Prediction of Response to Immune Checkpoint Inhibitor Therapy Using Early-Time-Point ^{18}F-FDG PET/CT Imaging in Patients with Advanced Melanoma

Steve Y. Cho*[1,2], Evan J. Lipson*[1], Hyung-Jun Im*[2,3], Steven P. Rowe[1], Esther Mena Gonzalez[1], Amanda Blackford[1], Alin Chirindel[1], Drew M. Pardoll[1], Suzanne L. Topalian[1], and Richard L. Wahl[1,4]

[1]*Johns Hopkins University School of Medicine and Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland;* [2]*University of Wisconsin School of Medicine and Public Health and Carbone Comprehensive Cancer Center, Madison, Wisconsin;* [3]*Department of Transdisciplinary Studies, Graduate School of Convergence Science and Technology, Seoul National University, Seoul, Korea; and* [4]*Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri*

The purpose of this study was to evaluate ^{18}F-FDG PET/CT scanning as an early predictor of response to immune checkpoint inhibitors (ICIs) in patients with advanced melanoma. **Methods:** Twenty patients with advanced melanoma receiving ICI prospectively underwent ^{18}F-FDG PET/CT at 3 scan intervals: before treatment initiation (SCAN-1), at days 21–28 (SCAN-2), and at 4 mo (SCAN-3). This study was approved by the institutional review board, and informed consent was received from all patients who were enrolled between April 2012 and December 2013. Tumor response at each posttreatment time point was assessed according to RECIST 1.1, immune-related response criteria, PERCIST (PERCIST 1.0), and European Organization for Research and Treatment of Cancer (EORTC) criteria. Performance characteristics of each metric to predict best overall response (BOR) at $\geq$ 4 mo were assessed. **Results:** Twenty evaluable patients were treated with ipilimumab (n = 16), BMS-936559 (n = 3), or nivolumab (n = 1). BOR at $\geq$ 4 mo included complete response (n = 2), partial response (n = 2), stable disease (n = 1), and progressive disease (n = 15). Response evaluations at SCAN-2 using RECIST 1.1, immune-related response criteria, PERCIST, and EORTC criteria demonstrated accuracies of 75%, 70%, 70%, and 65%, respectively, to predict BOR at $\geq$ 4 mo. Interestingly, the optimal PERCIST and EORTC threshold values at SCAN-2 to predict BOR were >15.5% and >14.7%, respectively. By combining anatomic and functional imaging data collected at SCAN-2, we developed criteria to predict eventual response to ICI with 100% sensitivity, 93% specificity, and 95% accuracy. **Conclusion:** Combining functional and anatomic imaging parameters from ^{18}F-FDG PET/CT scans performed early in ICI appears predictive for eventual response in patients with advanced melanoma. These findings require validation in larger cohorts.

Key Words: FDG; PET/CT; immune checkpoint inhibitor; melanoma; response assessment

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Immune checkpoint inhibitors (ICIs) blocking CTLA-4 (e.g., ipilimumab), PD-1 (e.g., nivolumab, pembrolizumab), or PD-L1 (e.g., atezolizumab, avelumab, durvalumab) have demonstrated objective tumor regressions in patients with advanced melanoma and other cancer types. Some drugs and drug combinations (e.g., nivolumab plus ipilimumab) can prolong survival in patients with melanoma (*1,2*). However, these drugs have mechanisms of action that differ from targeted agents and traditional cytotoxic chemotherapies, making assessment of therapeutic benefit (or lack thereof) in a given patient challenging, especially soon after initiation of therapy. In some cases, tumors assessed using standard CT imaging appear to enlarge before later regressing, likely due to the infiltration and proliferation of lymphocytes and other immune cells. Other tumors remain stable in size for a prolonged time, even after therapy has been stopped (*3–6*). Indeed, a variety of radiologic responses to ICIs has been described, some of which are linked to therapeutic benefit (*7,8*). Because traditional RECIST or World Health Organization criteria may be insufficient to characterize outcomes after administration of immune-based antineoplastic drugs, immune-related response criteria (irRC (*9*)) are increasingly being incorporated into clinical trials of cancer immunotherapies (*10,11*).

Several studies have investigated the utility of ^{18}F-FDG PET/CT imaging in early detection of response to targeted and chemotherapeutic agents in a variety of tumor types (*12–14*). Results from these studies and others suggest that functional imaging information obtained from ^{18}F-FDG PET/CT scans may complement data from anatomic imaging studies such as conventional spiral CT scanning and MRI.

Two ^{18}F-FDG PET–based tumor response evaluation criteria commonly used in studies of patients with solid tumors are PERCIST 1.0 and European Organization for Research and Treatment of Cancer (EORTC) 1999 criteria (*15,16*). Disease response to therapy has been evaluated in multiple studies encompassing a variety of tumor types using these metrics (*17–19*).

To investigate the utility of ^{18}F-FDG PET/CT as a tool to detect early evidence of response in patients with advanced melanoma receiving immune checkpoint blocking agents, we prospectively performed serial ^{18}F-FDG PET/CT imaging in patients with advanced melanoma undergoing ICI therapy, conducted several analyses to characterize changes in tumor burden and functional

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For correspondence or reprints contact: Steve Y. Cho, WIMR1, Rm. 7139, 1111 Highland Ave., Madison, WI 53705.
E-mail: scho@uwhealth.org
*Contributed equally to this work.
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parameters, and used these data to develop criteria to predict eventual clinical response to therapy.

MATERIALS AND METHODS

Study Design

This study was approved by the Johns Hopkins University and University of Wisconsin–Madison Institutional Review Boards in accordance with an assurance filed with and approved by the Department of Health and Human Services Subjects (ClinicalTrials.gov no. NCT01666353). Per institutional review board requirements, study data were anonymized during data collection and analysis. Twenty adult patients who were scheduled to initiate ICI therapy as their first or later systemic treatment for metastatic or unresectable melanoma at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center provided written informed consent to participate in this prospective study between April 2012 and December 2013. Subjects were required to have at least 1 lesion, >10 mm, that could be accurately measured in at least 1 dimension with spiral CT scanning. Patients were treated with ipilimumab at 3 mg/kg intravenously every 3 wk for a maximum of 4 doses (anti–CTLA-4; $n = 16$); BMS-936559 at 0.1–1 mg/kg intravenously every 2 wk until complete response, disease progression, or dose-limiting toxicity (anti–PD-L1; $n = 3$; ClinicalTrials.gov no. NCT00729664 (*20*)); or nivolumab at 3 mg/kg every 2 wk (anti–PD-1; $n = 1$; ClinicalTrials.gov no. NCT01621490 (*21*)). ^{18}F-FDG PET/CT imaging was performed within 4 wk before therapy (SCAN-1) was initiated, again between days 21 and 28 on therapy (SCAN-2), and at approximately 4 mo after treatment initiation (SCAN-3). Patients were observed until death or initiation of subsequent therapy for disease progression. Of note, because of the investigational nature of SCAN-2, data from that scan were not used to guide patient management decisions. Evaluable patients were required to have received at least 2 doses of ICI therapy and have undergone SCAN-1, SCAN-2, and at least 1 additional evaluation (radiographic or clinical) thereafter. Because of the poor performance of PET/CT imaging to detect brain metastases, intracranial lesions were not included in disease assessments.

Imaging

^{18}F-FDG PET/CT images were acquired on a Discovery DRX PET/CT scanner (GE Healthcare). ^{18}F-FDG PET/CT scanning was performed according to the Uniform Protocols for Imaging in Clinical Trials Protocol for ^{18}F-FDG PET/CT Imaging in Oncology Clinical Trials (*22*). Low-dose CT images were acquired for tissue attenuation correction and anatomic correlation. Patients were injected with 370 ± 37 MBq (10 ± 1 mCi) of ^{18}F-FDG and scanned supine, starting from the midthigh and through the vertex of skull, followed by a separate scan from the upper thigh through bilateral feet. Patients fasted for 4–6 h immediately before injection of ^{18}F-FDG.

Response Evaluation

^{18}F-FDG PET/CT images were reviewed and analyzed using MIRADA XD3 software (MIRADA Medical) by 2 nuclear medicine specialists with convened consensus review of PET and CT response evaluation. CT-based responses, assessed by study investigators, were characterized according to RECIST 1.1 (*23*) and irRC (*9*). ^{18}F-FDG PET–based responses were evaluated using PERCIST 1.0 (*24,25*) and EORTC 1999 criteria (*16*). Response criteria used in this study are summarized in Table 1. Because EORTC 1999 criteria do not include a prespecified number of target lesions, we considered all ^{18}F-FDG–avid lesions at SCAN-1 as target lesions. The sum of the SUV_{max} of all ^{18}F-FDG–avid metastatic lesions was measured for the EORTC 1999 criteria. An ^{18}F-FDG–avid lesion was defined as focal, abnormally increased ^{18}F-FDG uptake versus background with a corresponding anatomic lesion seen on CT scan, suggestive of metastasis.

CT-based antitumor responses based on changes observed from SCAN-1 to SCAN-2 and SCAN-1 to SCAN-3 were classified as complete response, partial response, stable disease, or progressive disease (PD). ^{18}F-FDG PET–based responses were classified as complete metabolic response, partial metabolic response, stable metabolic disease, or progressive metabolic disease. Percentage change in lesion dimensions (CT) or ^{18}F-FDG avidity (PET) from SCAN-1 to SCAN-2 were calculated using the following formula: [(SCAN-2 – SCAN-1)/SCAN-1) × 100]. The same formula was adapted for SCAN-1 to SCAN-3 calculations subtracting the SCAN-1 result from the SCAN-3 result. During and after the study period, patients were followed per standard-of-care imaging and clinical follow-up to assess best overall response (BOR) to ICI therapy. The duration of observation for each patient is included in Table 2. Radiographic changes observed at SCAN-2 were analyzed for their capacity to predict eventual clinical benefit, which we defined as CR or PR at 4 mo or stable disease lasting at least 6 mo. Confirmatory scans for PR and CR seen at SCAN-3 were not required.

Outcomes Analysis

Intercriteria agreements at SCAN-2 and SCAN-3 were assessed using κ-coefficients (*26*). The positive and negative predictive values of outcomes at SCAN-2 for clinical benefit were assessed for all 4 criteria. Receiver-operating-characteristic (ROC) analysis was used to assess the predictive value of continuous measurements and to find the optimal cutoff of measurements to predict clinical benefit. The Pearson correlation coefficient (r) was used for correlation analysis. Finally, a combined functional–anatomic approach was developed and evaluated to enhance the predictive value of the ^{18}F-FDG PET and CT measurements at SCAN-2 for clinical benefit. Statistical analyses were performed using MedCalc software version 10.1 (version 10.1; MedCalc Software).

RESULTS

Patient Characteristics

Twenty subjects were enrolled in the trial. Their mean age was 59.2 y (range, 42–72 y). Seven were women. Eleven patients had previously received systemic therapy for advanced melanoma, including nilotinib, high-dose interleukin-2, and temozolomide. One patient who received ipilimumab on the present trial had previously received nivolumab. All 20 enrolled subjects with metastatic melanoma were evaluable for response to therapy with ICIs. Sixteen patients received ipilimumab (anti–CTLA-4) as a standard-of-care therapy in the first- or later line setting. Three patients received BMS-936559 (anti–PD-L1) on a clinical trial in the second-line setting. One patient received nivolumab (anti–PD-1) on a clinical trial in the first-line setting.

Treatment Response

Tumor responses were measured by PET/CT according to 4 different criteria systems, after 3–4 wk of treatment (SCAN-2) and at about 4 mo (SCAN-3) (Table 2). The best overall responses for each patient, including information from standard-of-care radiographic imaging performed in addition to SCAN-2 and SCAN-3, are included in Table 2.

Five subjects classified as having derived clinical benefit from ICI therapy included 2 patients with CR at 4 mo, 2 patients with PR at 4 mo, and 1 patient with stable disease lasting 9 mo. The 5 subjects had been treated with ipilimumab. The remaining 15 patients experienced stable disease lasting less than 6 mo, or PD. No patient

TABLE 1
Summary of Treatment Response Criteria

Response	CT-based criteria		PET-based criteria		
	RECIST 1.1	irRC		PERCIST 1.0	EORTC
Complete response	Disappearance of all TLs and NLs; all LNs < 10 mm short axis	Resolution of all lesions (whether measurable or not) and no new lesions	Complete metabolic response	Complete resolution of ^{18}F-FDG uptake within measurable TL and disappearance of all other lesions to BBP levels	Complete resolution of ^{18}F-FDG uptake within TV so that it is indistinguishable from surrounding NT
Partial response	≥30% decrease in SoDs of TLs; NLs may persist but not unequivocally progress	Decrease in TB ≥ 50%, measured as SoPs of 2 largest perpendicular diameters of all ILs, relative to BL	Partial metabolic response	>30% RD and >0.8 AD in SUL_{peak} of HL	Reduction of 15%–25% in tumor SUV after 1 CoT and >25% after more than 1 CoT
Stable disease	Neither sufficient TR nor TG to qualify for PR or PD	Not meeting criteria for irCR or irPR, in absence of irPD	Stable metabolic disease	Not meeting criteria for CMR, PMR, or PMD	Increase in tumor SUV of <25% or decrease of <15% and no visible increase in extent of ^{18}F-FDG TU (20% in LD)
Progressive disease	≥20% increase in sum of diameters of TLs or unequivocal progression of NL or appearance of new lesion	Increase in TB ≥ 25% relative to nadir, measured as SoPs of 2 largest perpendicular diameters of all ILs	Progressive metabolic disease	>30% RI and >0.8 AI in SUL_{peak} of HL or unequivocal progression of ^{18}F-FDG–avid NL or appearance of new ^{18}F-FDG–avid lesion	Increase from BL in tumor SUV of >25% within tumor region, visible increase in extent of ^{18}F-FDG TU (20% in LD), or appearance of new ^{18}F-FDG uptake in MLs

TL = target lesion; NL = nontarget lesion; LN = lymph node; BBP = background blood-pool; TV = tumor volume; NT = normal tissue; SoDs = sum of diameters; TB = tumor burden; SoPs = sum of the products; IL = index lesion; BL = baseline; RD = relative decrease; AD = absolute decrease; SUL_{peak} = average SUV corrected by lean body mass within a 1-cm^3 spheric volume of interest; HL = hottest lesion; CoT = cycle of therapy; TR = tumor regression; TG = tumor growth; PR = partial response; PD = progressive disease; irCR = immune-related complete response; irPR = immune-related partial response; irPD = immune-related progressive disease; CMR = complete metabolic response; PMR = partial metabolic response; PMD = progressive metabolic disease; TU = tumor uptake; LD = longest dimension; RI = relative increase; AI = absolute increase; ML = metastatic lesion; SUV = for EORTC we used SUV_{max} (maximum voxel value of SUV).

with an early assessment categorized as PD by RECIST 1.1 later experienced an objective response to therapy.

Of note, baseline scans for patient 11 demonstrated a 1.1-cm retroperitoneal lymph node, proven by fine-needle aspirate to be metastatic melanoma. Although the patient met study entry criteria (at least 1 lesion, >10 mm, that could be accurately measured in at least 1 dimension with spiral CT scanning), the tumor did not qualify as measurable by RECIST 1.1 (≥1.5-cm short diameter). However, because the lesion was proven to be tumor by biopsy, and because we were able to measure it at baseline and after administration of therapy, we included this patient in our study.

Comparisons of Response Evaluations at SCAN-2 and SCAN-3

Comparisons of tumor response measurement criteria at SCAN-2, performed 21–28 d after ICI was initiated, demonstrated excellent degrees of intercriteria agreement. κ-coefficient values were calculated within the same imaging modality: RECIST 1.1 versus irRC (CT-based), 0.9; PERCIST versus EORTC (PET-based), 0.886. Comparisons between different modalities demonstrated lesser degrees of agreement, with κ-values between 0.48 and 0.7. At SCAN-3, performed 4 mo after ICI was initiated, all pairs of response criteria showed good to excellent correlation (κ-value range, 0.66–0.88), except irRC versus PERCIST (κ = 0.53) (Supplemental Table 1; supplemental materials are available at http://jnm.snmjournals.org).

Findings on Early PET/CT Associated with Eventual Clinical Outcomes

At SCAN-2, of the 4 metrics assessed, RECIST 1.1 demonstrated the highest predictive value for BOR at ≥ 4 mo (accuracy, 75%; Table 3). ROC analysis revealed that percentage change from SCAN-1 to SCAN-2 using RECIST 1.1, irRC, PERCIST, and EORTC criteria were predictive for BOR at ≥ 4 mo as follows: area under the curve, 0.853, 0.827, 0.680, and 0.600, respectively (Supplemental Table 2).

On the basis of the percentage change from SCAN-1 to SCAN-2 of target lesion dimensions (CT) or ^{18}F-FDG uptake (PET), we derived the predictive values of these measurements based on optimal threshold values, calculated using ROC analysis, to forecast outcomes at 4 mo (Table 4). Percentage change per RECIST

TABLE 2
Response Assessments, Excluding Brain Lesions, in 20 Patients with Metastatic Melanoma Receiving ICI Therapies

Patient no.	Treatment	Response at SCAN-2 (21–28 d)				Response at SCAN-3 (~4 mo)				Best overall response at ≥ 4 mo (RECIST 1.1)	Duration of observation (wk)*	Best overall response before SCAN-3 (RECIST 1.1)†
		RECIST 1.1	irRC	PERCIST	EORTC	RECIST 1.1	irRC	PERCIST	EORTC			
1	Ipilimumab	PD	PD	PMD	PMD	PD	PD	PMD	PMD	PD	10	—
2	Ipilimumab	SD	PD	SMD	SMD	SD	SD	PMR	PMR	SD > 6 mo	51	—
3	Ipilimumab	PD	PD	PMD	PMD	PD	PD	PMD	PMD	PD	15	—
4	Ipilimumab	PD	PD	PMD	PMD	PD	PD	PMD	PMD	PD	15	—
5	Ipilimumab	PD	PD	PMD	PMD	PD	PD	PMD	PMD	PD	18	—
6	BMS-936559	SD	SD	PMR	PMR	PD	PD	PMD	PMD	PD	23	uSD at 6 wk, PD at 12 wk
7	BMS-936559	SD	SD	SMD	SMD	PD	PD	PMD	PMD	PD	18	—
8	BMS-936559	PD	PD	PMD	PMD	PD	PD	PMD	PMD	PD	18	uSD at 6 wk, PD at 12 wk
9	Ipilimumab	PD	PD	PMD	PMD	PD	PD	PMD	PMD	PD	16	—
10	Ipilimumab	SD	SD	PMD	PMD	PD	PD	PMD	PMD	PD	17	—
11	Ipilimumab	SD	SD	PMD	PMD	CR	CR	PMR	PMR	CR	184	—
12	Ipilimumab	SD	SD	PMR	PMR	PD	PD	SMD	SMD	PD	17	—
13	Ipilimumab	PD	PD	PMD	PMD	PD	PD	PMD	PMD	PD	16	—
14	Ipilimumab	SD	SD	SMD	PMD	PR	PR	PMR	PMR	PR	28	—
15	Ipilimumab	PD	PD	PMD	PMD	PD	PD	PMD	PMD	PD	19	—
16	Ipilimumab	SD	SD	PMD	PMD	PR	SD	PMD	SMD	PR	40	—
17	Ipilimumab	PR	PR	SMD	PMR	CR	CR	PMR	PMR	CR	31	—
18	Nivolumab	SD	SD	PMR	SMD	PD	SD	PMD	PMD	PD	23	SD at 8 and 15 wk
19	Ipilimumab	PD	PD	PMD	PMD	PD	PD	PMD	PMD	PD	17	—
20	Ipilimumab	PD	PD	PMD	PMD	PD	SD	PMD	PMD	PD	16	—

*Duration of observation is calculated from time of first administration of ICI therapy on this trial. Patients who received ipilimumab were treated with maximum of 4 doses and observed thereafter. Patients who received anti–PD-1/PD-L1 continued to receive therapy until disease progression.

†Standard of care on-treatment radiographic assessments performed between SCAN-2 and SCAN-3 for 3 patients demonstrated transient disease stability. Their responses are characterized in last column.

PD = progressive disease; PMD = progressive metabolic disease; SD = stable disease; SMD = stable metabolic disease; PMR = partial metabolic response; PR = partial response; u = unconfirmed, seen only on 1 set of scans; CR = complete response.

Responses based on 4 criteria in 20 patients with metastatic melanoma after receiving ipilimumab (anti–CTLA-4), nivolumab (anti–PD-1), or BMS-936559 (anti–PD-L1). ^{18}F-FDG PET/CT imaging was performed before therapy (SCAN-1), again between days 21 and 28 (SCAN-2), and at approximately 4 mo posttreatment initiation (SCAN-3).

1.1 had the highest predictive value, with an accuracy of 85%. Intriguingly, optimal PERCIST and EORTC threshold values predictive of BOR were >15.5% and >14.7%, respectively, indicating that increased ^{18}F-FDG tumor uptake at SCAN-2 may correlate with eventual clinical benefit. Incorporating optimal thresholds using RECIST-based and PERCIST-based

TABLE 3
Performance of 4 Radiologic Evaluation Criteria Applied to Early (3–4 Week) PET/CT Scans in Predicting Best Overall Response (RECIST 1.1) to ICI Therapy at ≥ 4 Months

Response evaluation criteria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
RECIST1.1	100.0 (48.0–100.0)	66.7 (38.4–88.1)	50.0 (18.9–81.1)	100.0 (69.0–100.0)	75.0
irRC	80.0 (28.8–96.7)	66.7 (38.4–88.1)	44.4 (14.0–78.6)	90.9 (58.7–98.5)	70.0
PERCIST	60.0 (15.4–93.5)	73.3 (44.9–92.0)	42.9 (10.4–81.2)	84.6 (54.5–97.6)	70.0
EORTC	40.0 (6.5–84.6)	73.3 (44.9–92.0)	33.3 (5.3–77.3)	78.6 (49.2–95.1)	65.0

PPV = positive predictive value; NPV = negative predictive value.
Data in parentheses are 95% confidence intervals.

TABLE 4
Performance Characteristics of 5 Methods of Early Tumor Response Evaluation in Predicting Response (RECIST 1.1) to ICI Therapy at 4 Months

Method no.	Tumor response evaluation method description	SCAN-1 to SCAN-2 optimal percentage change cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
1	Change in sum of RECIST 1.1–based target lesion diameters	≤0	80.0 (28.8–96.7)	86.7 (59.5–98.0)	66.7 (22.7–94.7)	92.9 (66.1–98.8)	85.0
2	Change in sum of the products of the 2 largest perpendicular diameters of irRC-based index lesions	≤ −14.7	60.0 (15.4–93.5)	93.3 (68.0–98.9)	75.0 (20.3–95.9)	87.5 (61.6–98.1)	85.0
3	Change in SULpeak of the hottest lesion	>15.5	80.0 (28.8–96.7)	73.3 (44.9–92.0)	50.0 (16.0–84.0)	91.7 (61.5–98.6)	75.0
4	Change in sum of SUV_{max} of all ^{18}F-FDG–avid metastatic lesions	>14.7	80.0 (28.8–96.7)	66.7 (38.4–88.1)	44.4 (14.0–78.6)	90.9 (58.7–98.5)	70.0
	Methods 1 and 3, above, combined (PECRIT)		100.0 (48.0–100)	93.3 (68.0–98.9)	83.3 (36.1–97.2)	100.0 (76.7–100.0)	95.0

PPV = positive predictive value; NPV = negative predictive value; method 1 = change in sum of target lesion diameters, selected based on RECIST 1.1; method 2 = change in sum of the products of the 2 largest perpendicular diameters of index lesions, selected based on irRC criteria; method 3 = change in peak SUV, normalized by lean body mass, of the hottest lesion (SUL_{peak}) seen on PET scan (PERCIST 1.0); method 4 = change in the SUV_{max} of all ^{18}F-FDG–avid metastatic lesions; PECRIT = **PE**T/CT **C**riteria for early prediction of **R**esponse to **I**mmune checkpoint inhibitor **T**herapy.

Changes in tumor burden seen on PET/CT scans from baseline (SCAN-1) to 3–4 wk (SCAN-2) were calculated using 4 methods, each based on standard response criteria. Optimal cutoff percentage changes to predict response to ICI therapy based on RECIST 1.1 at 4 mo were determined from ROC analysis. Data in parentheses are 95% confidence intervals.

changes at SCAN-2, visualized on a 2-dimensional plot (Fig. 1), we retrospectively developed criteria for early of prediction eventual response (PET/CT criteria for Early Prediction of Response to ICI Therapy, incorporating RECIST-based and PERCIST-based changes seen 3–4 wk into treatment) (Fig. 2). Patients whose CT scans demonstrated an objective response by RECIST 1.1 at SCAN-2 maintained a response at 4 mo. Similarly, PD by

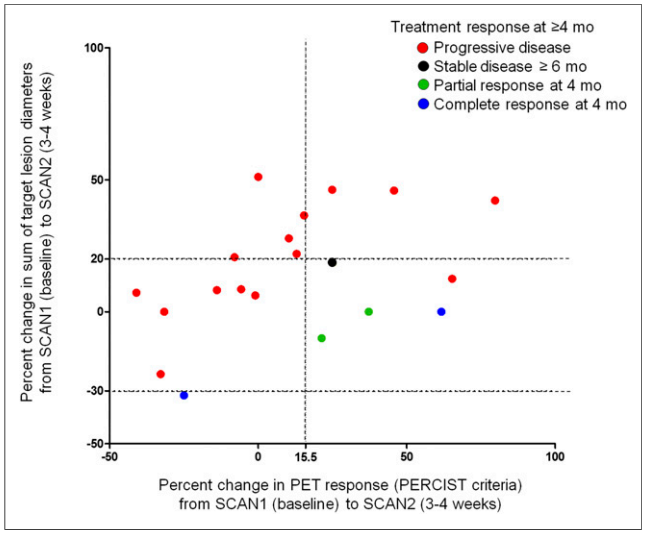

FIGURE 1. Scatterplot comparing early CT- and PET-based changes with response to ICI at ≥ 4 mo. Each dot represents a single patient, color coded according to best overall response at ≥ 4 mo. Two horizontal dashed lines on *y*-axis (+20% and −30%) correspond to thresholds for PD and PR, respectively, using RECIST 1.1, in absence of appearance of new tumor lesions. Vertical dashed line at +15.5% on *x*-axis represents a threshold associated with eventual response according to criteria proposed in Figure 2.

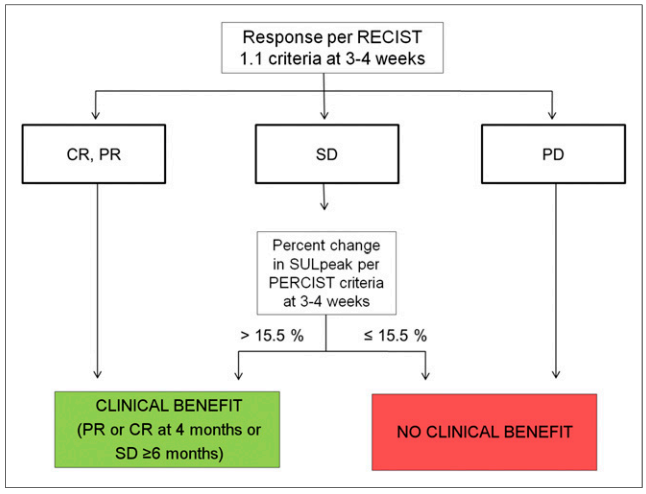

FIGURE 2. Patients whose CT scans performed 3–4 wk into therapy demonstrate an objective response (PR or CR by RECIST 1.1) are predicted to maintain a response at 4 mo. Similarly, PD detected at that same interval predicts continued disease progression at 4 mo. In patients with stable disease by RECIST 1.1 at 3–4 wk, an increase > 15.5% in SULpeak of hottest lesion by PET is associated with eventual clinical benefit (PR or CR at 4 mo or stable disease ≥ 6 mo). Sensitivity, specificity, and accuracy of algorithm to predict response at 4 mo were 100%, 93.3%, and 95.0%, respectively. CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease; SULpeak = average SUV corrected by lean body mass within a 1-cm^3 spheric volume of interest.

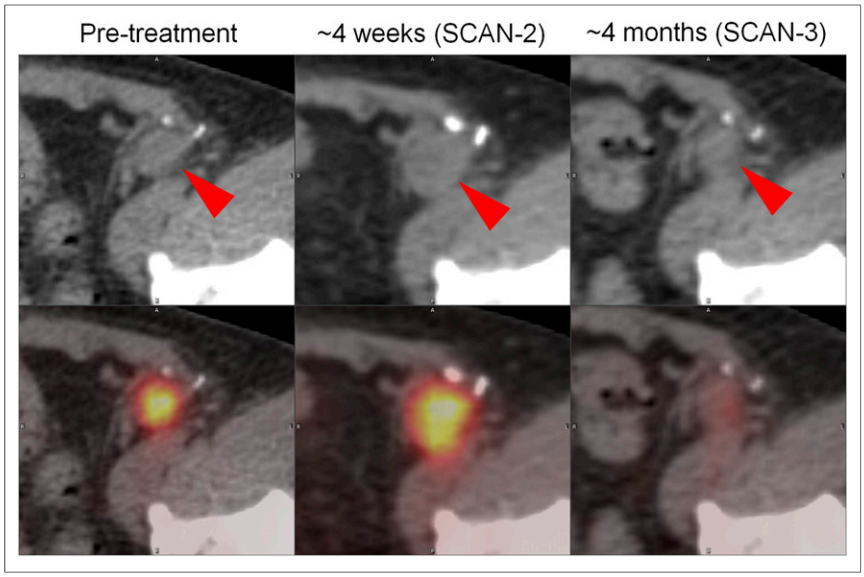

FIGURE 3. PET/CT images demonstrating representative changes in melanoma inguinal lymph node metastasis (red arrowheads) at 4 wk and 4 mo after initiation of ipilimumab. At about 4 wk (SCAN-2), sum of target lesion diameters assessed by CT scan (top) increased by 18.6% (stable disease by RECIST 1.1). During that same interval, PET imaging revealed 25.1% increase in SULpeak (average SUV corrected by lean body mass within a 1-cm^3 spheric volume of interest) (PERCIST). Imaging at approximately 4 mo revealed a marked improvement in ^{18}F-FDG avidity of inguinal lymph node metastasis. Similar pattern was observed in this patient's other sites of disease, including hepatic, nodal, and soft-tissue metastases. Patient's metastases outside of brain remained stable for 51 wk.

RECIST 1.1 at SCAN-2 was associated with disease progression at 4 mo. However, in patients with stable disease at SCAN-2, an increase $>$ 15.5% in SULpeak (average SUV corrected by lean body mass within a 1-cm^3 spheric volume of interest) of the hottest lesion was associated with eventual clinical benefit, providing a potentially informative indicator based on dual criteria. A case study is provided in Figure 3. The sensitivity, specificity, and accuracy of the proposed criteria to predict response by RECIST 1.1 at 4 mo were 100%, 93.3%, and 95.0%, respectively (Table 4). The predictive capacities of 4 different methods of measurement of changes in tumor burden from SCAN-1 to SCAN-2 to predict eventual response are provided in Supplemental Table 3.

DISCUSSION

As the use of immune checkpoint blockade agents increases, so too does the challenge of assessing their antitumor efficacy in patients whose posttherapy CT scans may demonstrate unconventional or delayed patterns of response. Although a midtreatment tumor biopsy might provide useful information about the viability of tumor cells and the activity of the immune response within a lesion, biopsy is not always possible because tumors may be inaccessible or multiple. Additionally, biopsies of a single lesion may not accurately capture patients experiencing a mixed response (concomitant regression/progression of individual metastases). Thus, early, whole-body noninvasive indicators of drug efficacy could help to better predict which patients might respond to therapy and guide clinicians in adjusting treatment regimens as appropriate.

Even in patients in whom conventional CT scanning performed at traditional intervals (every 2–3 mo) turns out to be an accurate gauge of therapeutic response, there may still be benefits to early identification of patients not predicted to respond. Early discontinuation of ICI could mitigate the risk for immune-related adverse events, reduce the cost of the therapy, and allow for initiation of a different treatment approach.

Here, we prospectively evaluated the utility of a baseline and follow-up ^{18}F-FDG PET/CT scan, performed early in the course of ICI, as a predictor of BOR at $\geq$ 4 mo. Because human melanomas consistently have high glucose metabolism, ^{18}F-FDG PET/CT imaging is particularly well suited for detecting these tumors, some of which are difficult to identify by standard CT scans (*27,28*). PET imaging, performed as early as 7 d after initiation of radioimmunotherapy, has been shown to be predictive of outcomes in patients with lymphoma (*29*). However, glucose metabolism is sensitive but not specific for neoplastic growth, because other processes such as inflammation involve glucose utilization. Indeed, ^{18}F-FDG PET/CT has been used to detect and monitor treatment efficacy in various inflammatory/infectious processes such as osteomyelitis, prosthesis infection, fever of unknown origin, and sarcoidosis (*30*).

Consequently, we were not surprised to observe that patients with stable anatomic disease and modest to markedly increased ^{18}F-FDG uptake at SCAN-2 tended to demonstrate eventual tumor regression. Our findings suggest an early inflammatory response at the site of tumor brought about by ICI. These observations are consistent with gene expression profiling analyses demonstrating a correlation between an immunologically active tumor microenvironment and an antitumor response to ipilimumab (*31*). A similar biology has emerged in the PD-1 literature, in which immune activation reflected by PD-L1 expression in the presence of immune cell infiltrates in pretreatment tumor biopsies correlates with tumor regression (*1*).

Our observations also support a potential mechanism for pseudoprogression, in which apparent tumor growth on conventional CT scans may reflect an increased density of activated inflammatory cells within the tumor microenvironment. Similar findings were reported by Ribas et al., who demonstrated lymphoid cell activation after the administration of tremelimumab, a CTLA-4 antagonist (*32*).

Sachpekidis et al. performed a study similar to ours, which investigated the predictive value of ^{18}F-FDG PET/CT performed after 2 cycles (~6 wk) of ipilimumab in predicting final response to therapy (*33*). Response classifications were based on EORTC 1999 criteria, which mainly incorporate changes in tumor metabolic activity rather than changes in tumor dimensions. The 2 patients in that study who demonstrated a partial metabolic response at the end of treatment were metabolically classified as having progressive metabolic disease on early PET/CT. Thus, the authors concluded that those 2 patients were incorrectly classified based on early PET/CT. The results of our study suggest that a combination of changes in lesional dimensions along with changes in

^{18}F-FDG uptake may provide a more accurate predictor of eventual response.

Intercriteria agreements between RECIST 1.1, PERCIST, and EORTC were good to excellent at SCAN-3, performed 4 mo after ICI was initiated, which is in accordance with a previous report using cytotoxic chemotherapy (*19*). However, interestingly, intercriteria agreement between the PET and CT modalities was not good in the early course of ICI therapy. This disagreement should be caused by the paradoxically increased ^{18}F-FDG uptake in the responding tumor in the early course of ICI therapy. Thus, we could incorporate the different response information from PET and CT to propose an early response criteria (PET/CT criteria for Early Prediction of Response to ICI Therapy).

Other potential methods for prediction of ICI therapy response include measurement of circulating tumor DNA in plasma. Small trials have shown that circulating tumor DNA level changes can mirror radiologic changes in tumor burden and may predict eventual response to ICI (*34,35*). These emerging technologies, which require only serial blood sampling and laboratory analysis, may compare favorably with PET/CT in terms of feasibility and accessibility among an increasing population of patients undergoing therapy with ICI.

Our study is limited by a relatively small sample size, a lack of intravenous contrast agent in many of the CT scans, and a predominance of anti-CTLA-4–directed therapy. Additionally, brain MRI was not routinely performed as a part of our investigation, and because PET/CT imaging is not well-suited for detecting melanoma brain metastases, patients may have had undetected brain metastases during the study period. However, these preliminary findings suggest that PET/CT scans obtained early in the course of ICI therapy, particularly ipilimumab, appear predictive for eventual response in patients with advanced melanoma.

CONCLUSION

Combining functional and anatomic parameters obtained from PET/CT scans performed early in the course of ICI therapy may predict eventual response in patients with advanced melanoma. Increased ^{18}F-FDG uptake in the early course of ICI therapy may be associated with immune activation and favorable outcome. Given the rapidly increasing use of ICI for patients with a variety of malignancies, further prospective study is warranted to assess our proposed tumor assessment criteria in larger cohorts of patients with various cancer types, treated with other checkpoint inhibitors, both as monotherapy and in combination.

DISCLOSURE

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