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

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

[1]Johns Hopkins University School of Medicine and Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; [2]University of Wisconsin School of Medicine and Public Health and Carbone Comprehensive Cancer Center, Madison, WI; [3]Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO.

*Drs. Cho, Lipson and Im contributed equally to this manuscript.

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Corresponding author:
Steve Y. Cho
WIMR1, Rm 7139
1111 Highland Ave
Madison, WI 53705
Email: scho@uwhealth.org
Office: 608-263-5048
Fax: 608-265-7390

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Abstract

To evaluate ^{18}F-fluorodeoxyglucose-positron emission tomography/CT (FDG-PET/CT) scanning as an early predictor of response to immune checkpoint inhibitors (ICI) in patients with advanced melanoma.

Methods: Twenty patients with advanced melanoma receiving ICI prospectively underwent FDG PET/CT at three scan intervals: prior to treatment initiation (SCAN-1), at days 21-28 (SCAN-2), and at 4 months (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 post-treatment time point was assessed according to RECIST1.1, immune-related response criteria (irRC), PET response criteria in solid tumors (PERCIST 1.0) and EORTC criteria. Performance characteristics of each metric to predict best overall response (BOR) at ≥4 months were assessed.

Results: Twenty evaluable patients were treated with ipilimumab (n=16), BMS-936559 (n=3) or nivolumab (n=1). BOR at ≥4 months included complete response (n=2), partial response (n=2), stable disease (n=1) and progressive disease (n=15). Response evaluations at SCAN-2 using RECIST1.1, irRC, PERCIST and EORTC criteria demonstrated accuracies of 75%, 70%, 70%, and 65%, respectively, to predict BOR at ≥4 months. Interestingly, the optimal PERCIST and EORTC threshold values at SCAN-2 to predict BOR were >15.5% and >14.7%, respectively. By combining anatomical 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 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.

Immune checkpoint inhibitors (ICI) 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 which 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 computed tomographic (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 period of time, even after therapy has been stopped (*3-6*). Indeed, a variety of radiologic responses to ICI have been described, some of which are linked to therapeutic benefit (*7,8*). Because traditional Response Evaluation Criteria In Solid Tumors (RECIST) or World Health Organization (WHO) criteria may be insufficient to characterize outcomes after administration of immune-based anti-neoplastic drugs, immune-related response criteria (irRC; Ref.(*9*)) are increasingly being incorporated into clinical trials of cancer immunotherapies (*10,11*).

Several studies have investigated the utility of 2-deoxy-2-(^{18}F)fluoro-D-glucose or ^{18}F-FDG positron emission tomography / computed tomography (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 FDG-PET/CT scans may complement data from anatomic imaging studies such as conventional spiral CT scanning and magnetic resonance imaging (MRI).

Two FDG-PET-based tumor response evaluation criteria commonly used in studies of patients with solid tumors are 1) PET Response Criteria in Solid Tumors (PERCIST 1.0), and 2) European Organisation for Research and Treatment of Cancer (EORTC) 1999 criteria (*15,16*). Using these metrics, disease response to therapy has been evaluated in multiple studies encompassing a variety of tumor types (*17-19*).

In order to investigate the utility of 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 FDG-PET/CT imaging in patients with advanced melanoma undergoing ICI therapy, conducted several analyses in order to characterize changes in tumor burden and functional parameters, and utilized 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 (IRB) in accordance with an assurance filed with and approved by the Department of Health and Human Services Subjects (ClinicalTrials.gov number NCT01666353). As per IRB requirements, study data was 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 one lesion, >10mm, that could be accurately measured in at least one dimension with spiral CT scan. Patients were treated with ipilimumab at 3mg/kg intravenously every 3 weeks for a maximum of 4 doses (anti-CTLA-4; n=16); BMS-936559 at 0.1-1 mg/kg intravenously every 2 weeks until complete response, disease progression or dose-limiting toxicity (anti-PD-L1; n=3; ClinicalTrials.gov number, NCT00729664, Ref.(*20*)); or nivolumab 3 mg/kg every 2 weeks (anti-PD-1; n=1; ClinicalTrials.gov number NCT01621490; Ref.(*21*)). FDG-PET/CT imaging was performed within four weeks prior to initiating therapy (SCAN-1), again between days 21 and 28 on therapy (SCAN-2), and at approximately 4 months 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 two doses of ICI therapy and have undergone SCAN-1, SCAN-2, and at least one additional evaluation (radiographic or clinical) thereafter. Due to the poor performance of PET/CT imaging to detect brain metastases, intracranial lesions were not included in disease assessments.

Imaging

FDG-PET/CT images were acquired on a Discovery DRX PET/CT scanner (GE Healthcare). FDG-PET/CT scan 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 acquired for tissue attenuation correction and anatomic correlation. Patients were injected with 370 ± 37 MBq (10 ± 1 mCi) of ^{18}F-FDG and scanned in the supine position, starting from the mid-thigh and through the vertex of skull,

followed by a separate scan from the upper thigh through bilateral feet. Patients fasted for 4-6 hours immediately prior to injection of ^{18}F-FDG.

Response Evaluation

FDG-PET/CT images were reviewed and analyzed using MIRADA XD3 software (MIRADA Medical, Denver, CO, USA) by two nuclear medicine specialists with convened consensus review of PET and CT response evaluation. CT-based responses, assessed by study investigators, were characterized according to RECIST1.1 (*23*) and irRC (*9*). 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 pre-specified number of target lesions, we considered all FDG-avid lesions at SCAN-1 as target lesions. An FDG-avid lesion was defined as focal, abnormally increased FDG uptake versus background with a corresponding anatomic lesion seen on CT scan, suggestive of metastasis.

CT-based anti-tumor responses based on changes observed from SCAN-1 to SCAN-2 and SCAN-1 to SCAN-3 were classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). FDG-PET-based responses were classified as complete metabolic response (CMR), partial metabolic response (PMR), stable metabolic disease (SMD) or progressive metabolic disease (PMD). Percentage change in lesion dimensions (CT) or 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 in order 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 months or SD lasting at least 6 months. Confirmatory scans for PR and CR seen at SCAN-3 were not required.

Outcomes Analysis

Inter-criteria agreements at SCAN-2 and SCAN-3 were assessed using kappa coefficients (*26*). The positive and negative predictive values of outcomes at SCAN-2 for clinical benefit were assessed for all four 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. Pearson's correlation coefficient (r) was used for correlation analysis. Finally, a combined functional/anatomical approach was developed and evaluated to enhance the predictive value of the FDG-PET and CT measurements at SCAN-2 for clinical benefit. Statistical analyses were performed using MedCalc software version 10.1 (MedCalc Software, Belgium).

RESULTS

Patient Characteristics

Twenty subjects were enrolled on the trial. Their mean age was 59.2 years (range, 42-72). Seven were female. Eleven patients had previously received systemic therapy for advanced melanoma, including nilotinib, high-dose interleukin-2, 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 immune checkpoint inhibitors. 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 four different criteria systems, after 3-4 weeks of treatment (SCAN-2) and at about 4 months (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 months, 2 patients with PR at 4 months, and 1 patient with SD lasting 9 months. The five subjects had been treated with ipilimumab. The remaining 15 patients experienced stable disease lasting less than 6 months, or PD. No patient with an early assessment categorized as PD by RECIST1.1 later experienced an objective response to therapy.

Of note, baseline scans for patient 11 demonstrated a 1.1cm retroperitoneal lymph node, proven by fine needle aspirate to be metastatic melanoma. Although the patient met study entry criteria (at least one lesion, >10mm, that could be accurately measured in at least one dimension with spiral CT scan), the tumor did not qualify as “measurable” by RECIST 1.1 criteria (≥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 days after initiating ICI, demonstrated excellent degrees of inter-criteria agreement. Kappa coefficient values were calculated within the same imaging modality: RECIST1.1 vs. irRC (CT-based), 0.9; PERCIST vs. EORTC (PET-based), 0.886. Comparisons between different modalities demonstrated lesser degrees of agreement, with kappa values between 0.48 and 0.7. At SCAN-3, performed 4 months after initiating ICI, all pairs of response criteria showed good to excellent correlation (kappa value range: 0.66 - 0.88), except irRC vs. PERCIST (kappa=0.53) (**Supplemental Table 1**).

Findings on Early PET/CT Associated with Eventual Clinical Outcomes

At SCAN-2, of the four metrics assessed, RECIST 1.1 demonstrated the highest predictive value for BOR at ≥4 months (Accuracy=75%; **Table 3**). ROC analysis revealed that percent change from SCAN-1 to SCAN-2 using RECIST1.1, irRC, PERCIST and EORTC criteria were predictive for BOR at ≥4 months as follows: area under curve = 0.853, 0.827, 0.680, and 0.600, respectively (**Supplemental Table 2**).

Based on the percent change from SCAN-1 to SCAN-2 of target lesion dimensions (CT) or 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 months (**Table 4**). Percent change per RECIST1.1 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 FDG tumor uptake at SCAN-2 may correlate with eventual clinical benefit. Incorporating optimal thresholds using RECIST-based and PERCIST-based 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, PEPRIT) (**Fig. 2**). Patients whose CT scans demonstrated an objective response by RECIST 1.1 at SCAN-2 maintained a response at 4 months. Similarly, progressive disease by RECIST 1.1 at SCAN-2 was associated with disease progression at 4 months. However, in patients with stable disease at SCAN-2, an increase >15.5% in SULpeak 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 **Fig. 3**. The sensitivity, specificity and accuracy of the proposed criteria to predict response by RECIST1.1 at 4 months were 100%, 93.3% and 95.0 %, respectively (**Table 4**). The predictive capacities of four 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 anti-tumor efficacy in patients who's post-therapy CT scans may demonstrate unconventional or delayed patterns of response. Although a mid-treatment 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 and/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 non-invasive 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 where conventional CT scanning performed at traditional intervals (every 2-3 months) 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 (irAEs), 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 FDG-PET/CT scan, performed early in the course of ICI, as a predictor of BOR at ≥4 months. Because human melanomas consistently have high glucose metabolism, 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 days 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, since other processes such as inflammation involve glucose utilization. Indeed, 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 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 anti-tumor response to ipilimumab (*31*). A similar biology has emerged in the PD-1 literature, where immune 3activation reflected by PD-L1 expression in the presence of immune cell infiltrates in pretreatment tumor biopsies correlates 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 and colleagues, who demonstrated lymphoid cell activation after the administration of tremelimumab, a CTLA-4 antagonist (*32*).

Sachpekidis and colleagues performed a study similar to ours that investigated the predictive value of FDG-PET/CT performed after two cycles (approximately 6 weeks) of ipilimumab in predicting final response to therapy (*33*). Response classifications were based on EORTC 1999 criteria, which mainly incorporates changes in tumor metabolic activity rather than changes in tumor dimensions. The two patients on 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 two 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 FDG uptake may provide a more accurate predictor of eventual response.

Inter-criteria agreements between RECIST 1.1, PERCIST, and EORTC were good to excellent at SCAN-3, performed 4 months after initiating ICI, which is in accordance with

a previous report using cytotoxic chemotherapy (*19*). However, interestingly, inter-criteria 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 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 a early response criteria, PERPRIT.

Other potential methods for prediction of ICI therapy response include measurement of circulating tumor DNA (ctDNA) in plasma. Small trials have shown that ctDNA level changes can mirror radiological 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 to 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 MRIs were 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 performed 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 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.

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FIGURE LEGENDS

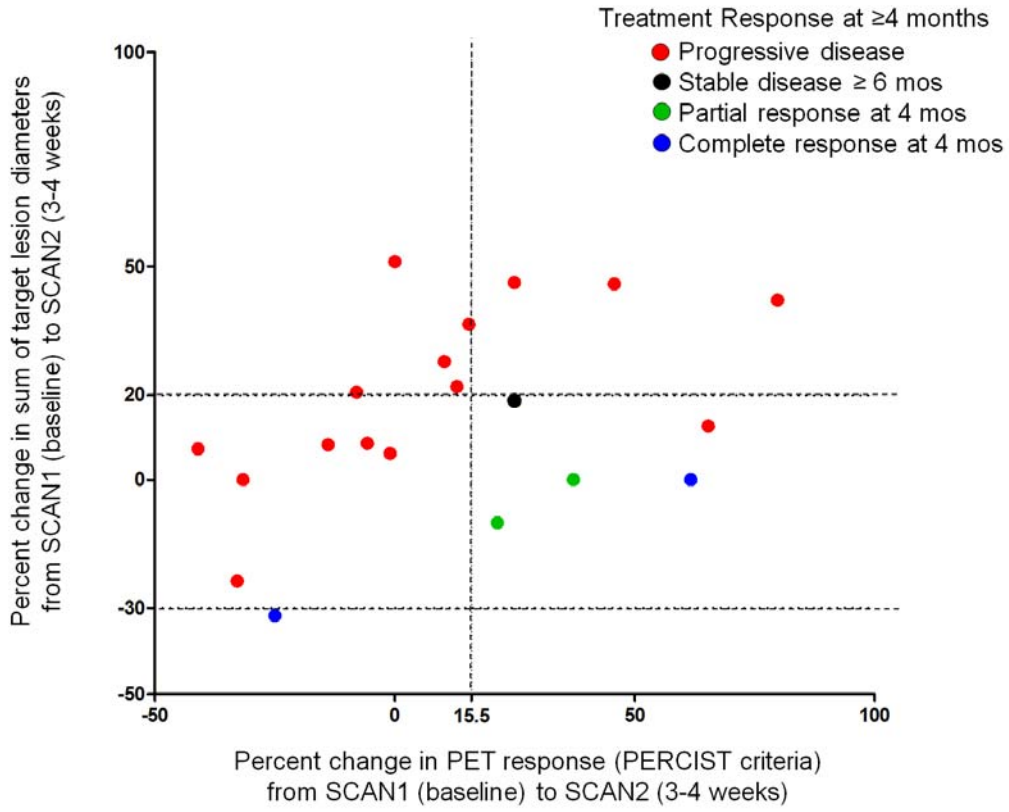

FIGURE 1: Scatter plot comparing early CT- and PET-based changes with response to immune checkpoint inhibition at ≥4 months. X-axis: percent change in PET response per PERCIST criteria from SCAN-1 (baseline) to SCAN-2 (3-4 weeks). Y-axis: percent change in sum of longest diameters (short diameters for lymph nodes) of target lesions from SCAN-1 (baseline) to SCAN-2 (3-4 weeks). Each dot represents a single patient, color coded according to best overall response at ≥4 months. (red, PD; black, SD ≥ 6 months; green, PR; blue, CR) The two horizontal dashed lines on the Y-axis (+20% and -30%) correspond to thresholds for PD and PR, respectively, using RECIST 1.1 criteria, in the absence of the appearance of new tumor lesions. The vertical dashed line at +15.5% on the X-axis represents a threshold associated with eventual response according to the criteria proposed in Figure 2.

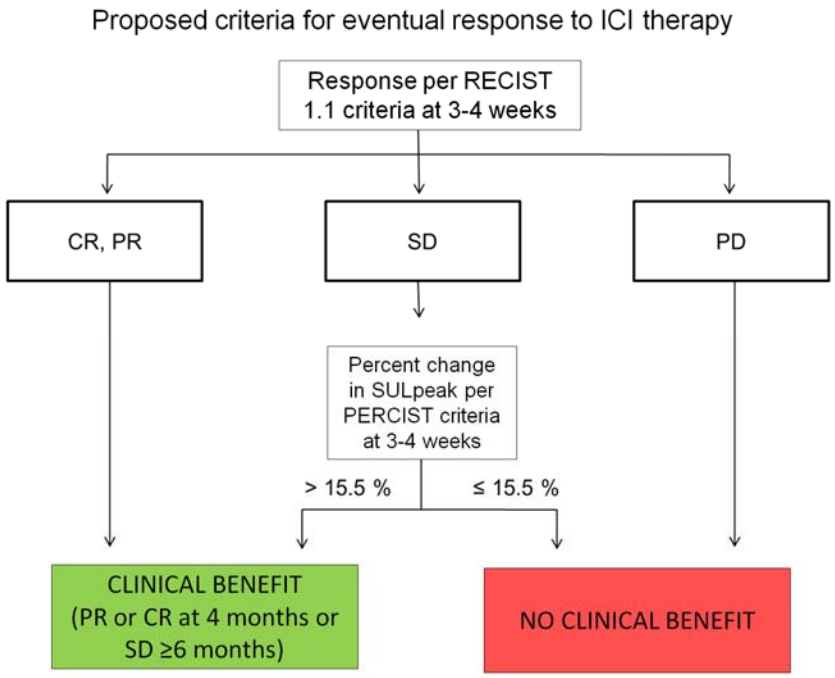

FIGURE 2: PET/CT **C**riteria for early prediction of **R**esponse to **I**mmune checkpoint inhibitor **T**herapy (PECRIT), a proposed criteria for early prediction of eventual response to ICI therapy incorporating RECIST-based and PERCIST-based changes seen 3-4 weeks into treatment. Patients whose CT scans performed 3-4 weeks into therapy demonstrate an objective response (PR or CR by RECIST 1.1 criteria) are predicted to maintain a response at 4 months. Similarly, progressive disease detected at that same interval predicts continued disease progression at 4 months. In patients with stable disease by RECIST1.1 at 3-4 weeks, an increase >15.5% in SULpeak of the hottest lesion by PET is associated with eventual clinical benefit (PR or CR at 4 months or SD ≥6 months). The sensitivity, specificity and accuracy of the algorithm to predict response at 4 months were 100%, 93.3% and 95.0 %, respectively. CR, complete response; PD, progressive disease; PERCIST, PET response criteria in solid tumors; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; SULpeak, average standardized uptake value corrected by lean body mass within a 1-cm^3 spherical volume of interest.

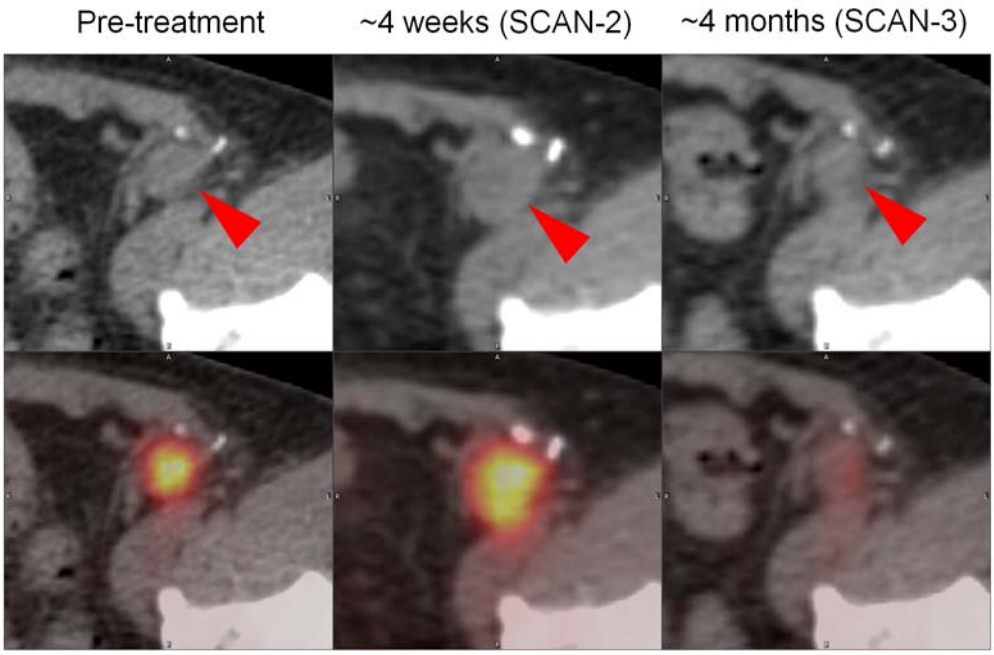

FIGURE 3: PET/CT scan images demonstrating representative changes in a melanoma inguinal lymph node metastasis (red arrowheads) at 4 weeks and 4 months after initiation of ipilimumab. At about 4 weeks (SCAN-2), the sum of target lesion diameters assessed by CT scan (top row of images) increased by 18.6 percent (stable disease by RECIST 1.1 criteria). During that same interval, PET imaging revealed a 25.1 percent increase in SULpeak (PERCIST criteria). Imaging at approximately 4 months revealed a marked improvement in the FDG avidity of the inguinal lymph node metastasis. A similar pattern was observed in this patient's other sites of disease, including hepatic, nodal and soft tissue metastases. The patient's metastases outside of the brain remained stable for 51 weeks.

TABLE 1

Summary of Treatment Response Criteria

CT-based criteria			PET-based criteria		
	RECIST 1.1	**irRC**		**PERCIST 1.0**	**EORTC**
Complete Response	Disappearance of all target and non-target lesions; all lymph nodes <10 mm short axis	Resolution of all lesions (whether measurable or not) and no new lesions	Complete Metabolic Response	Complete resolution of FDG uptake within measurable target lesion and disappearance of all other lesions to background blood-pool levels	Complete resolution of FDG uptake within the tumor volume so that it is indistinguishable from surrounding normal tissue
Partial Response	≥ 30% decrease in sum of diameters of target lesions; non-target lesions may persist but not unequivocally progress	Decrease in tumor burden ≥50%, measured as the sum of the products of the two largest perpendicular diameters of all index lesions, relative to baseline	Partial Metabolic Response	>30% relative decrease and >0.8 absolute decrease in SULpeak of the hottest lesion	Reduction of 15-25% in tumor SUV after 1 cycle of therapy, and >25% after more than 1 treatment cycle
Stable Disease	Neither sufficient tumor regression nor growth 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 FDG tumor uptake (20% in the longest dimension)
Progressive Disease	≥ 20% increase in sum of diameters of target lesions or unequivocal progression of non- target lesion or appearance of new lesion	Increase in tumor burden ≥25% relative to nadir, measured as the sum of the products of the two largest perpendicular diameters of all index lesions	Progressive Metabolic Disease	>30% relative increase and >0.8 absolute increase in SULpeak of the hottest lesion or unequivocal progression of FDG-avid non-target lesion or appearance of new FDG–avid lesion	Increase from baseline in tumor SUV of >25% within the tumor region, visible increase in the extent of FDG tumor uptake (20% in the longest dimension), or appearance of new FDG uptake in metastatic lesions

CR, complete response; CT, computed tomography; EORTC, European Organisation for Research and Treatment of Cancer; FDG, fluorodeoxyglucose; irCR, immune-related complete response; irPD, immune-related progressive disease**;** irPR, immune-related partial response; irRC, immune-related Response Criteria; PD, progressive disease; PERCIST, PET response criteria in solid tumors; PET, positron emission tomography; PMD, progressive metabolic disease; PMR, partial metabolic response; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; SMD, stable metabolic disease; SULpeak, average standardized uptake value corrected by lean body mass within a 1-cm^3 spherical volume of interest; SUVmax, maximum voxel value of standardized uptake value.

TABLE 2

Response Assessments, Excluding Brain Lesions, in 20 Patients with Metastatic Melanoma Receiving Immune Checkpoint Inhibitor Therapies.

Pt No.	Treatment	Response at SCAN-2 (21-28 days)				Response at SCAN-3 (~4 months)				Best overall response at ≥4 months (RECIST 1.1)	Duration of observation (weeks)*	**Best overall response prior to SCAN-3 (RECIST 1.1)
		RECIST1.1	irRC	PERCIST	EORTC	RECIST1.1	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 months	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 wks, PD at 12 wks
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 wks, PD at 12 wks
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 15wks
19	Ipilimumab	PD	PD	PMD	PMD	PD	PD	PMD	PMD	PD	17	-
20	Ipilimumab	PD	PD	PMD	PMD	PD	SD	PMD	PMD	PD	16	-

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). FDG-PET/CT imaging was performed prior to therapy, again between days 21 and 28 (SCAN-2), and at approximately 4 months post-treatment initiation (SCAN-3). *Duration of observation is calculated from the time of first administration of ICI therapy on this trial. Patients who received ipilimumab were treated with a 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 three patients demonstrated transient disease stability. Their responses are characterized in the last column. CR, complete response; EORTC, European Organisation for Research and Treatment of Cancer; FDG, fluorodeoxyglucose; irRC, immune-related Response Criteria; PD, progressive disease; PERCIST, PET response criteria in solid tumors; PET, positron emission tomography; PMD, progressive metabolic disease; PMR, partial metabolic response; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; SMD, stable metabolic disease; u, unconfirmed, seen only on one set of scans.

TABLE 3

Performance of Four Radiologic Evaluation Criteria Applied to Early (3-4 weeks) PET/CT Scans in Predicting Best Overall Response (RECIST 1.1) to Immune Checkpoint Inhibitor Therapy at ≥4 Months.

	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	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

CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; irRC, immune-related Response Criteria; NPV, negative predictive value; PERCIST, PET response criteria in solid tumors; PPV, positive predictive value; RECIST, Response Evaluation Criteria In Solid Tumors.

TABLE 4

Performance Characteristics of Four Methods of Early Tumor Response Evaluation in Predicting Response (RECIST 1.1) to Immune Checkpoint Inhibitor Therapy at 4 Months.

Method number	Tumor response evaluation method description	SCAN-1 to SCAN-2 optimal percent change cutoff	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	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 two 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 SUVmax of all 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

Changes in tumor burden seen on PET/CT scans from baseline (SCAN-1) to 3-4 weeks (SCAN-2) were calculated using 4 methods, each based on standard response criteria. Method 1: change in sum of target lesion diameters, selected based on RECIST 1.1 criteria. Method 2: Change in sum of the products of the two largest perpendicular diameters of index lesions, selected based on irRC criteria. Method 3: Change in peak standardized uptake value, normalized by lean body mass, of the hottest lesion (SULpeak) seen on PET scan. (PERCIST 1.0). Method 4: Change in the sum of maximum standardized uptake value (SUVmax) of all FDG-avid metastatic lesions. Optimal cutoff percent changes to predict response to immune checkpoint inhibitor therapy based on RECIST 1.1 at 4 months were determined from ROC analysis. **PE**T/CT **C**riteria for early prediction of **R**esponse to **I**mmune checkpoint inhibitor **T**herapy (PECRIT), CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

Supplementary Table 1. Inter-criteria agreement between response assessment criteria (RECIST, irRC, EORTC, PERCIST) at SCAN-2 (3-4 weeks) and SCAN-3 (approx. 4 months).

	Kappa coefficient*	
Compared criteria	SCAN-2	SCAN-3
RECIST1.1 vs. irRC	0.9	0.765
PERCIST vs. EORTC	0.886	0.875
RECIST1.1 vs. PERCIST	0.7	0.733
RECIST1.1 vs. EORTC	0.6	0.875
irRC vs. PERCIST	0.588	0.529
irRC vs. EORTC	0.479	0.659

* Kappa values were calculated based on degree of agreement on tumor response between criteria. At each time point, responses were classified into one of two categories: [CR+PR+SD] vs. [PD]. EORTC, European Organisation for Research and Treatment of Cancer 1999 criteria; irRC, immune-related Response Criteria; PERCIST, PET response criteria in solid tumors; RECIST, Response Evaluation Criteria In Solid Tumors

Supplementary Table 2. Receiver operator characteristic (ROC) curve analyses performed to estimate capacity of CT- and PET-based measurements (continuous percentage change) collected at 3-4 weeks to predict best overall response to immune checkpoint inhibitor therapy at ≥4 months as measured by RECIST 1.1.

Tumor response evaluation method description	Area under curve (AUC)	95% confidence interval
1) Change in sum of RECIST 1.1-based target lesion diameters	0.853	0.625 to 0.968
2) Change in sum of the products of the two largest perpendicular diameters of irRC-based index lesions	0.827	0.594 to 0.955
3) Change in SULpeak of the hottest lesion	0.680	0.437 to 0.867
4) Change in sum of SUVmax of all FDG-avid metastatic lesions	0.600	0.361 to 0.808

Method 1: change in sum of target lesion diameters, selected based on RECIST 1.1 criteria. Method 2: Change in sum of the products of the two largest perpendicular diameters of index lesions, selected based on irRC criteria. Method 3: Change in peak standardized uptake value, normalized by lean body mass, of the hottest lesion (SULpeak) seen on PET scan. (PERCIST 1.0). Method 4: Change in the sum of maximum standardized uptake value (SUVmax) of all FDG-avid metastatic lesions. FDG, fluorodeoxyglucose; irRC, immune-related Response Criteria; PERCIST, PET response criteria in solid tumors; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.

Supplementary Table 3. Percent change in tumor burden SCAN-1 to SCAN-2 measured using 4 methods, compared with response per RECIST1.1 at SCAN-2 and best overall response at ≥4 months.

	Method of measuring SCAN-1 to SCAN-2 percent change in tumor burden					
Pt No.	1) Percent change in sum of RECIST 1.1-based target lesion diameters	2) Percent change in sum of the products of the two largest perpendicular diameters of irRC-based index lesions	3) Percent change in SULpeak of the hottest lesion	4) Percent change in sum of SUVmax of all FDG-avid metastatic lesions	Tumor response per RECIST 1.1 at SCAN-2	Best overall response at ≥4 months
1	46.27	136.77	24.94	43.10	PD	PD
2	18.60	45.88	25.05	18.58	SD	SD
3	42.19	80.58	79.80	95.76	PD	PD
4	27.85	88.42	10.35	6.49	PD	PD
5	51.11	248.21	0.00	14.66	PD	PD
6	0.00	14.96	-31.60	-45.11	SD	PD
7	6.19	7.23	-0.96	-5.73	SD	PD
8	36.54	51.22	15.46	38.98	PD	PD
9	21.95	58.43	12.97	4.68	PD	PD
10	12.50	26.14	65.35	57.41	SD	PD
11	0.00	20.00	61.70	113.21	SD	CR
12	7.26	18.35	-41.02	-40.32	SD	PD
13	8.57	47.95	-5.74	1.80	PD*	PD
14	-10.00	-28.95	21.39	36.79	SD	PR
15	45.95	150.84	45.74	63.24	PD	PD
16	0.00	-14.66	37.22	37.26	SD	PR
17	-31.71	-44.68	-25.00	-63.25	PR	CR
18	-23.64	-44.07	-32.81	-23.51	SD	PD
19	8.22	38.66	-13.91	-29.11	PD*	PD
20	20.73	38.03	-7.98	-1.82	PD	PD

Changes in tumor burden seen on PET/CT scans from baseline (SCAN-1) to 3-4 weeks (SCAN-2) were calculated using 4 methods, each based on standard response criteria. Method 1: change in sum of target lesion diameters, selected based on RECIST 1.1 criteria. Method 2: Change in sum of the products of the two largest perpendicular diameters of index lesions, selected based on irRC criteria. Method 3: Change in peak standardized uptake value, normalized by lean body mass, of the hottest lesion (SULpeak) seen on PET scan. (PERCIST 1.0). Method 4: Change in the sum of maximum standardized uptake value (SUVmax) of all FDG-avid metastatic lesions. CR, complete response; FDG, fluorodeoxyglucose; irRC, immune-related Response Criteria; PD, progressive disease; PD*, progressive disease due to appearance of new lesion on SCAN-2; PERCIST, PET response criteria in solid tumors; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.

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

Steve Y Cho, Evan J Lipson, Hyung-Jun Im, Steven P. Rowe, Esther Mena, Amanda Blackford, Alin Chirindel, Drew M Pardoll, Suzanne L Topalian and Richard L. Wahl

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