:17. https://doi.org/10.1186/s13075-015-0529-1.

[32] Bulatov E, Valiullina A, Sayarova R, Rizvanov A. Promising new therapeutic targets for regulation of inflammation and immunity: RING-type E3 ubiquitin ligases. Immunol Lett 2018;202:44–51. https://doi.org/10.1016/j.imlet.2018.08.001.

[33] Ethun CG, Bilen MA, Jani AB, Maithel SK, Ogan K, Master VA. Frailty and cancer: Implications for oncology surgery, medical oncology, and radiation oncology. CA Cancer J Clin 2017;67:362–77. https://doi.org/10.3322/caac.21406.

[34] Lu J-F, Bruno R, Eppler S, Novotny W, Lum B, Gaudreault J. Clinical pharmacokinetics of bevacizumab in patients with solid tumors. Cancer Chemother Pharmacol 2008;62:779–86. https://doi.org/10.1007/s00280-007-0664-8.

[35] Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res 2006;23:1275–84. https://doi.org/10.1007/s11095-006-0205-x.

[36] Bajaj G, Wang X, Agrawal S, Gupta M, Roy A, Feng Y. Model-Based Population Pharmacokinetic Analysis of Nivolumab in Patients With Solid Tumors. CPT Pharmacometrics Syst Pharmacol 2017;6:58–66. https://doi.org/10.1002/psp4.12143.

[37] Pyzik M, Rath T, Kuo TT, Win S, Baker K, Hubbard JJ, et al. Hepatic FcRn regulates albumin homeostasis and susceptibility to liver injury. Proc Natl Acad Sci USA 2017;114:E2862–71. https://doi.org/10.1073/pnas.1618291114.

[38] Tabrizi M, Bornstein GG, Suria H. Biodistribution mechanisms of therapeutic monoclonal antibodies in health and disease. AAPS J 2010;12:33–43. https://doi.org/10.1208/s12248-009-9157-5.

[39] Wang W, Wang EQ, Balthasar JP. Monoclonal antibody pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther 2008;84:548–58. https://doi.org/10.1038/clpt.2008.170.

[40] Mould DR, Green B. Pharmacokinetics and pharmacodynamics of monoclonal antibodies: concepts and lessons for drug development. BioDrugs 2010;24:23–39. https://doi.org/10.2165/11530560-000000000-00000.

[41] Waki M, Kral JG, Mazariegos M, Wang J, Pierson RN, Heymsfield SB. Relative expansion of extracellular fluid in obese vs. nonobese women. Am J Physiol 1991;261:E199-203. https://doi.org/10.1152/ajpendo.1991.261.2.E199.

Figure Legends:

Figure 1: Cumulative incidence of irALT over time since first infusion of nivolumab

| Number at risk | 92 | 80 | 63 | 47 | 36 | 30 | 22 | 13 | 9 | 8 |
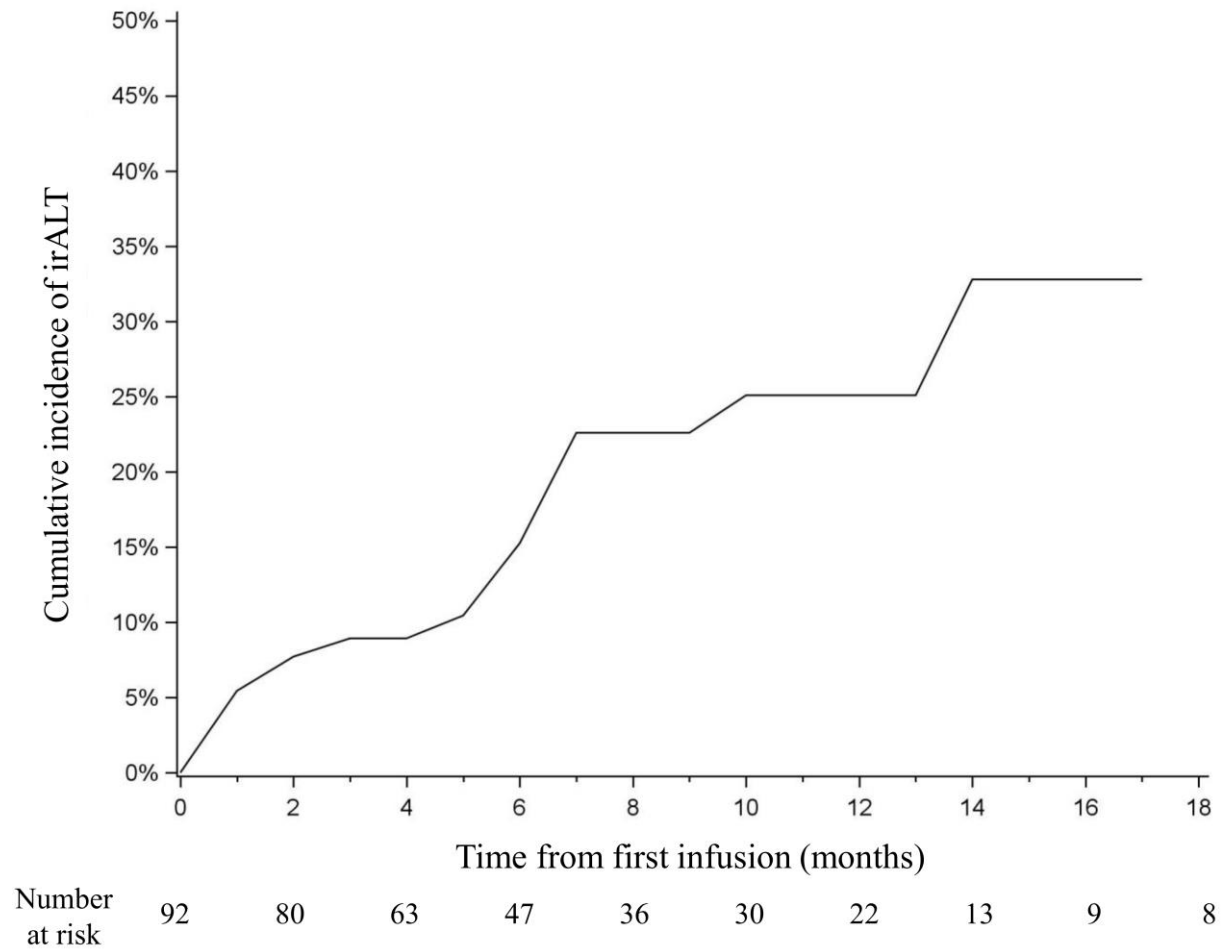
Tables

	n = 92
Age (years), median (IQR)	64.6 (56.3-69.8)
Gender: Male/Female, n (%)	58 (63) / 34 (37)
ECOG Performans status: 0-1/≥2, n (%)	56 (60.9) / 36 (39.1)
Tumor type, n (%)	
Lung cancer	66 (71.7)
Renal Cell Carcinoma	17 (18.5)
Melanoma	7 (7.6)
Others	2 (2.2)
Number of metastatic sites: 1/≥2, n (%)	32 (34.8) / 60 (65.2)
CNS metastasis at treatment initiation	21 (22.8)
First line treatment, n (%)	11 (12.0)
Systemic steroid use at 1st cycle of nivolumab	12 (13.0)
Baseline thyroid disorder	11 (12.0)

Abbreviation: IQR = interquartile range, ECOG = Eastern Cooperative Oncology Group, CNS = central nervous system

Table 1: Baseline characteristics

	n = 92
BMI (kg/m^2), n (%)	
BMI < 18.5	2 (2.2)
18.5 ≤ BMI < 25	52 (56.5)
25 ≤ BMI < 30	25 (27.2)
BMI ≥ 30	13 (14.1)
SMI (cm^2/m^2) , median (IQR)	43.8 (39.3-50.4)
Sarcopenia	
Sarcopenic patient, n (%)	45 (51.7)
Missing data, n (%)	5 (5.4)
Sarcopenia and BMI ≥ 25, n (%)	21 (24.1)
Serum Albumin (g/L), median (IQR)	40.0 (36.0-42.0)
Serum Albumin < 35 g/L, n (%)	22 (23.9)
Missing data, n (%)	1 (1.1)
Lymphocytes (cells/mm^3)	1215 (935-1830)
C reactive protein (mg/L)	10.8 (4.4-29.4)
IgG (g/L)	10.3 (7.6-13.0)

Abbreviation: BMI = Body Mass Index, IQR = interquartile range, SMI : skeletal muscle index, IgG = Immunoglobulin G

Table 2: Nutritional and inflammation parameters

	Univariate			Multivariate		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Gender: Female	2.82	1.14-6.98	0.02	2.86	0.85-9.64	0.09
BMI $\geq$ 25 kg/m^2	4.62	1.82-11.72	0.001	**5.94**	1.25-28.29	**0.03**
CRP	0.98	0.96-0.99	0.01	0.95	0.77-1.17	0.61
IgG	0.88	0.77-1.01	0.06	0.90	0.77-1.06	0.21
Alb < 35 g/L	0.09	0.02-0.40	0.002	**0.09**	0.01-0.59	**0.01**
ALAT	1.03	0.99-1.06	0.11	1.42	0.93-2.16	0.10
Sarcopenia	1	0.42-2.38	1.00	-	-	-

Abbreviation: OR = Odds Ratio; CI = Confidence Interval; CRP = C reactive Protein; IgG = Immunoglobulin G; Alb = Serum Albumin; ALAT = alanine aminotransferase;

Table 3: Factors influencing nivolumab plasma trough level at day 14 (C_{min} > median value)

	irALT (n=17)	No ALT (n=70)	univariate			multivariate		
			OR	95% CI	p	OR	95% CI	p
Age (years)	65.0 (60.9-73.4)	64.5 (55.0-69.7)	1.03	0.97-1.09	0.30			
Gender: Female	11 (64.7)	21 (30.0)	4.28	1.40-13.10	0.01	2.67	0.77-9.27	0.12
ECOG PS $\geq$ 2	4 (23.5)	30 (42.9)	0.41	0.12-1.38	0.15	0.52	0.12-2.31	0.39
Lung cancer vs other cancers	10 (58.8)	53(75.7)	0.46	0.15-1.39	0.17	0.43	0.11-1.73	0.24
Baseline thyroid disorder	4 (23.5)	7 (10.0)	2.77	0.71-10.85	0.14	1.91	0.38-9.58	0.43
Baseline systemic steroid	1 (5.9)	10 (14.3)	0.37	0.04-3.15	0.37			
BMI $\geq$ 25 kg/m^2	8 (47.1)	27 (38.6)	1.42	0.49-4.11	0.52			
CRP	12.2 (4.20-33.8)	8.80 (5.50-13.9)	0.97	0.94-1.01	0.11	0.76	0.49-1.19	0.23
Albumin < 35 g/L	3 (17.6)	15 (21.4)	0.79	0.20-3.10	0.73			
Sarcopenia	**13 (76.5)**	**32 (45.7)**	**3.86**	**1.14-13.01**	**0.03**	**3.84**	**1.02-14.46**	**0.047**
C_{min} > median value	32 (48.5)	9 (56.3)	1.37	0.45-4.10	0.58			

Abbreviation : OR = Odds Ratio, CI = Confidence Interval, PS = Performans Status, BMI = Body Mass Index, CRP = C Reactive Protein,
C_{min} = nivolumab plasma trough level on day 14

Results are expressed as median (interquartile range) or number (%). Patients with no available CT scan were excluded from the analysis of predictive factors of acute limiting toxicity.

Table 4: Predictive factors of immune related Acute Limiting Toxicity (irALT) related to Nivolumab