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Higher BMI, But Not Sarcopenia, Is Associated With Pembrolizumab-related Toxicity in Patients With Advanced Melanoma

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Abstract. *Background/Aim: To determine whether BMI and sarcopenia were related to treatment-limiting toxicity or efficacy of pembrolizumab treatment in melanoma patients. Patients and Methods: Medical records for melanoma patients undergoing pembrolizumab treatment at Duke University from January 2014 to September 2018 were reviewed. Pre-treatment measurements such as BMI were collected. Pre-treatment CT imaging was used to determine psoas muscle index (PMI). Patients in the lowest sex-specific tertile of PMI were sarcopenic. Logistic regression measured associations with treatment toxicity and response. Kaplan-Meier analysis assessed progression-free survival (PFS) and overall survival (OS). Results: Among 156 patients, the overall objective response rate was 46.2% and 29 patients (18.6%) experienced treatment-limiting toxicity. Sarcopenia was not significantly associated with toxicity, response, or survival. However, obese patients (BMI >30) experienced higher rates of toxicity (p=0.0007). Conclusion: Sarcopenia did not appear to predict clinically relevant outcomes. Obesity, however, represents a readily available predictor of pembrolizumab toxicity.*

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Immune checkpoint inhibitor (ICI) therapies, including those targeting the programmed death (PD)-1 receptor, have significantly improved the outcomes for patients with unresectable or metastatic melanoma. Studies have suggested that easily measured patient markers such as body mass index (BMI) and radiographic sarcopenia can help predict response and toxicity to targeted immunotherapies (1, 2). These factors can, therefore, impact treatment decisions in choosing one drug versus another depending on individual patient characteristics.

Several other clinical predictors of immune checkpoint inhibitor treatment outcomes such as baseline tumor volume, lactate dehydrogenase and presence of lung metastases have been previously identified. Relative changes in S100 levels have been found to predict survival in metastatic melanoma patients treated with pembrolizumab (3). Nevertheless, additional reliable predictors of treatment response are needed (4-7). Severe adverse events (AEs) associated with pembrolizumab, in particular, are uncommon, but do occur and can even be life-threatening, with toxicities ranging from the more common pneumonitis, colitis and thyroiditis, to rare reported cases of bullous pemphigoid, demyelinating polyradiculopathy, and acute heart failure from autoimmune myocarditis (8-10).

Baseline patient body parameters such as BMI and sarcopenia could play a useful role in predicting pembrolizumab response and toxicity. Further, understanding the efficacy and toxicity of pembrolizumab in adult patients could better inform therapeutic options for pediatric patients as well (11). Baseline BMI is already routinely recorded in clinical practice and is therefore an easily accessible biomarker. Sarcopenia, however, is a separately reportable

health condition in the 10th edition of the International Classification of Diseases (ICD-10), and is defined as muscle failure due to adverse changes that accrue across a lifetime (12). As it is difficult to accurately gauge muscle quality and quantity, measurements on radiographic imaging have been used as surrogates for sarcopenia in clinical research.

Recent retrospective studies have revealed a possible "obesity paradox" in which higher BMI is associated with better survival in melanoma patients treated with immunotherapy (13, 14). Radiographic sarcopenia has been shown to be a reliable predictor of prognosis in patients with stage III melanoma and has been associated with worse toxicity and lower survival rates in response to immunotherapy (15-17). Recently published reports have indicated that skeletal muscle mass may modify the association between BMI and mortality (18, 19). Sarcopenia and obesity have therefore emerged as patient characteristics of interest in the evaluation of cancer prognosis and PD-1 inhibitor therapy outcomes (1, 14, 20).

We conducted a retrospective study to investigate whether BMI and the aforementioned simple measure for sarcopenia correlates with toxicity and response to pembrolizumab in the treatment of advanced melanoma.

Patients and Methods

Overview and inclusion criteria. A search tool (DEDUCE) was used to find all patients with advanced cutaneous melanoma who initiated pembrolizumab treatment (200 mg intravenously every three weeks) at Duke University Medical Center between January 2014 and September 2018, with last follow-up date April 4th, 2019. Patients were excluded from the analysis if they received pembrolizumab as an adjuvant therapy following complete surgical resection, if they had mucosal or choroidal melanoma, or did not undergo computerized tomography (CT) imaging spanning the L3-L4 vertebrae within 3 months of starting treatment. This retrospective study was approved by the Duke University Institutional Review Board, and written informed consent was not required.

We performed a retrospective chart review and recorded data elements including demographic information, primary tumor characteristics (Breslow thickness, Clark level, and number of mitotic figures), baseline laboratory results (albumin, creatinine), previous treatments, concurrent treatments (immunotherapy and radiation), and baseline BMI. Dates of best response, tumor progression, and death, if applicable, were also recorded.

Response assessment. Response to pembrolizumab was assessed using body CT scans performed with or without positron emission tomography (PET). The response determination made by the treating oncologist was recorded. Response was categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) using RECIST v1.1 principles (2). If the patient had neither a sufficient decrease in lesions to qualify for an objective response designation, nor a sufficient increase to qualify for a PD designation, the patient was recorded as experiencing SD.

Toxicity assessment. Toxicity was assessed by conducting a chart review of each individual patient's outpatient oncology visits and hospital admission notes. Events were categorized according to the Common Terminology Criteria for Adverse Events v5.0, and a patient was recorded as experiencing a treatment-limiting toxicity if their symptoms led to the permanent discontinuation of pembrolizumab treatment (21).

Anthropometric measurements. Within 1 week prior to treatment initiation, weight was measured with a medical balance beam scale, and height was measured with a stadiometer. The BMI was calculated as follows: BMI (in kg/m^2)=weight (in kg)/height^2 (in m^2).

Image analysis. Cross-sectional area of a single psoas muscle was measured following the example set by a prior study using this method (22). All measurements were performed by a board-certified radiologist (LH) with fellowship training in abdominal imaging, who was blinded to clinical outcomes. All measurements were made manually, using electronic calipers, on the picture archiving and communication system (PACS) (Centricity 6.0, GE Healthcare). After identifying the third non-rib bearing lumbar vertebra, an image was chosen at the level of the transverse process. On this image, the size of the right psoas was determined by measuring and recording the longest anterior-posterior dimension and longest medial-lateral dimension. If the right psoas appeared asymmetrically large or small compared with the left, both psoas muscles were measured and averaged.

The psoas area at the L3 level was normalized for height to calculate the psoas muscle index (PMI) using the following equation: PMI (in cm^2/m^2)=cross-sectional area of psoas muscle (in cm^2)/height^2 (in m^2). This is shown in Figure 1.

Statistical analysis. The goal of this study was to assess the potential association between body composition factors (such as BMI and sarcopenia) and clinical outcomes among patients treated with pembrolizumab. Patients were categorized as obese, overweight, or low-average weight according to the guidelines published by the National Institutes of Health and Center for Disease Control and Prevention. In the absence of a standard definition of sarcopenia, patients were dichotomized according to their PMI or contrast density values relative to the other patients in the sample of the same gender. Patients in the lower third for the pertinent value were categorized as sarcopenic. Two definitions for sarcopenia were used to analyze the same group of patients. Results are presented for the PMI-based definition.

Patients were assessed for differences in demographics, cancer, and treatment characteristics by sarcopenic status and BMI category using Wilcoxon rank sum tests for continuous variables and chi-square or Fisher's exact (where appropriate) for categorical variables. Differences in progression-free survival (PFS) and overall survival (OS) were evaluated using the Kaplan Meier method. All statistical analyses were conducted using SAS software, version 9.4.

Results

Patients. This study included 156 patients with advanced melanoma (AJCC 7 staging system). The sample was 96% white (n=150), 58% male (n=91) and 73% overweight or obese (n=114). By the time of treatment initiation, 84% had

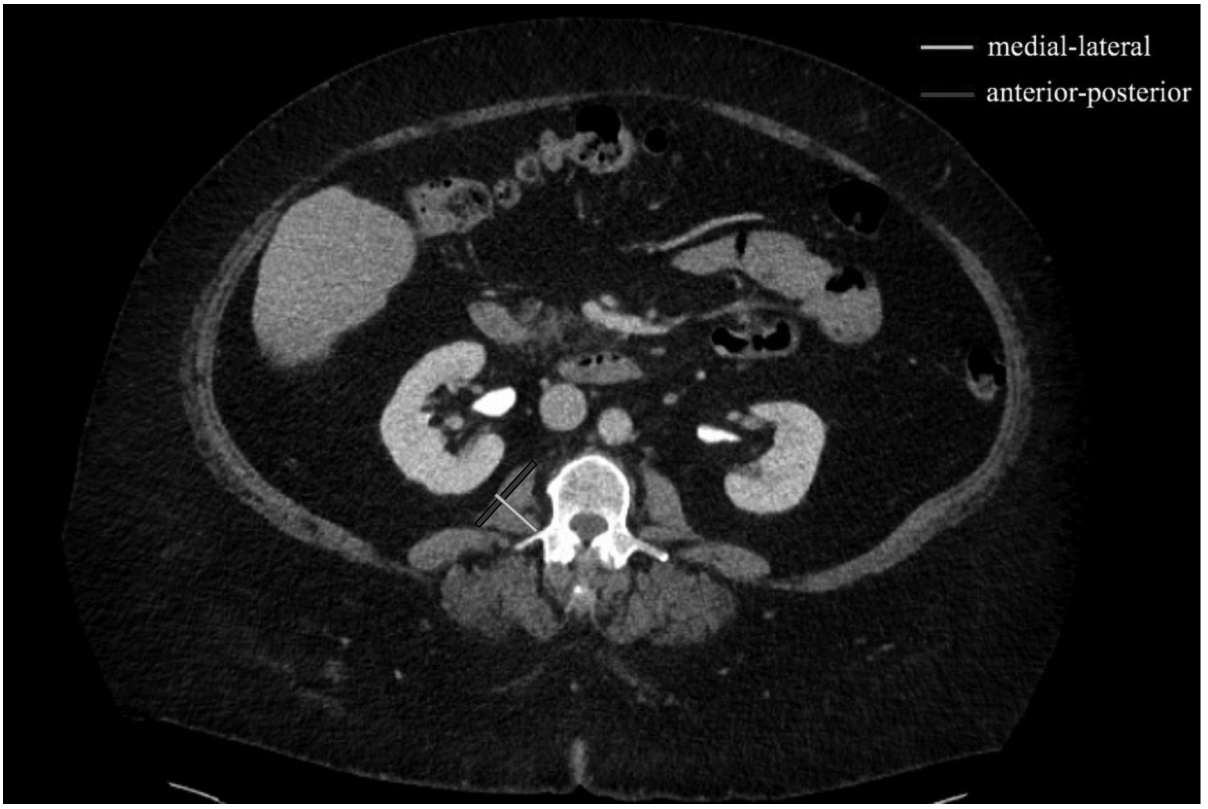

Figure 1. *Demonstration of how a single psoas cross-sectional area measurement was performed. This figure was created using an anonymized CT scan cross-section at the L3 vertebrae. The light blue line represents the longest medial-lateral diameter. The red line represents the longest anterior-posterior diameter. These diameters were then multiplied together and normalized by patient height^2 (m^2).*

metastatic stage IV melanoma (n=131) and 15% had low albumin (<3.5 mg/dl). Forty-nine patients (32%) had a confirmed BRAF V600E mutation. Patients underwent a median of 8 cycles (range=1-49 cycles) for a median of 5.5 months of pembrolizumab treatment (range=0.7-41.4 months). Sixteen patients (9%) received concurrent treatment including: talimogene laherparepvec (T-VEC) (n=5), denosumab (n=4), dabrafenib/trametinib (n=2), Dynavax SD-101 (on clinical trial) (n=2), and 1 patient each received temozolomide, pomalidomide, and paclitaxel). The patient characteristics are summarized in Table I.

Clinicopathologic differences across sarcopenic designations. Fifty-three patients (34%) in the bottom sex-specific tertile for PMI were categorized as sarcopenic. The baseline clinicopathologic characteristics of the patients are compared by sarcopenia status and are summarized in Table II. Overall, sarcopenic patients were older (p=0.01), had lower BMI (p<0.0001), and were more likely to have abnormally low albumin levels <3.5 g/dl (p=0.02) compared to non-sarcopenic patients.

Clinicopathologic differences across BMI categories. After patients were divided into BMI groups as conducted in a prior study (23), 42 patients (27%) fell into the low/average BMI group (BMI less than 25), 56 patients (36%) were overweight (BMI greater than or equal to 25 and less than 30) and 58 patients (37%) were obese (BMI of 30 or greater). Other than the previously mentioned differences in sarcopenia rates, patients in the three BMI categories differed in sex, with obese patients being more likely to be men (p=0.047). Otherwise, there were no statistical differences in baseline clinicopathologic characteristics among patients grouped by BMI. These comparisons are summarized in Table III.

Response. The overall objective response rate (PR or CR) was 46% (72 patients). We observed a CR rate of 28% (43 patients) and a PR rate of 19.0% (29 patients). There were 13 patients who achieved SD and were therefore included in the disease control group, a total of 85 patients (54%) achieved disease control (SD + PR + CR), and 71 patients (46%) who progressed without responding. In unadjusted

analysis, patients differed in rates of objective response based on neither sarcopenic status (Table IV) nor BMI category (Table V).

Toxicity. Twenty-nine patients (19%) experienced a toxicity that was severe enough to cause permanent cessation of pembrolizumab treatment. The most common treatment-stopping toxicities were GI- and skin-related, with 6 patients each (3.8%). While there were no differences in toxicity based on sarcopenic status, BMI category was statistically associated with toxicity (p=0.0004). Specifically, obese patients had higher rates of treatment-ending toxicity (35% compared to 7% and 12%) (Table V).

Progression-free survival (PFS) and overall survival (OS). Sixty-one patients (39%) died, five of which did not have disease progression and 94 patients (60%) progressed. There were no statistical differences in PFS and OS by sarcopenic status or BMI category. The median PFS for sarcopenic patients was 12.8 months (95%CI=4.8-41.4 months) compared to 12.2 months (95%CI=6.6-23.6 months) for non-sarcopenic patients. Patients with low-to-average BMI had median PFS of 12.2 months (95%CI=5.0-30.7) compared to 10.3 months (95%CI=5.7-19.5) for overweight and 16.9 months [95% CI 4.9-NE (non-estimable)] for obese patients, log-rank p=0.95. The log-rank test for differences in OS curves by sarcopenic status or BMI category resulted in p=0.48 and p=0.75, respectively. Median follow-up for the sample was 32.9 months (95%CI=30.4-39.9 months) with slight differences by BMI category that were not statistically significant: 41.6 months (95%CI=27.1-43.6) for low-average BMI vs 31.2 months (95%CI=26.7-35.0) for overweight to obese patients, log-rank p=0.08.

Discussion

This study investigated the potential impact of sarcopenia and BMI on the efficacy and toxicity of pembrolizumab therapy in patients with advanced melanoma. To the best of our knowledge, this is the first study to employ a simple measure of sarcopenia (lumbar cross-sectional area of a single psoas muscle) to examine outcomes of melanoma patients treated with pembrolizumab. Sarcopenia, defined using PMI calculated from simple psoas cross-sectional area, was associated with older age, lower BMI, and lower albumin. There is published evidence showing that muscle function and muscle mass are associated with these three factors, suggesting that our simple psoas measurement may have been a good surrogate for sarcopenia (24-26). However, this measure was not found to be associated with the efficacy and toxicity of pembrolizumab. Further, we did not find evidence to suggest that sarcopenia or BMI groupings correlated with survival outcomes. Interestingly, though,

Table I. *Patient, cancer and treatment characteristics*.

	All patients (n=156)	
	n	%
Median age at treatment start (Min-Max)		66 (21-93)
Patient gender		
Female	65	41.7
Male	91	58.3
Patient race		
Caucasian	150	96.2
African American	5	3.2
American Indian or Alaskan Native	1	0.6
Median BMI (Min-Max)		28.5 (16.4-71.5)
BMI category		
Low-average (BMI <25)	42	26.9
Overweight (25≤BMI<30)	58	37.2
Obese (BMI ≥30)	56	35.9
ECOG status		
Performance status 0	63	40.4
Performance status 1	36	23.1
Performance status 2	7	4.5
Performance status 3	3	1.9
Performance status not reported	47	30.1
Albumin		
Low (<3.5 g/dl)	24	15.4
Normal (5.5≥Albumin≥3.5 g/dl)	132	84.6
High (>5.5 g/dl)	0	0
Creatinine		
Low (female <0.6, male <0.9 mg/dl)	24	15.4
Normal (female 0.6-1.1, male 0.9-1.3 mg/dl)	119	75.0
High (female >1.1, male >1.3 mg/dl)	15	9.6
Chronic kidney disease diagnosis		
Yes	40	25.6
No	116	74.4
AJCC 7 stage at treatment start		
IIIC	25	16.0
IV	131	84.0
Median Breslow thickness (Q1-Q3) (missing for 39/156 patients)		2.5 (0.3-28.0)
Primary site		
Head/neck	38	24.4
Trunk	31	19.9
Upper extremity	30	19.2
Lower extremity	41	26.3
Metastatic	16	10.3
Presence of *BRAF* V600E mutation		
Unknown	6	3.8
Wild-type	101	64.7
Mutant	49	31.4
Median number of cycles (Min-Max)		8 (1-49)
Concurrent cancer diagnosis		
No	134	85.9
Yes	22	14.1
Concurrent radiation therapy		
No	152	97.4
Yes	4	2.6
Concurrent treatment		
No	142	91.0
Yes	14	9.0
Median time on Pembro, months (Min-Max)		5.5 (0.7-41.4)

Sex-specific creatinine levels were defined using the University of Rochester Online Health Encyclopedia.

Table II. *Patient, cancer and treatment characteristics by sarcopenic status*.

	PMI-based definition				
	Not sarcopenic n=103		Sarcopenic n=53		
	N	%	N	%	*p*-Value
Median age at treatment start (Q1-Q3)	65.1 (54.3-71.9)		68.5 (62.0-77.0)		0.01
Patient gender					0.98
Female	43	41.0	22	41.5	
Male	60	58.3	31	58.5	
Patient race					0.78
Caucasian	98	95.1	52	98.1	
African American	4	3.9	1	1.9	
American Indian or Alaskan Native	1	1.0	0	0	
Median BMI (Q1-Q3)	29.1 (26.5-34.0)		25.3 (22.2-29.0)		<0.0001
BMI category					<0.0001
Low-Average (BMI <25)	17	16.2	25	47.2	
Overweight (25≤BMI<30)	38	36.9	18	34.0	
Obese (BMI ≥30)	48	46.6	10	18.9	
Albumin					0.02
Low (<3.5 g/dl)	11	10.7	13	24.5	
Normal (5.5≥Albumin≥3.5 g/dl)	92	89.3	40	75.5	
Creatinine					0.17
Low (female <0.6, male <0.9 mg/dl)	14	13.6	10	18.9	
Normal (female 0.6-1.1, male 0.9-1.3 mg/dl)	76	73.8	41	77.4	
High (female >1.1, male >1.3 mg/dl)	13	12.6	2	3.8	
Stage at treatment start					0.49
IIIC	18	17.5	7	13.2	
IV	85	82.5	46	86.8	
Median Breslow thickness (Q1-Q3) missing for 39/156 patients; 26/103 non sarcopenic and 13/53 sarcopenic	2.7 (1.3-4.5)		2.3 (1.3-4.2)		0.48
Primary melanoma site					0.71
Head/neck	22	21.4	16	30.2	
Trunk	20	19.4	11	20.8	
Upper extremity	20	19.4	10	18.9	
Lower extremity	29	28.2	12	22.6	
Metastatic	12	11.7	4	7.5	
Presence of BRAF V600 mutation					1.00
Unknown	4	3.9	2	3.8	
BRAF Wild-type	67	65.0	34	64.2	
BRAF Mutant	32	31.1	17	32.1	
Median number of treatment cycles (Q1-Q3)	8.0 (4-13)		8.0 (3-20)		0.79
Concurrent cancer diagnosis					0.22
No	91	88.3	43	81.1	
Yes	12	11.7	10	18.9	
Concurrent radiation therapy					1.00
No	100	97.1	52	98.1	
Yes	3	2.9	1	1.9	
Concurrent treatment					0.08
No	97	94.2	45	84.9	
Yes	6	5.8	8	15.1	
Median time on Pembro, months (Q1-Q3)	5.5 (2.7-10.3)		5.3 (2.1-13.8)		0.95

Continuous variables were compared using Wilcoxon rank sum tests and categorical variables by chi-square or Fisher's exact (where appropriate). Percentages are within sarcopenic status.

patients with obesity were more likely to experience a toxicity leading to treatment cessation.

Most published studies that used radiographic imaging to quantify sarcopenia employed specialized software such as SYNAPSE VINCENT (Fujifilm Medical, Tokyo, Japan) and Slice-O-Matic (Tomovision, Montreal, Quebec, Canada) to calculate total muscle cross-sectional area (27). Although such tools may be automated and could more accurately

Table III. *Patient, cancer and treatment characteristics by BMI category.*

	BMI Category						
	Low-average n=42		Overweight n=56		Obese n=58		
	n	%	n	%	n	%	*p*-Value
Median age at treatment start (Q1-Q3)	68.4 (57.0-77.0)		67.8 (55.9-75.9)		65.3 (55.2-68.9)		0.17
Patient gender							0.047
Female	22	52.4	26	44.1	17	29.8	
Male	20	47.6	30	53.6	41	70.7	
Patient race							0.44
Caucasian	42	100.0	54	96.4	54	93.1	
African American	0	0	2	3.6	3	5.2	
American Indian or Alaskan Native	0	0	0	0	1	1.7	
Albumin							0.81
Low (<3.5 g/dl)	6	14.3	10	17.9	8	13.8	
Normal (5.5≥Albumin≥3.5 g/dl)	36	85.7	46	82.1	50	86.2	
Creatinine							0.42
Low (female <0.6, male <0.9 mg/dl)	9	21.4	5	8.9	10	17.2	
Normal (female 0.6-1.1, male 0.9-1.3 mg/dl)	30	71.4	46	82.1	41	70.7	
High (female >1.1, male >1.3 mg/dl)	3	7.1	5	8.9	7	12.1	
Stage at treatment start							0.90
IIIC	7	16.7	8	14.3	10	17.2	
IV	35	83.3	48	85.7	48	82.8	
Median Breslow thickness (Q1-Q3) missing for 39/156 patients; 9/42 Low-average, 15/56 Overweight, and 15/58 Obese	2.2 (1.1-3.0)		2.7 (1.3-5.7)		2.6 (1.3-4.5)		0.42
Primary site							0.84
Head/neck	9	21.4	15	26.8	14	24.1	
Trunk	6	14.3	11	19.6	14	24.1	
Upper extremity	10	23.8	12	21.4	8	13.8	
Lower extremity	11	26.2	14	25.0	16	27.6	
Metastatic	6	14.3	4	7.1	6	10.3	
Presence of BRAF V600E mutation							0.77
Unknown	2	4.8	3	5.4	1	1.7	
BRAF Wild-type	25	59.5	36	64.3	40	69.0	
BRAF Mutant	15	35.7	17	30.4	17	29.3	
Median number of cycles (Q1-Q3)	8.5 (4-21)		7.0 (4-13)		7.5 (4-12)		0.38
Concurrent cancer diagnosis							0.47
No	34	81.0	48	85.7	52	89.7	
Yes	8	19.0	8	14.3	6	10.3	
Concurrent radiation therapy							0.84
No	41	97.6	54	96.4	57	98.3	
Yes	1	2.4	2	3.6	1	1.7	
Concurrent treatment							0.69
No	37	88.1	51	91.1	54	93.1	
Yes	5	11.9	5	8.9	4	6.9	
Median time on Pembro, months (Q1 - Q3)	6.2 (2.1-13.8)		5.4 (2.2-9.1)		5.1 (3.0-11.0)		0.70
PMI-based sarcopenia definition							
Not sarcopenic	17	40.5	38	67.9	48	82.8	<0.0001
Sarcopenic	25	59.5	18	32.1	10	17.2	
Density-based sarcopenia definition*							
Did not have a contrast scan (not included)	9	21.4	5	8.5	10	17.2	
Not sarcopenic	23	54.8 (69.7)	35	62.5 (68.6)	29	50.0 (60.4)	0.60
Sarcopenic	10	23.8 (30.3)	16	28.6 (31.4)	19	32.8 (39.6)	

Continuous variables were compared using Kruskal-Wallis tests and categorical variables by chi-square or Fisher's exact (where appropriate). Percentages are within BMI group. *Patients who did not have a contrast scan were not included in the test comparing BMI groups on Density-Based Sarcopenia Definition; percentages in parentheses are specifically among those in the corresponding BMI group who had a scan.

Table IV. *Toxicity and treatment response by sarcopenic status.*

	PMI-based definition						
	All		Not sarcopenic		Sarcopenic		
	n	%	n	%	n	%	*p*-Value
Toxicity leading to pembrolizumab cessation							0.95
No	127	81.4	84	81.6	43	81.1	
Yes	29	18.6	19	18.4	10	18.9	
Objective response determination							0.88
Non-responders (SD, PD)	84	53.8	55	53.4	29	54.7	
Responders (CR, PR)	72	46.2	48	46.6	24	45.3	

Percentages are within sarcopenic status.

Table V. *Toxicity and treatment response by BMI category.*

	BMI category								
	All		Low-average		Overweight		Obese		
	n	%	n	%	n	%	n	%	*p*-Value
Toxicity leading to pembrolizumab cessation									**0.0004**
No	127	81.4	37	88.1	52	92.9	38	65.5	
Yes	29	18.6	5	11.9	4	7.1	20	34.5	
Objective response determination									0.40
Non-responders (SD or NONE)	84	53.8	26	61.9	30	53.6	28	48.3	
Responders (CR or PR)	72	46.2	16	38.1	26	46.4	30	51.7	

Percentages are within BMI category. *p*-values <0.05 are shown in bold.

quantify muscle surface area, these methods are costly, requiring additional training and software. In contrast, this study employs an expedient and accessible measure of the cross-sectional area of the psoas muscle, which has been successfully used in the past to study major surgical complications after colorectal carcinoma resection (22). To our knowledge, no study has yet evaluated sarcopenia in the context of pembrolizumab treatment for melanoma using this simple method.

Only limited research has been published on sarcopenia in patients treated with PD-1 inhibitors, yet existing evidence indicates that radiographic sarcopenia may be associated with higher frequency of toxicity and lower response rates (23, 28). In contrast with these prior studies, no relationship between sarcopenia and treatment outcomes were identified in this study. While it is possible that sarcopenia is not relevant to pembrolizumab outcomes in this population, it is also plausible that the impact of sarcopenia is masked by the small sample size or some variable not accounted for in this study. Perhaps sarcopenic patients experienced unmeasured disadvantages such as lower quality of life and decreased daily function, but if these impacts were present, they did not appear to affect treatment outcomes or survival (29). It is also possible that sarcopenia itself is a confounding variable related to other variables associated with the outcomes of interest. Although the described method of defining sarcopenia did not find a direct association between sarcopenia and clinical outcomes in this sample, it was found to be associated with albumin, age, and BMI.

In contrast with these prior studies, no relationship between sarcopenia and treatment outcomes were identified in this study. Our results suggest that higher BMI is associated with greater likelihood of toxicity. Thus far, there is a paucity of evidence relating BMI and the risk of pembrolizumab-related toxicity; two retrospective studies published from the same institution show that sarcopenic overweight patients experience more early acute limiting toxicity from PD-1 inhibitors (1, 30). In contrast, pharmacokinetic studies predicted that although body weight influences the clearance and volume of distribution of monoclonal antibodies, weight has no clinically

relevant impact on pembrolizumab treatment (31, 32). In fact, in one such study, the effects of body weight on the volume of distribution and clearance of pembrolizumab appear to be minimal in comparison to the effects of body weight on the other PD-1 inhibitor drug, nivolumab (33). Yet, our results suggest that obesity may augment the risk of pembrolizumab toxicity. Therapeutic antibodies such as pembrolizumab are primarily eliminated by protein catabolism in multiple tissue types. It is possible that the relative lack of lean tissue in patients with obesity leads to reduced elimination and exposure ton increased concentrations of the drug (34). This would hold especially true if pembrolizumab was administered on a weight-based dosing regimen; however, it is given in a fixed dose to all patients. Another explanation may involve the fact that monoclonal antibodies are largely confined to vascular and interstitial spaces due to their large molecular weight and hydrophilicity (32). As BMI increases, there may be a greater increase in body mass in proportion to the volume of distribution, thereby concentrating the drug in a smaller space relative to total body mass. Altered cardiac performance and adipose tissue blood flow in patients with obesity may also play a role in heightened toxicity to pembrolizumab (35). Lastly, it has been posited that adipokines and obesity-related inflammation could contribute to toxicity (1).

Finally, no correlation between BMI and treatment response or survival was found, notwithstanding the reported "obesity paradox" in which obesity has been associated with superior treatment outcomes in patients receiving BRAF-targeted and immunologic therapies (10, 12, 36). Moreover, there is a documented direct relationship between occurrence of immune-related adverse events and improved clinical response to immune checkpoint inhibitor treatment (37-39). As this study suggests that obesity is correlated with pembrolizumab toxicity, we would have also expected obesity to correlate with positive treatment outcomes.

Ultimately, the findings in this study suggest that while a simple measure of radiographic sarcopenia may correlate with patient age, albumin and BMI, it is not necessarily predictive of toxicity and response to pembrolizumab. BMI, however, appears to be a readily available baseline patient measure which corresponds to heightened toxicity.

Our findings should be interpreted in the context of several study limitations. First, this was a retrospective single-institution analysis with a relatively small sample size which limited subgroup and multivariate analyses. Moreover, this study illustrates only one of many ways to measure sarcopenic status, and it is possible that more accurate, automated approaches could be implemented and further developed. Future studies on pembrolizumab for the treatment of melanoma could explore other strategies for determining sarcopenia, including single-distance measurement of the temporalis muscle, measurement of all lumbar muscles, hand-grip strength, and the ECOG (Eastern Cooperative Oncology Group) performance score (12, 40). Other variables associated with nutritional status and muscle mass, such as albumin and creatinine, may be examined in further studies to explore these specific patient factors and how they influence individual response to immunotherapy.

Conclusion

Our findings indicate that sarcopenia was not predictive of efficacy or toxicity associated with pembrolizumab treatment of patients with advanced melanoma. However, higher BMI, a routinely measured and readily available baseline characteristic, was associated with treatment-limiting toxicity. While further study is warranted to elucidate the basis of this relationship, knowledge that patients with higher BMI are at higher risk for these toxicities could inform decision-making and provide anticipatory guidance when choosing the right therapy for an individual patient.

Conflicts of Interest

April K.S. Salama received research funding (paid to institution) from Bristol Myers Squibb, Celldex, Immunocore, Merck Consultant: Array.

Authors' Contributions

J.B.H and P.J.M. devised the project and main conceptual ideas. J.B.H and S.R. performed the retrospective chart review. L.H. carried out radiologic measurements. C.R. and S.J. conducted the statistical analysis. G.B., B.A.H, A.K.S.S. and P.J.M. supervised the project. All Authors provided critical feedback and helped in the critical analysis and writing of the manuscript.

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References

1 Heidelberger V, Goldwasser F, Kramkimel N, Jouinot A, Huillard O, Boudou-Rouquette P, Chanal J, Arrondeau J, Franck N, Alexandre J, Blanchet B, Leroy K, Avril MF, Dupin N and Aractingi S: Sarcopenic overweight is associated with early acute limiting toxicity of anti-PD1 checkpoint inhibitors in melanoma patients. Invest New Drug *35(4)*: 436-441, 2017. PMID: 28396974. DOI: 10.1007/s10637-017-0464-x

2 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer *45*: 228-247, 2009. PMID: 19097774. DOI: 10.1016/j.ejca.2008.10.026

3 Simetić L, Blažičević K, Međugorac K, Golčić M and Herceg D: Relative change in S100 as a biomarker of survival in

patients with metastatic melanoma treated with pembrolizumab. Anticancer Res *40(4)*: 2157-2163, 2020. PMID: 32234909. DOI: 10.21873/anticanres.14175

4 Hopkins AM, Rowland A, Kichenadasse G, Wiese MD, Gurney H, McKinnon RA, Karapetis CS and Sorich MJ: Predicting response and toxicity to immune checkpoint inhibitors using routinely available blood and clinical markers. Br J Cancer *117(7)*: 913-920, 2017. PMID: 28950287. DOI: 10.1038/bjc.2017.274

5 Gibney GT, Weiner LM and Atkins MB: Predictive biomarkers for checkpoint inhibitor-based immunotherapy. Lancet Oncol *17(12)*: e542-e551, 2016. PMID: 27924752. DOI: 10.1016/S1470-2045(16)30406-5

6 Tsai KK, Loo K, Khurana N, Algazi AP, Hwang J, Sanchez R, Krummel M, Rosenblum M, Tumeh P and Duad A: Clinical characteristics predictive of response to pembrolizumab in advanced melanoma. J Clin Oncol *33(suppl 15):* 9031-903, 2015. DOI: 10.1200/jco.2015.33.15_suppl.9031

7 Weide B, Martens A, Hassel JC, Berking C, Postow MA, Bisschop K, Simeone E, Mangana J, Schilling B, Di Giacomo AM, Brenner N, Kahler K, Heinzerling L, Gutzmer R, Bender A, Gebhardt C, Romano E, Friedegund M, Martus P, Maio M, Blank C, Schadendorf D, Dummer R, Ascierto PA, Hospers G, Garbe C and Wolchok JD: Baseline biomarkers for outcome of melanoma patients treated with pembrolizumab. Clin Cancer Res *22(22):* 5487, 2016. PMID: 27185375. DOI: 10.1158/1078-0432.CCR-16-0127

8 Carlos G, Anforth R, Chou S, Clements A and Fernandez-Penas P: A case of bullous pemphigoid in a patient with metastatic melanoma treated with pembrolizumab. Melanoma Res *25(3):* 265-268, 2015. PMID: 25831416. DOI: 10.1097/CMR.0000000000000155

9 de Maleissye MF, Nicolas G and Saiag P: Pembrolizumab-induced demyelinating polyradiculoneuropathy. New Engl J Med *375(3):* 296-297, 2016. PMID: 27468083. DOI: 10.1056/NEJMc1515584

10 Läubli H, Balmelli C, Bossard M, Pfister O, Glatz K and Zippelius A: Acute heart failure due to autoimmune myocarditis under pembrolizumab treatment for metastatic melanoma. J Immunother Cancer *3(1):* 11, 2015. PMID: 25901283. DOI: 10.1186/s40425-015-0057-1

11 Marjanska A, Galazka P, Marjanski M, Wysocki M, and Styczynki J: Efficacy and toxicity of pembrolizumab in pediatric metastatic recurrent melanoma. Anticancer Res *39(7)*: 3945-3947, 2019. PMID: 31262925. DOI: 10.21873/anticanres.13547

12 Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA and Schneider SM: Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing *48(1):* 16-31, 2018. PMID: 31081853. DOI: 10.1093/ageing/afz046

13 McQuade JL, Daniel CR, Hess KR, Mak C, Wang DY, Rai RR, Park JJ, Haydu LE, Spencer C, Wongchenko M and Lane S: Association of body-mass index and outcomes in patients with metastatic melanoma treated with targeted therapy, immunotherapy, or chemotherapy: a retrospective, multicohort analysis. Lancet Oncol *19(3):* 310-322, 2018. PMID: 29449192. DOI: 10.1016/S1470-2045(18)30078-0

14 Naik GS, Waikar SS, Johnson AE, Buchbinder EI, Haq R, Hodi FS, Schoenfeld JD and Ott PA: 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 *7(1):* 89, 2019. PMID: 30922394. DOI: 10.1186/s40425-019-0512-5

15 Daly LE, Power DG, O'Reilly Á, Donnellan P, Cushen SJ, O'Sullivan K, Twomey M, Woodlock DP, Redmond HP and Ryan AM: The impact of body composition parameters on ipilimumab toxicity and survival in patients with metastatic melanoma. Br J Cancer *116:* 310, 2017. PMID: 28072766. DOI: 10.1038/bjc.2016.431

16 Sabel MS, Lee J, Cai S, Englesbe MJ, Holcombe S and Wang S: Sarcopenia as a prognostic factor among patients with stage III melanoma. Ann Surg Oncol *18(13):* 3579-3585, 2011. PMID: 21822551. DOI: 10.1245/s10434-011-1976-9

17 Sabel MS, Lee J, Wang A, Lao C, Holcombe S and Wang S: Morphomics predicts response to ipilimumab in patients with stage IV melanoma. J Surg Oncol *112(4)*: 333-337, 2015. PMID: 26251199. DOI: 10.1002/jso.24003

18 Martin L, Birdsell L, MacDonald N, Reiman T, Clandinin MT, McCargar LJ, Murphy R, Ghosh S, Sawyer MB and Baracos VE: Cancer cachexia in the age of obesity: Skeletal muscle depletion is a powerful prognostic factor, independent of Body Mass Index. J Clin Oncol *31(12):* 1539-1547, 2013. PMID: 23530101. DOI: 10/1200/jco.2012.45.2722

19 Abramowitz MK, Hall CB, Amodu A, Sharma D, Androga L and Hawkins M: Muscle mass, BMI, and mortality among adults in the United States: A population-based cohort study. PLoS *13(4)*: e0194697-e0194697, 2018. PMID: 29641540. DOI: 10.1371/journal.pone.0194697

20 Baracos VE and Arribas L: Sarcopenic obesity: Hidden muscle wasting and its impact for survival and complications of cancer therapy. Ann Oncol *29(suppl 2)*: ii1-ii9, 2018. PMID: 29506228. DOI: 10.1093/annonc/mdx810

21 National Institutes of Health: Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. National Cancer Institute, 2017.

22 Jones KI, Doleman B, Scott S, Lund JN and Williams JP: Simple psoas cross-sectional area measurement is a quick and easy method to assess sarcopenia and predicts major surgical complications. Colorectal Dis *17(1):* O20-O26, 2015. PMID: 25328119. DOI: 10.1111/codi.12805

23 Cortellini A, Verna L, Porzio G, Bozzetti F, Palumbo P, Masciocchi C, Cannita K, Parisi A, Brocco D, Tinari N and Ficorella C: Predictive value of skeletal muscle mass for immunotherapy with nivolumab in non-small cell lung cancer patients: A "hypothesis-generator" preliminary report. Thorac Cancer *10(2):* 347-351, 2019. PMID: 30600905. DOI: 10.1111/1759-7714.12965

24 Fukuoka Y, Narita T, Fujita H, Morii T, Sato T, Sassa MH and Yamada Y: Importance of physical evaluation using skeletal muscle mass index and body fat percentage to prevent sarcopenia in elderly Japanese diabetes patients. J Diabetes Investig *10(2):* 322-330, 2019. PMID: 30098231. DOI: 10.1111/jdi.12908

25 Baumgartner RN, Koehler KM, Romero L and Garry PJ: Serum albumin is associated with skeletal muscle in elderly men and women. Am J Clin Nutr *64(4):* 552-558, 1996. PMID: 8839499. DOI: 10.1093/ajcn/64.4.552

26 Mitchell WK, Williams J, Atherton P, Larvin M, Lund J and Narici M: Sarcopenia, dynapenia, and the impact of advancing age on human skeletal muscle size and strength: A quantitative

review. Front Physiol *3*: 260, 2012. PMID: 22934016. DOI: 10.3389/fphys.2012.00260

27 Shiroyama T, Nagatomo I, Koyama S, Hirata H, Nishida S, Miyake K, Fukushima K, Shirai Y, Mitsui Y, Takata S and Masuhiro K: Impact of sarcopenia in patients with advanced non–small cell lung cancer treated with PD-1 inhibitors: A preliminary retrospective study. Scientific Rep *9(1):* 2447, 2019. PMID: 30792455. DOI: 10.1038/s41598-019-39120-6

28 Young A, Quach HT, Davis EJ, Moslehi J, Williams GR and Johnson DB: Impact of body composition on outcomes from anti-programmed death-1 (PD-1) treatment. J Clin Oncol *37(suppl 15):* 9516-9516, 2019. DOI: 10.1200/JCO.2019.37.15_suppl.9516

29 Cheung WY, Bayliss MS, White MK, Stroupe A, Lovley A, King-Kallimanis BL and Lasch K: Humanistic burden of disease for patients with advanced melanoma in Canada. Support Care Cancer *26(6):* 1985-1991, 2018. PMID: 29322243. DOI: 10.1007/s00520-017-4025-9

30 Heidelberger V, Kramkimel N, Huillard O, Rouquette PB, Chanal J, Arrondeau J, Franck N, Alexandre J, Blanchet B, Dupin N and Aractingi S: Sarcopenia associated with a body mass index (BMI) > 25 kg/m^2 predicts severe acute toxicity of nivolumab and pembrolizumab in melanoma patients. Ann Oncol *27(suppl_6)*, 2016. DOI: 10.1093/annonc/mdw379.25

31 Ahamadi M, Freshwater T, Prohn ME, Li CH, De Alwis DP, De Greef R, Elassaiss-Schapp J, Kondic A and Stone JA: Model-based characterization of the pharmacokinetics of pembrolizumab: A humanized anti–PD-1 monoclonal antibody in advanced solid tumors. CPT Pharmacometrics Syst Pharmacol *6(1):* 49-57, 2017. PMID: 27863186. DOI: 10.1002/psp4.12139

32 Dirks NL and Meibohm B: Population pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokin *49(10):* 633-659, 2010. PMID: 20818831. DOI: 10.2165/11535960-000000000-00000

33 Hendrikx JJ, Haanen JB, Voest EE, Schellens JH, Huitema AD and Beijnen JH: Fixed dosing of monoclonal antibodies in oncology. Oncologist *22(10):* 1212-1221, 2017. PMID: 28754722. DOI: 10.1634/theoncologist.2017-0167

34 Mahmood I: Pharmacokinetic allometric scaling of antibodies: Application to the first-in-human dose estimation. J Pharm Sci-US *98(10):* 3850-3861, 2009. PMID: 19177515. DOI: 10.1002/jps.21682

35 Cheymol G: Effects of obesity on pharmacokinetics. Clin Pharmacokin *39(3):* 215-231, 2000. PMID: 11020136. DOI: 10.2165/00003088-200039030-00004

36 Wang Z, Aguilar EG, Luna JI, Dunai C, Khuat LT, Le CT, Mirsoian A, Minnar CM, Stoffel KM, Stufgill IR and Grossenbacher SK: Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade. Nat Med *25(1)*: 141-151, 2019. PMID: 30420753. DOI:10.1038/s41591-018-0221-5

37 Gu Y, Menzies AM, Long GV, Fernando SL and Herkes G: Immune mediated neuropathy following checkpoint immunotherapy. J Clin Neurosc *45:* 14-17, 2017. PMID: 28765062. DOI: 10.1016/j.jocn.2017.07.014

38 Hua C, Boussemart L, Mateus C, Routier E, Boutros C, Cazenave H, Viollet R, Thomas M, Roy S, Benannoune N and Tomasic G: Association of vitiligo with tumor response in patients with metastatic melanoma treated with pembrolizumab. JAMA Dermatol *152(1):* 45-51, 2016. PMID: 26501224. DOI: 10.1001/jamadermatol.2015.2707

39 Downey SG, Klapper JA, Smith FO, Yang JC, Sherry RM, Royal RE, Kammula US, Hughes MS, Allen TE, Levy CL and Yellin M: Prognostic factors related to clinical response in patients with metastatic melanoma treated by CTL-associated antigen-4 blockade. Clin Cancer Res *13(22):* 6681, 2007. PMID: 17982122. DOIL: 10.1158/1078-0432.CCR-07-0187

40 Furtner J, Berghoff AS, Schöpf V, Reumann R, Pascher B, Woitek R, Asenbaum U, Pelster S, Leitner J, Widhalm G and Gatterbauer B: Temporal muscle thickness is an independent prognostic marker in melanoma patients with newly diagnosed brain metastases. J Neurooncol *140(1):* 173-178, 2018. PMID: 3008154. DOI: 10.1007/s11060-018-2948-8

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