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The impact of body composition parameters on ipilimumab toxicity and survival in patients with metastatic melanoma

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Background: Body composition is an important predictor of drug toxicity and outcome. Ipilimumab (Ipi), a monoclonal antibody used to treat metastatic melanoma, has specific toxicities. No validated biomarkers that predict Ipi toxicity and efficacy exist. Also, the impact of Ipi on body composition has not been established.

Methods: Patients with metastatic melanoma treated with Ipi between 2009 and 2015 were included. Body composition was assessed by computed tomography at baseline and after four cycles of Ipi. Sarcopenia and low muscle attenuation (MA) were defined using published cut-points. All adverse events (AEs) and immune-related AEs (irAEs) were recorded (Common Terminology Criteria For Adverse Event V.4.0).

Results: Eighty-four patients were included in this study (62% male, median age 54 years). At baseline, 24% were sarcopenic and 33% had low MA. On multivariate analysis, sarcopenia and low MA were significantly associated with high-grade AEs (OR = 5.34, 95% CI: 1.15–24.88, $P = 0.033$; OR = 5.23, 95% CI: 1.41–19.30, $P = 0.013$, respectively), and low MA was associated with high-grade irAEs (OR = 3.57, 95% CI: 1.09–11.77, $P = 0.036$). Longitudinal analysis ($n = 59$) revealed significant reductions in skeletal muscle area (SMA), total body fat-free mass, fat mass (all $P < 0.001$) and MA ($P = 0.030$). Mean reduction in SMA was 3.3%/100 days (95% CI: −4.48 to −1.79%, $P < 0.001$). A loss of SMA ⩾7.5%/100 days (highest quartile) was a significant predictor of overall survival in multivariable Cox regression analysis (HR: 2.1, 95% CI: 1.02–4.56, $P = 0.046$).

Conclusions: Patients with sarcopenia and low MA are more likely to experience severe treatment-related toxicity to Ipi. Loss of muscle during treatment was predictive of worse survival. Treatments to increase muscle mass and influence outcome warrant further investigation.

In Europe, malignant melanoma of the skin is the seventh and tenth most common cancer diagnosed in women and men, respectively (International Agency for Research on Cancer, Cancer Fact Sheets 2012). Traditionally, patients with metastatic melanoma have been known to have a dismal prognosis, with a median overall survival of 8–10 months and a 5-year survival rate of 10% (Garbe *et al*, 2011). Curative surgical options are available in the early stages of the disease; however, once the disease has progressed to an advanced stage, treatment options are largely confined to systemic therapy and long-term remission is uncommon.

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In the modern era, due in part to advances in therapies that stimulate an immune-mediated antitumour response, more treatment options are available for those with advanced melanoma. Ipilimumab, a novel anticytotoxic T-cell lymphocyte-4 monoclonal antibody, was the first of its kind to demonstrate a significant survival benefit in previously treated metastatic melanoma patients (median OS 10.1 months *vs* 6.4 months in gp100 vaccine group; 1- and 2-year survival rates of 45.6% and 23.5%, respectively, in the ipilimumab arm) (Hodi *et al*, 2010). Following the release of this phase III data, ipilimumab was approved by the US Food and Drug Administration and by the European Medicines Association at a dose of $3\,mg\,kg^{-1}$ body weight in patients with metastatic melanoma.

Ipilimumab augments T-cell activation and proliferation with the goal of reducing immune tolerance to cancer-specific antigens (Robert and Ghiringhelli, 2009). As a result, ipilimumab can result in an activation of immune responses against normal tissue, which can result in 'immune-related adverse events (irAEs)' (Hodi *et al*, 2010). The irAEs have been well described. Approximately 61% of patients treated with ipilimumab experience an irAE (any grade), whereas 17% of patients experience a high-grade irAE (grades III and IV) (Bertrand *et al*, 2015). IrAEs most commonly affect the gastrointestinal (GI) tract, the skin or endocrine glands (Hodi *et al*, 2010; Bertrand *et al*, 2015). Such adverse effect can be treated effectively with immunosuppressive agents (Weber *et al*, 2012). To date, little is known in relation to factors predicting ipilimumab toxicity.

Over the past decade, sarcopenia (low muscle mass) and its relationship to adverse clinical outcomes has been extensively studied and shown to be associated with increase length of hospital stay (Pichard *et al*, 2004), postoperative infections (Lieffers *et al*, 2012), functional impairment and decreased survival in both malignant (Tan *et al*, 2009; Martin *et al*, 2013) and non-malignant (Montano-Loza *et al*, 2012) populations. Sarcopenia and its relationship to anticancer treatment toxicity has been particularly topical in the literature, and studies have consistently demonstrated that sarcopenia is associated with poorer treatment tolerance and increased prevalence of dose-limiting toxicity (DLT) to many anticancer/chemotherapeutic drugs, for example, epirubicin (Prado *et al*, 2011), capecitabine (Prado *et al*, 2009), sunitinub (Huillard *et al*, 2013; Cushen *et al*, 2014), 5-FU and leucovorin (Prado *et al*, 2007). More recently, low muscle attenuation (MA), which refers to a poor quality skeletal muscle (increased intramuscular adipose tissue) has been the focus of much research. Low MA has been identified as a predictor of reduced survival in renal cell carcinoma (Antoun *et al*, 2013b) and stage III melanoma (Sabel *et al*, 2011), as well as lung and GI malignancies (Martin *et al*, 2013; Blauwhoff-Buskermolen *et al*, 2016).

To our knowledge, the association between altered/abnormal body composition, that is, sarcopenia and low MA, and the incidence of treatment-related AEs to ipilimumab has not yet been reported. With increasing use of ipilimumab in clinical practice, there is an urgent need for potential biomarkers that are predictive of treatment toxicity. The primary aim of this study was to investigate if body composition, specifically sarcopenia and low MA, assessed by computed tomography (CT) could predict toxicity to ipilimumab in patients with metastatic melanoma. A secondary aim of this study was to determine the changes in body composition that occur during treatment and to assess if these changes impact on survival.

MATERIALS AND METHODS

Study population. We performed a retrospective medical record review of all consecutive adult patients treated with ipilimumab at two university teaching hospitals between the years of 2009 and 2015. Patients were excluded from this study if they lacked an evaluable pre-treatment CT image. This study was approved by the local ethics committee and conducted according to good clinical practice and applicable laws.

Clinical details. Clinical and pathological data was collected by a retrospective chart review, including information on patient demographics, primary tumour site/stage, the extent of metastatic disease, biochemistry results and oncological treatment. Patient's date of death (if present) or date of last follow-up was recorded.

Anthropometry and body composition. Weight and height closest to the initiation of cycle 1 of treatment was recorded from the medical charts. Body mass index (BMI) was calculated (weight (kg) height (m^{-2})).

Pre- and post-treatment CT images taken as part of routine patient care were accessed from the hospitals electronically stored database. Body composition was evaluated using CT images, as described previously (Heymsfield *et al*, 1997). The third lumbar vertebrae (L3) was chosen as the standard landmark (Shen *et al*, 2004) and two consecutive transverse CT images where both transverse processes were clearly visible were analysed using the OsiriX software version 4.1.1 (Pixmeo, Geneva, Switzerland) and the average result reported. Different tissue compartments were manually outlined and segmentation of the skeletal muscle and adipose tissue was based on Hounsfield unit (HU) thresholds (-29 to $+150$, and -30 to -190 HU, respectively (Mitsiopoulos *et al*, 1998). Cross-sectional areas (cm^2) for muscle and adipose tissue were automatically calculated by summing tissue pixels and multiplying by pixel surface area after applying HU thresholds. Mean MA is reported for the entire muscle area at L3. Anonymised CT images were analysed by the two trained study assessors (LD and SC) who were blinded to the order of images (pre- and post-ipilimumab treatment). Pre-treatment images were taken before treatment administration (mean 39 ± 31 days). Post-treatment images were taken after the final dose of ipilimumab was administered (mean 35 ± 31 days). The mean number of days between the two scans was 146 ± 40 days. To account for variation in the exact duration of scan intervals, changes in tissue are expressed as % change/100 days to provide a standard measure for all patients.

The lumbar cross-sectional areas of muscle and fat are linearly related to whole-body measures (Shen *et al*, 2004). Estimates of whole-body fat mass (FM) and fat-free mass (FFM) were calculated using published regression equations as follows (Mourtzakis *et al*, 2008): FFM (kg) $= 0.3 \times$ (skeletal muscle cross-sectional area at L3 (cm^2)) $+ 6.06$; $r^2 = 0.88$, FM (kg) $= 0.042 \times$ (Adipose tissue cross-sectional area at L3 (cm^2)) $+ 11.2$; $r^2 = 0.77$. Gender- and BMI-specific cut-points were used to define sarcopenia and low MA (Martin *et al*, 2013).

Treatment tolerability. Toxicity profiles were recorded on all patients by reviewing patient's medical notes. Toxicity was recorded across all administered cycles of ipilimumab. The standard dose for ipilimumab is $3\,mg\,kg^{-1}$ body weight administered intravenously over a 90-min period every 3 weeks for four doses. Adverse events were classified according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. For further analyses, toxicity was divided into grades I–II and grades III–IV. An irAE was defined as an AE that was associated with exposure to ipilimumab and that was consistent with an immune-related phenomenon. The irAEs recorded were those most commonly reported. A high-grade AE/irAE was defined as a grade III–IV toxicity. A high-grade AE included all high-grade AEs, both general and immune-related high-grade AEs. Any dose delays or early cessation of treatment as

a result of significant toxicity (grades III–IV) was recorded, and in this study it was defined as a DLT.

Statistical assessment. Statistical analysis was completed using SPSS (version 21.0, SPSS Inc., Chicago, IL, USA). Data are expressed as mean ± s.d. or median (IQR) where appropriate.

Comparisons between groups of patients were assessed using χ^2 test for categorical variables and unpaired *t*-tests and Mann–Whitney *U*-tests to test for differences between continuous variables. Paired *t*-tests were used to assess changes in body composition. The McNemar's test was to test for significances in paired categorical data.

Logistic regression analyses were used to test associations between treatment toxicity and measures of body composition (baseline sarcopenia *vs* not sarcopenic and low MA *vs* without low MA). Variables that had significance of $P \leqslant 0.25$ on univariate analysis were eligible for inclusion in multivariate analysis.

Survival curves were constructed using the Kaplan–Meier technique and log-rank test was used to compare survival between groups of patients. Survival was measured from the date of the baseline (pre-treatment) CT image until the date of death or censored date (study completion). Median follow-up time (time in study) for the entire cohort was 12.8 months [IQR: 5.45–21.7 months; 9.2 months (IQR 4.8–15.3 months) for patients who had died and 24.1 months for censored cases (IQR 15.5–33.4 months)] and 70% of patients had died by completion of the study. Cox proportional hazards analyses was performed, and hazard ratios (HR) with 95% confidence intervals (CI) calculated. All *P*-values were two sided, and the level of significance was $P < 0.05$.

RESULTS

Participants. From July 2010 to July 2015, 96 patients received ipilimumab, of which 84 patients met the criteria for study analysis (12 patients lacked an evaluable CT image). MA analysis was carried out on all patients with a contrast-enhanced CT image ($n = 72$).

Patient characteristics. Baseline characteristics are presented in Table 1. In brief, among the 84 patients studied, 62% were male with a median age of 54 years (IQR 43–66 years). The majority of patients (79%) had stage M1c metastatic disease, with the most common metastatic sites being lung (70%) and liver (41%). Ipilimumab was first-line treatment in 34.5% of patients.

Anthropometry. Table 2 describes the body composition features of the cohort. Fifty-nine patients (70%) were considered overweight or obese (BMI $\geqslant 25\,kg\,m^{-2}$), while very few (only two patients) were clinically underweight by WHO standards. Twenty patients (24%) were sarcopenic (20 of 84) and 24 (24 of 72) (33.3%) were considered to have a low MA.

Sarcopenic patients differed significantly from non-sarcopenic patients as expected with a lower skeletal muscle area (SMA) (161.2 *vs* 121.4 cm^2, $P \leqslant 0.001$), skeletal muscle index (SMI) (54.7 *vs* 41.1 $cm^2\,m^{-2}$, $P < 0.001$) and FFM (54.4 *vs* 42.5 kg, $P < 0.001$). Sarcopenic patients had a lower mean MA (41.2 *vs* 34.7 HU) ($P = 0.008$), and a higher prevalence of those with low MA (64.7% *vs* 23.6%, $P = 0.004$). A trend was observed that sarcopenic patients were older (60 *vs* 53 years, $P = 0.087$).

Patients with low MA were significantly older (mean 64 *vs* 48 years, $P \leqslant 0.001$) and had a significantly lower SMA (126.11 *vs* 156.54 cm^2, $P \leqslant 0.001$), SMI (44.75 *vs* 52.88 $cm^2\,m^{-2}$, $P \leqslant 0.001$) and FFM (53.02 *vs* 46.5 kg, $P = 0.022$) compared with those without low MA, as a result patients' with low MA had a higher prevalence of sarcopenia (45.8% *vs* 12.5%, $P = 0.004$). The mean HU in those with and without low MA was 30.3 *vs* 44.4 HU, respectively ($P \leqslant 0.001$). Patients with sarcopenia or low MA and those without were otherwise similar in terms of clinical features. No significant association was observed between the prevalence of sarcopenia or low MA and the extent of metastatic disease.

Patients with a BMI $\geqslant 25\,kg\,m^{-2}$, as expected weighed more (90.3 *vs* 65.8 kg, $P \leqslant 0.001$) and had a significantly higher SMI (54.2 *vs* 45.01 $cm^2\,m^{-2}$, $P \leqslant 0.001$) compared with those with a BMI $< 25\,kg\,m^{-2}$; however, these patients had a significantly lower MA (37.45 HU *vs* 44.64 HU, $P = 0.001$). Patients were otherwise similar.

The incidence of high-grade (grades III–IV) AEs and irAEs. The frequencies of ipilimumab-associated AEs and irAEs are shown in Table 3. In our study, 60 (71%) patients experienced an AE and 47 (56%) experienced an irAE. Many AE reported were of grades I–II; however, 35 (42%) patients experienced a high-grade AE, with 25 (30%) patients experiencing a high-grade irAE.

Sarcopenia, low MA and treatment tolerability. No significant difference was observed in the prevalence of any grade I–II AEs or grade I–II irAEs in patients with sarcopenia or low MA and in those without (results not shown).

Patients with sarcopenia experienced more high-grade AEs compared with their non-sarcopenic counterparts (65% *vs* 34%, $P = 0.030$, univariate OR = 3.54, 95% CI: 1.23–10.17, $P = 0.019$) and appeared to be more susceptible to a high-grade irAE (45% *vs* 25%); however, this did not reach statistical significance. When considering individual high-grade AEs or irAEs separately, only fatigue was significantly more prevalent in sarcopenic patients (35% *vs* 9.4%, $P = 0.011$) (Supplementary Table 1). Patients with low MA were more likely to experience a high-grade AE (75% *vs* 31%, $P = 0.001$, univariate OR = 7.46, 95% CI: 2.45–22.66, $P \leqslant 0.001$), and more likely to experience a high-grade irAE (54% *vs* 23%, $P = 0.017$, univariate OR = 4.49, 95% CI: 1.64–13.5, $P = 0.004$). Patients with low MA had a higher incidence of colitis (16.7% *vs* 2.1%, $P = 0.039$) (Supplementary Table 1).

Table 1. Baseline characteristics, values expressed as *n* (%), unless stated otherwise

Characteristic	*n* = 84
Age (years)	
Median (IQR)	54 (43–66)
Range	22–85
Gender	
Male	52 (62)
Female	32 (38)
M stage	
M1a	9 (11)
M1b	9 (11)
M1c	66 (78)
Metastatic site	
Lung	59 (70)
Liver	34 (41)
Bone	23 (27)
Brain	19 (23)
Other	64 (76)
Ipilimumab first-line treatment	29 (34.5)
Number of doses of ipilimumab	
Median	4
Range	1–4
Completed all four cycles of ipilimumab	60 (71)
Early cessation of treatment	24 (29)
Progression of disease	10 (12)
Treatment-related toxicity	12 (14)
Death	2 (3)

Abbreviation: IQR = interquartile range.

On multivariate logistic regression analysis (Table 4) including age, gender, BMI, sarcopenia and low MA, patients with sarcopenia, low MA and a BMI $\geqslant 25\,kg\,m^{-2}$ were at a significantly increased risk of experiencing a high-grade AE (OR = 5.34, 95% CI: 1.15–24.88, $P = 0.033$; OR = 5.23, 95% CI: 1.41–19.30, $P = 0.013$; and OR = 4.01, 95% CI: 1.03–15.69, $P = 0.046$, respectively). Patients with low MA were at a significantly increased risk of experiencing a high-grade irAE (OR = 3.57, 95% CI: 1.09–11.77, $P = 0.036$).

Sarcopenia, low MA and the incidence of a DLT. Overall, 15 patients (18%) experienced a DLT. Twelve patients (14.3%) discontinued ipilimumab treatment because of a high-grade irAE, with the most common events being skin toxicity (rash) (four patients), diarrhoea (two patients) and colitis (two patients). Six patients experienced a dose delay, while three patients experienced both a dose delay and early cessation of treatment. Patients who experienced a DLT were older (53 years *vs* 63 years, $P = 0.017$) and had a significantly lower mean MA (41.2 HU *vs* 33.4 HU, $P = 0.003$). The prevalence of DLT was more common in patients with low MA compared with those without low MA (37.5% or 9 of 24 *vs* 10.4% or 5 of 48, $P = 0.011$). Sarcopenic patients appeared to be more susceptible to experience a DLT (25.0% or 5 of 20 *vs* 15.6% or 10 of 64, respectively); however, this did not reach statistical significance.

Changes in body composition. Longitudinal changes in body composition during four cycles of ipilimumab were examined in patients where both pre- and post-treatment CT images were available ($n = 59$).

Significant decreases were observed across all body composition parameters (see Table 5). The mean decrease in SMA was 3.3% (s.d. 5.84%) (95% CI: −4.48 to −1.79%, $P \leqslant 0.001$) per 100 days. The prevalence of sarcopenia increased from 17% (or 10 of 59) at baseline to 32% (or 19 of 59) by the second CT scan in this subgroup of patients.

Effect of change on survival. Patients with a muscle loss of $\geqslant 7.5\%$/100 days (quartile four; highest muscle loss) had significantly lower overall survival compared with those with a muscle loss $< 7.5\%$/100 days (quartiles 1–3; minor muscle loss/stable or gain). The median survival was 9.5 months (95% CI: 1.5–17.6 months) for those with the highest muscle loss ($\geqslant 7.5\%$) *vs* 21.8 months (95% CI: 14.3–29.4 months) in those with a muscle loss $< 7.5\%$/100 days (log rank; $P = 0.029$; univariate Cox regression, HR: 2.14, 95% CI: 1.06–4.28, $P = 0.033$) (Figure 1). On multivariate analysis, muscle loss of $\geqslant 7.5\%$ remained

Table 3. Adverse events and immune-related adverse events reported

Adverse event	Any grade, *n* (%)	Grades I–II, *n* (%)	Grades III–IV, *n* (%)
Any adverse event	60 (71.4)	53 (63.1)	35 (41.7)
Any immune-related event	47 (56.0)	39 (46.4)	25 (29.8)
General adverse event			
Fatigue	38 (45.2)	25 (29.8)	13 (15.5)
Nausea	15 (17.9)	15 (17.9)	0 (0)
Vomiting	6 (7.2)	5 (6.0)	1 (1.2)
Constipation	7 (8.3)	5 (6.0)	2 (2.4)
Abdominal pain	3 (3.6)	1 (1.2)	2 (2.4)
Anorexia	12 (14.3)	11 (13.1)	1 (1.2)
Pyrexia	8 (9.5)	7 (8.3)	1 (1.2)
Headache	4 (4.8)	4 (4.8)	0 (0)
Cough	4 (4.8)	4 (4.8)	0 (0)
Dyspnoea	2 (2.4)	2 (2.4)	0 (0)
Anaemia	13 (15.5)	10 (11.9)	3 (3.6)
Immune-related adverse event			
Dermatologic/skin			
Pruritus	8 (9.5)	8 (9.5)	0 (0)
Rash	20 (23.8)	13 (15.5)	7 (8.3)
Gastrointestinal			
Diarrhoea	24 (28.5)	20 (23.8)	4 (4.8)
Colitis	6 (7.2)	1 (1.2)	5 (6.0)
Endocrine			
Hypothyroidism	2 (2.4)	2 (2.4)	0 (0)
Hypopituitarism	6 (7.1)	1 (1.2)	5 (6.0)
Hypophysitis	1 (1.2)	0 (0)	1 (1.2)
Adrenal insufficiency	1 (1.2)	0 (0)	1 (1.2)
Abnormal hepatic function	1 (1.2)	0 (0)	1 (1.2)
Musculoskeletal			
Arthritis	8 (9.6)	5 (6.0)	3 (3.6)
Other[a]	20 (23.8)	11 (13.0)	9 (10.7)

[a]Oral toxicity (mucositis, ulcers) grades I–II (7.1%), pericarditis grade III (1.2%), sarcoidosis grade III (1.2%), ocular toxicity (conjunctivitis, blurred vision, dry eyes) grades I–II (4.8%), lower limb weakness grade II (1.2%), neuropathy grade II (1.2%), ataxia grade II (2.4%), ataxia grade III (1.2%), confusion grade III (2.4%) and grade V sepsis (1.2%).

Table 2. Nutritional characteristics, values given as mean (s.d.), unless stated otherwise

Characteristic	Males ($n = 52$)	Females ($n = 32$)	Total ($n = 84$)
BMI ($kg\,m^{-2}$), median (IQR)	27.6 (24.9–30.1)	26.5 (23.3–29.5)	26.9 (24.4–30.4)
Underweight ($\leqslant 18.5\,kg\,m^{-2}$), *n* (%)	0 (0)	2 (6.3)	2 (2)
Normal (18.5–24.9 $kg\,m^{-2}$), *n* (%)	13 (25)	10 (31)	23 (28)
Overweight (25–29.9 $kg\,m^{-2}$) *n* (%)	24 (46)	14 (44)	38 (45)
Obese ($\geqslant 30.0\,kg\,m^{-2}$), *n* (%)	15 (29)	6 (19)	21 (25)
Skeletal muscle area (cm^2)	174.7 (32.1)	114.3 (13.3)	151.6 (39.6)
Skeletal muscle index ($cm^2\,m^{-2}$)	56.4 (9.6)	43.4 (5.2)	51.4 (10.4)
Sarcopenia, *n* (%)	10 (19.2)	10 (31.3)	20 (23.8)
Muscle attenuation[a] (HU)	39.8 (7.9)	38.8 (10.2)	39.4 (8.9)
Low muscle attenuation[a], *n* (%)	12 (27.9)	12 (41.4)	24 (33.3)
Adipose tissue area (cm^2)	401.3 (182.5)	259.4 (133.6)	350.2 (179.2)
Adipose tissue index ($cm^2\,m^{-2}$)	129.0 (57.5)	98.8 (50.4)	118.2 (56.6)
Estimated FFM (kg)	58.5 (9.6)	40.3 (4.0)	51.6 (11.9)
Estimated FM (kg)	28.1 (7.7)	22.1 (5.6)	25.9 (7.5)

Abbreviations: BMI = body mass index; CT = computed tomography; FM = fat mass; FFM = fat-free mass; HU = Hounsfield units; IQR = interquartile range; MA = muscle attenuation; s.d. = standard deviation.
[a]MA assessed for 72 patients (43 men and 29 women). Twelve patients (3 women and 9 men) lacked suitable contrast-enhanced CT images for MA analysis.

Table 4. Risk of toxicity during ipilimumab treatment in relation to BMI, sarcopenia and low MA determined by multiple logistic regressions

		Model 1[a]			Model 2[a]		
		High-grade AE			High-grade irAE		
	n	OR	95% CI	*P*-value	OR	95% CI	*P*-value
BMI ($>25\,kg\,m^{-2}$)	59	4.01	1.03–15.69	0.046	2.46	0.67–9.02	0.173
Sarcopenia	20	5.34	1.15–24.88	0.033	2.17	0.58–8.11	0.248
Low MA	24	5.23	1.41–19.30	0.013	3.57	1.09–11.77	0.036

Abbreviations: AE = adverse event; BMI = body mass index; irAE = immune-related adverse event; MA = Muscle Attenuation.
[a]Adjusted for gender and age (>65 *vs* <65 years) as potential confounders.

independently associated with shorter survival when adjusted for gender, age (<65 *vs* >65 years) and stage of disease (M1c *vs* M1a or M1b) as potential confounders (HR: 2.1, 95% CI: 1.02–4.56, $P = 0.046$). Neither sarcopenia nor low MA at baseline was associated with shorter survival.

DISCUSSION

To our knowledge, this is the first study to examine the relationship between body composition and ipilimumab toxicity in patients with metastatic melanoma. Our findings point to sarcopenia and low MA as potential sources of variation in toxicity to ipilimumab.

Overall, 24% of our cohort was sarcopenic before commencing treatment and 33% of these patients had a low MA. We are not aware of any other reports that describe the prevalence of sarcopenia or low MA in patients with metastatic melanoma. The prevalence of sarcopenia in this cohort is considerably lower than previously reported for other advanced stage cancers (Tan *et al*, 2009; Huillard *et al*, 2013).

In our study, 56% of patients experienced an irAE of any grade, while 30% of patients experienced a high-grade irAE (grades III and IV). The incidence of toxicity in this cohort is similar to those reported previously (Bertrand *et al*, 2015; Horvat *et al*, 2015). A recent meta-analysis published in 2015, which included 81 articles and a total of 1265 patients from 22 clinical trials (Bertrand *et al* 2015), reported the overall incidence of all-grade irAE to be 61% (95% CI: 56–66%) and the incidence of high-grade irAEs to be 17% (95% CI: 10–23%) for patients receiving an ipilimumab dose of $3\,mg\,kg^{-1}$ (Bertrand *et al*, 2015). Although the incidence of high-grade irAEs in our study (30%) is higher than reported in the meta-analysis (17%), it is not uncommon and is similar with that reported by Horvat *et al* (2015), where the incidence of high-grade irAE was reported to be 31% in 298 melanoma patients treated with $3\,mg\,kg^{-1}$ of ipilimumab (Horvat *et al*, 2015). The prevalence of toxicity within our study and that of Horvat *et al* (2015) may be more representative of patients treated in clinical practice and less representative of prior clinical trial participants.

We report that patients with sarcopenia were at an increased risk of experiencing a high-grade AE compared with their non-sarcopenic counterparts (OR = 5.34, 95% CI: 1.15–24.88, $P = 0.033$). Several other studies reported associations between sarcopenia and increased chemotherapy toxicity in a variety of cancers including breast (Prado *et al*, 2009), colon (Prado *et al*, 2007), oesophageal (Anandavadivelan *et al*, 2015), thyroid (Massicotte *et al*, 2013) and renal cancer (Huillard *et al*, 2013; Cushen *et al*, 2014). The majority of therapies studied included anticancer drugs based on body surface area (e.g., capecitabine (Prado *et al*, 2009) and 5-flurouracil (Prado *et al*, 2007; Barret *et al*, 2014; Ali *et al*, 2016), which has been shown to correlate weakly with LBM ($r^2 = 0.37$) (Prado *et al*, 2008). Additionally, increased toxicity has been observed in patients with sarcopenia/low LBM treated with flat-dosed targeted therapies such as sunitinib (Huillard *et al*, 2013; Cushen *et al*, 2014) and vandetanib (Massicotte *et al*, 2013).

More recently, reduced MA is increasingly being linked to poorer clinical outcomes in malignant populations. Sabel *et al* (2011) reported low (psoas) MA to be associated with disease-free ($P = 0.04$) and distant disease-free survival ($P = 0.0002$) in stage III melanoma patients (Sabel *et al*, 2011). Martin *et al* (2013) supported these findings and reported low MA was predictive of poorer survival in 1473 lung and GI cancer patients (HR: 1.36, 95% CI: 1.2–1.6) (Martin *et al*, 2013). In this study, patients with low MA were at an increased risk and more frequently experienced high-grade AEs (OR = 5.23, 95% CI: 1.41–19.30, $P = 0.013$; 75% *vs* 31%, $P = 0.001$) and high-grade irAE (OR = 3.57, 95% CI: 1.09–11.77, $P = 0.036$; 54% *vs* 23%, $P = 0.017$) compared with those without low MA. More importantly, these patients were more susceptible to experience a DLT, either a dose delay or early cessation of treatment as a result of significant toxicity (37.5% *vs* 10.4%, $P = 0.011$). However, the explanations for these observations are unclear. In contrast to these findings, Rollins *et al* (2015) found no association between low MA and the incidence of toxicity or ability to complete palliative chemotherapy in pancreatic cancer patients (Rollins *et al*, 2015) and Blauwhoff-Buskermolen *et al* (2016) similarly reported no association with baseline sarcopenia or low MA and treatment modifications (DLT) in metastatic colorectal cancer patients (Blauwhoff-Buskermolen *et al*, 2016). There are few studies examining this relationship. We reported that patients with a BMI $>25\,kg\,m^{-2}$ were at an increased risk of experiencing a high-grade AE (OR = 4.01, 95% CI: 1.03–15.69, $P = 0.046$); however, it is important to note that patients with BMI $>25\,kg\,m^{-2}$ had a lower MA compared with patients with a normal BMI ($P = 0.001$), and the increased risk of toxicity is most likely attributed to the low MA.

Several explanatory mechanisms of increased toxicity in those with sarcopenia or low lean body mass have been hypothesised (Antoun *et al*, 2013a). One potential explanation is pharmacokinetic parameter changes induced by malnutrition or obesity, which could result in alterations in the distribution, metabolism and clearance of anticancer drugs, increasing the risk of toxic events. Alternatively, there is a growing body of literature to suggest that patients with sarcopenia are generally more susceptible to acute medical events such as infections (Lieffers *et al*, 2012), post-operative complications (Peng *et al*, 2011; van Vugt *et al*, 2015) and poorer prognosis (Martin *et al*, 2013; Montano-Loza *et al*, 2012). Another plausible explanation for increased toxicity in patients with sarcopenia and low MA may be attributed to systemic inflammation, which is known to underlie both conditions. Rollins *et al* (2015) reported that patients with low MA had significantly greater levels of systemic inflammation (white cell count, neutrophil–lymphocyte ratio and C-reactive protein) than in those without low MA (Rollins *et al*, 2015). Similarly an association between sarcopenia, low MA and the host inflammatory response

Table 5. Changes in measures of body composition by CT between pre- and post-treatment imaging in patients treated with ipilimumab

			Change			Change per 100 days			Relative change per 100 days (%)		
Tissue	**First CT scan Mean (s.d.)**	**Second CT scan Mean (s.d.)**	**Mean**	**95% CI**	***P-value***	**Mean**	**95% CI**	***P-value***	**Mean**	**95% CI**	***P-value***
Skeletal muscle area (cm^2)	151.3 (37.2)	144.2 (37.2)	−7.1	−10.2 to −3.9	<0.001	−5.2	−2.9 to −7.4	<0.001	−3.3	−4.5 to −1.8	<0.001
Total adipose tissue area (cm^2)	310.9 (130.7)	276.8 (131.1)	−34.1	−51.9 to −16.3	<0.001	−22.8	−11.4 to −34.2	<0.001	−6.8	−10.7 to −2.9	<0.001
FFM[a] (kg)	50.9 (10.6)	48.8 (10.4)	−2.1	−3.1 to −1.2	<0.001	−1.6	−0.9 to −2.3	<0.001	−3.0	−4.3 to −1.6	<0.001
FM[b] (kg)	24.3 (5.5)	22.8 (5.5)	−1.5	−2.2 to −0.7	<0.001	−1.1	−0.6 to −1.7	<0.001	−4.5	−2.3 to −6.7	<0.001
Muscle attenuation (HU)	40.5 (8.6)	38.8 (10.2)	−1.7	−3.8 to −0.3	0.019	−1.2	0.2 to −2.6	0.08	−3.0	−5.8 to −0.3	0.030

Abbreviations: CT = computed tomography; FM = fat mass; FFM = fat-free mass; HU = Hounsfield units; s.d. = standard deviation.
[a]FFM (kg) = 0.3 × (skeletal muscle cross-sectional area at L3 (cm^2)) + 6.06; $r^2 = 0.88$.
[b]FM (kg) = 0.042 × (adipose tissue cross-sectional area at L3 (cm^2)) + 11.2; $r^2 = 0.77$.

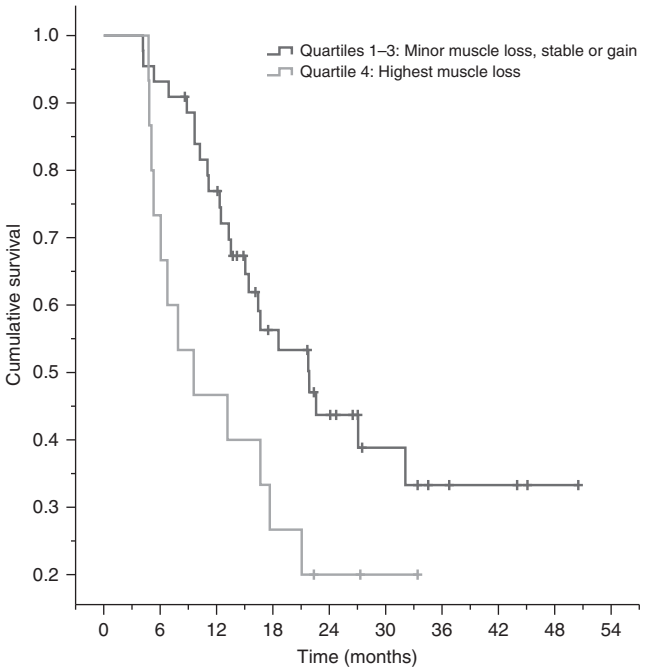

Figure 1. Patients with a muscle loss of ⩾7.5%/100 days (quartile four, highest amount of muscle loss) had significantly lower overall survival compared with those with a muscle loss <7.5%/100 days (quartiles one to three; minor muscle loss/stable or gain). Censored cases are indicated by +.

was observed in a large cohort ($n = 763$) of patients with operable colorectal cancer (Malietzis *et al*, 2016).

Treatment toxicity may be as a result of systemic inflammation. It has been reported that patients with a higher inflammatory response had an increased risk of severe hematological toxicity (neutropenic fever or severe thrombocytopenia) following chemotherapy (Alexandre *et al*, 2003). Similarly, patients with inflammation and lymphopenia at baseline were more susceptible to febrile neutropenia following treatment with docetaxel (Alexandre *et al*, 2007). Consistent with the expected immune-stimulating effect of ipilimumab, increases in absolute lymphocyte count during treatment have frequently been observed in melanoma patients (Postow *et al*, 2013). Ipilimumab may augment existing systemic inflammation in patients, resulting in the increased incidence of high-grade AEs in those with sarcopenia and high-grade AEs, irAEs and DLTs in those with low MA.

In our study, patients treated with ipilimumab lost on average 3.32 ± 5.84% of skeletal muscle per 100 days, which is comparable to 3.1 ± 12%/100 days reported in advanced pancreatic cancer patients (Tan *et al*, 2009), but is at a lower rate compared with ovarian cancer patients undergoing neoadjuvant chemotherapy (5.2 ± 9.8%/100 days) (Rutten *et al*, 2016). Other studies have reported significant reductions in skeletal muscle in a variety of cancer types (Antoun *et al*, 2010; Miyamoto *et al*, 2015; Rollins *et al*, 2015), but failed to report these as % change/100 days, which makes it difficult to compare with our cohort.

Patients with metastatic melanoma with the highest amount of muscle loss (⩾7.5% highest quartile) were at a significantly increased risk of mortality on multivariate analysis (HR: 2.1, 95% CI: 1.02–4.55; $P = 0.046$). Our results are in line with those reported in colorectal cancer patients, where a loss of muscle >9% SMA over 3 months of chemotherapy was independently associated with reduced survival (HR: 4.47, 95% CI: 2.21–9.05,

$P<0.001$) (Blauwhoff-Buskermolen *et al*, 2016) and a loss of muscle >2%/100 days was independently associated with significantly reduced survival in ovarian cancer patients (HR: 1.77, 95% CI: 1.018–3.088, $P=0.043$) (Rutten *et al*, 2016). In our study, sarcopenia and low MA at baseline were not associated with reduced survival. This is in contrast to some (Prado *et al*, 2008; Tan *et al*, 2009; Martin *et al*, 2013) but not all studies (Stene *et al*, 2015; Blauwhoff-Buskermolen *et al*, 2016).

It should be acknowledged that muscle loss is both multifactorial and complex, and significant losses of muscle in this cohort may be attributed to multiple factors. The change in body composition during ipilimumab treatment may simply reflect the evolution of systemic disease; however, response to treatment was not assessed within this patient group. It is often difficult to evaluate the clinical response in patients treated with immunotherapy agents as the patterns of response differ from those with cytotoxic chemotherapy. Radiologically, patients may have a transient worsening of disease, before disease stabilises or regresses and responses in patients can take appreciably longer to become apparent. In line with this, disease regression is frequently observed well after the completion of initial induction period. In addition to catabolic effects caused by the underlying malignancy and advancing disease, muscle loss may be partially explained by the potential systemic inflammation caused by ipilimumab, as well as decreased physical activity and reduced food intake commonly experienced by patients with advanced cancer.

The main limitations of our study are its retrospective nature and relatively small sample size, particularly in the subgroup analysis. Patients were excluded from the analysis if CT scans were not available, which may result in selection bias. The mean time between imaging and initiation of treatment was 39 days (s.d. 31 days), indicating a few outliers outside the ideal target window of 30 days. Owing to the exploratory nature of this study, multiple statistical tests were performed, increasing the risk of committing type 1 errors. These results should be regarded as hypothesis-generating and further prospective studies are needed to validate these results in larger cohort of metastatic melanoma patients as well as in other cancer types and treatments.

However, despite the limitations, our results highlight for the first time the potential use of body composition assessment to identify patients at increased risk of experiencing severe toxicity to immunotherapy, that is, ipilimumab. Additionally, this study reports for the first time the changes in body composition experienced by patients while undergoing treatment with ipilimumab, and the adverse effect this has on survival. Potential treatments to increase muscle mass and their effectiveness to improve clinical outcomes warrants further investigation. With the advent of novel immune checkpoint inhibitors showing significant activity in many solid and liquid tumours, for example, pembrolizumab and nivolumab in melanoma, lung cancer, colon cancer, ovarian cancer, bladder cancer, glioblastima, head and neck cancers, and Hodgkin lymphoma (American Society of Clinical Oncology Education Book 2016), in conjunction with the lack of validated clinical and molecular biomarkers that predict response, outcome and toxicity, the importance of body composition defined by cross-sectional imaging criteria should not be underestimated.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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