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 Chiriringhelli, 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 (Liefers 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), sunitinib (Huillard et al, 2013; Cushman et al, 2014), S-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.
Body composition, ipilimumab toxicity and survival

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 ≥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 cm², P < 0.001), skeletal muscle index (SMI) (54.7 vs 41.1 cm² 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 ≤ 0.001) and had a significantly lower SMA (126.1 vs 156.5 cm², P ≤ 0.001), SMI (44.75 vs 52.88 cm² m−2, P ≤ 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 ≤ 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.

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 ≤ 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).
On multivariate logistic regression analysis (Table 4) including age, gender, BMI, sarcopenia and low MA, patients with sarcopenia, low MA and a BMI ≥ 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 overall 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 with 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 < 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 ≥7.5%/100 days (quartile four; highest muscle loss) had a significantly lower mean MA (41.2 HU vs 38.8 HU, P = 0.011). Sarcopenic patients appeared to have a significantly lower overall mean MA (41.2 HU vs 38.8 HU, P = 0.017) per 100 days. The prevalence of sarcopenia increased from 17% to 32% (or 19 of 59) by the second CT scan in this subgroup of patients.

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On multivariate logistic regression analysis (Table 4) including age, gender, BMI, sarcopenia and low MA, patients with sarcopenia, low MA and a BMI ≥ 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).

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Effect of change on survival. Patients with a muscle loss of ≥7.5%/100 days (quartile four; highest muscle loss) had a 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: 1.79% vs 7.5%/100 days (quartile four; highest muscle loss) had a significantly lower overall survival compared with 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 ≥7.5% remained significant.
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\textsuperscript{-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\textsuperscript{-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 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., capcitabine (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\textsuperscript{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; Cusen 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 (psosas) 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 at 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 = 5.37, 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 Blauwhof-Buskermolen et al (2016) similarly reported no association with baseline sarcopenia or low MA and treatment modifications (DLT) in metastatic colorectal cancer patients (Blauwhof-Buskermolen et al, 2016). There are few studies examining this relationship. We reported that patients with a BMI > 25 kg m\textsuperscript{-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\textsuperscript{-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

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

| Model 1* | Model 2* |
|----------|----------|
| **High-grade AE** | **High-grade irAE** |
| n | OR | 95% CI | P-value | OR | 95% CI | P-value |
| BMI (>25 kg m\textsuperscript{-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.

*Adjusted for gender and age (>65 vs <65 years) as potential confounders.
Table 5. Changes in measures of body composition by CT between pre- and post-treatment imaging in patients treated with ipilimumab

| Tissue                          | Mean (s.d.) | P-value | 95% CI          | P-value |
|---------------------------------|-------------|---------|-----------------|---------|
| Skeletal muscle area (cm²)      | 151.3 (37.2) | <0.001  | 7.1 to 29.5     | <0.001  |
| Total adipose tissue area (cm²) | 310.9 (130.7)| <0.001  | 34.1 to 51.9    | <0.001  |
| FFM (kg)                        | 24.3 (5.5)   | 0.001   | 1.5 to 3.1      | 0.001   |
| Muscle attenuation (HU)         | 40.5 (8.6)   | 0.001   | 0.9 to 4.3      | 0.001   |
| Abbreviations: CT = computed tomography; FFM = fat-free mass; HU = Hounsfield units; s.d. = standard deviation.

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 immunestimulating 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,
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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, glioblastoma, 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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