F-18 FDG PET/CT for monitoring of ipilimumab therapy in patients with metastatic melanoma

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Running title: Ipilimumab response using imPERCIST

Word count:

Abstract

Immune checkpoint inhibitors (ICIs) are now commonly used to treat patients with metastatic malignant melanoma. While concerns have been raised that the inflammatory response induced by ICIs may limit the ability of ^{18}F-FDG PET/CT to assess tumor response, systematic analyses on the use of ^{18}F-FDG PET/CT in this setting are mostly lacking. Thus, we set out to evaluate the association between tumor response on ^{18}F-FDG PET/CT and prognosis in patients with metastatic malignant melanoma treated with ipilimumab.

Methods: We analyzed 60 consecutive patients with metastatic melanoma who underwent ^{18}F-FDG PET/CT scans at both pre- and post-treatment to evaluate treatment response after completion of ipilimumab therapy. Tumor response was assessed by the change in the sum of SULpeak of up to 5 lesions according to PET Response Criteria in Solid Tumors (PERCIST5). New lesions on PET that appeared suspicious for metastases were considered progressive metabolic disease (PMD). Because immunotherapy may cause new inflammatory lesions that are detectable on ^{18}F-FDG PET/CT, we also evaluated an immunotherapy-modified response classification (imPERCIST5). In this classification, new lesions do not define PMD per se; rather, PMD requires an increase in the sum of SULpeak by 30%. The correlation between tumor response according to these three definitions and overall survival (OS) was evaluated and compared to known prognostic factors.

Results: In responders and non-responders, the two-year OS was 66% vs. 29% for imPERCIST5 (p=0.003). After multivariate analysis, imPERCIST5 remained prognostic (HR 3.853; 95% CI 1.498-9.911; p=0.005). New sites of focal FDG uptake occurred more often in patients with PMD (n=24) by imPERCIST5 than in those with SMD (n=7) or PMR (n=4). In patients with PMR, two of four isolated new lesions regressed spontaneously during follow-up.

Conclusion: In patients with metastatic melanoma treated with ipilimumab, tumor response

according to PERCIST was associated with OS. Our data suggest that PMD should not be defined by the appearance of new lesions, but rather by an increase in the sum of SULpeak.

Key words: Immune checkpoint inhibitor; ipilimumab; melanoma; PERCIST; ^{18}F-FDG

Introduction

Ipilimumab is a fully human IgG1 monoclonal antibody that blocks cytotoxic T lymphocyte antigen (CTLA-4), a negative regulator of the immune response (*1-3*). Clinical studies have shown that ipilimumab significantly improves survival of patients with metastatic melanoma when compared to chemotherapy; in fact, patients responding to ipilimumab may survive for 5+ years (*4, 5*). However, only about 15-20% of patients with metastatic melanoma have an objective radiographic response to ipilimumab, although such responses and stable disease can be durable (*6, 7*). Assessing tumor response to ipilimumab and other checkpoint inhibitors by size criteria has been found to be challenging because tumor infiltration by immune cells may cause delayed tumor shrinkage or even a temporary increase in tumor size ("pseudo- progression") (*8, 9*). To overcome these difficulties, new response criteria have been developed for assessing the efficacy of immune checkpoint inhibitors (ICIs) (*10-12*). These new criteria require confirmation of tumor progression on a follow-up scan, and in contrast to the commonly used Response Criteria in Solid Tumors (RECIST), they do not necessarily consider the appearance of new lesions as progression of disease (*13*).

The use of ^{18}F-fludeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) to monitor treatment with ICIs has also been questioned because tumor infiltration by immune cells may cause a transient increase in metabolic activity (*14*). A few studies and case reports have suggested that the presence and appearance of FDG-avid lesions in patients treated with checkpoint inhibitors may be due to immune cell infiltrates (*15, 16*). However, the frequency of pseudo-progression as seen on ^{18}F-FDG PET/CT is not well documented, and it remains unclear if pseudo-progression has a significant impact on tumor response assessment by PET Response Criteria in Solid Tumors (PERCIST) (*16-18*).

The purpose of this retrospective study was to investigate the relationship between changes in ^{18}F-FDG tumor uptake—using standard PERCIST and immunotherapy-modified PERCIST (imPERCIST)—and survival in patients with advanced melanoma undergoing treatment with ipilimumab.

Methods

Patients

The institutional review board approved this retrospective single-center study and waived the informed consent requirement. The study was compliant with the Health Insurance Portability and Accountability Act (HIPAA).

Our hospital information system was screened for patients with metastatic melanoma who had received ipilimumab monotherapy from 2010-2015 and had undergone ^{18}F-FDG PET/CT at both pre- and post-treatment. All patients underwent brain MRI or CT as well as ^{18}F-FDG PET/CT before initiation of therapy. Patients with metastatic disease limited to the brain or without hypermetabolic lesions outside the brain were excluded from analysis. Other exclusion criteria were as follows: advanced primary cancer other than melanoma; treatment with other checkpoint inhibitors prior to or during ipilimumab therapy; no lesion on ^{18}F-FDG PET/CT exceeding the limits for minimum standardized uptake value (SUV) normalized to lean body mass (SUL) as defined by PERCIST (1.5 × liver SUL + 2 SDs of liver SUL); and FDG uptake time differing by more than 30 minutes between baseline and follow-up scans.

^{18}F-FDG PET/CT protocol

Before injection of ^{18}F-FDG, patients fasted for at least six hours. If plasma glucose levels were <200 mg/dl, patients were injected IV with 444-555 MBq of radiotracer. After injection, patients rested for 60-90 minutes before image acquisition. At baseline and follow-up, 25 and 21 cases, respectively, were scanned outside of the PERCIST-recommended time window of 50-70 minutes post-injection. In 16 paired scans, the difference in uptake time at baseline versus follow-up was > 15 min (in 8 cases, the baseline scan was done > 15 minutes earlier, and in another 8 cases, it was done > 15 minutes later than the respective follow-up scan). ^{18}F-FDG PET/CT scans were performed with General Electric PET/CT systems (GE Discovery Series: VCT, ST, STE, 600, and 690). Of the 60 paired exams, 35 (58%) were performed with the same scanner type. The medical physics group at our institution has harmonized the acquisition and reconstruction parameters to

minimize SUV differences between scanners and keep them within 10% as tested by regular phantom studies. Cross-calibration between the dose calibrator and PET scanners is performed monthly. Eleven cases showed the difference of > 0.3 SUL unit of liver uptake between baseline and follow-up scans.

Scans were generally acquired with an axial field of view from the vertex to the toes (n = 47). In 13 patients, only images from the base of the skull to the mid-thighs were obtained because no lesions in the extremities were expected clinically. Low-dose CT images during PET/CT were used for attenuation correction of the PET emission scan and for anatomical orientation. PET/CT images were reconstructed using an ordered-subset expectation maximization algorithm and a Gaussian filter using the standard manufacture-supplied reconstruction software.

Image analysis

One experienced physician board-certified in both diagnostic radiology and nuclear medicine reviewed all ^{18}F-FDG PET/CT images. An FDG-avid lesion was defined as focal, abnormally increased ^{18}F-FDG uptake vs. background, with or without a corresponding anatomic lesion on the CT scan and suggestive of metastasis. At the time of image analysis, the reviewer was unaware of the results of any other imaging tests and the clinical outcome of the patient. Image analysis was performed using PET VCAR software by visually examining all the images on a computer display and the workstation (Advantage Workstation; GE Healthcare).

To determine SUL, the reviewer placed a sphere or cube as the volume of interest (VOI) around the target lesion. Within this VOI, the software searched for the 1.0 cm^3 sphere that encompassed the voxels with the highest average SUL. This SUL was reported as SULpeak. Response of SULpeak (%) was defined as (sum of baseline SULpeak - sum of follow-up SULpeak) / (sum of baseline SULpeak) * 100.

Response to ipilimumab therapy was classified as complete metabolic response (CMR), partial metabolic response (PMR), stable metabolic disease (SMD), or progressive metabolic disease (PMD). Three different approaches were used to assess response: in the first approach

(PERCIST5), we followed the recommendations of PERCIST (*18*). Briefly, CMR was defined as the resolution of all malignant lesions and was nominally assigned an SULpeak of zero for quantitative analysis. ^{18}F-FDG uptake of a lesion was considered resolved if it was less than mean liver activity and indistinguishable from the surrounding background. In patients with metabolically active lesions on the follow-up scan, the SULpeak of up to 5 lesions on the baseline and follow-up scan was summed (maximum of two per organ). Since the 'hottest' lesions were selected in each scan, target lesions on follow-up scans were not necessarily the same as target lesions at baseline. If the sum of SULpeak decreased by at least 30%, tumor response was classified as PMR. Conversely, PMD was defined as an increase of the sum of SULpeak by at least 30% or the appearance of new hypermetabolic lesions on follow-up ^{18}F-FDG PET/CT scan. Cases not meeting the definitions for CMR, PMR, or PMD were classified as SMD.

For the second analysis (PERCIST1), the lesions with the highest SULpeak between the baseline and follow-up scans were selected (not necessarily the same lesion except a new lesion on the follow-up scan). An increase of SULpeak by 30% or more was considered PMD, and a decrease by 30% or more PMR. As for PERCIST5, the appearance of new lesions alone resulted in a PMD classification.

The third analysis (imPERCIST5, or "immunotherapy-modified PERCIST," 5-lesion analysis) was performed in the same way as described for PERCIST5, but the appearance of new lesions alone did not result in PMD. Thus, PMD was only defined by an increase of the sum of SULpeaks by 30%. New lesions were included in the sum of SULpeak if they showed higher uptake than existing target lesions or if fewer than 5 target lesions were detected on the baseline scan. A case illustrating the three different response classifications is shown in **Figure 1.** A comparison of PERCIST and imPERCIST is shown in **Supplemental Table 3**.

Statistical analysis

Statistical analysis was performed using software (SPSS, version 24, Chicago, IL) and R 3.4.3 for

Windows (R Foundation for Statistical Computing, Vienna, Austria). Data were presented as means ± standard deviations (SD), and a p value of 0.05 or less was considered significant. Concordance between response assessments of two analyses was evaluated using κ-statistics. Overall survival (OS) was defined as time from start of ipilimumab therapy until death from any cause or last follow-up visit. Patients who remained alive were censored at last follow-up. For OS analysis, the data were dichotomized into responders (CMR and PMR) and non-responders (SMD and PMD). The log-rank (Mantel-Cox) test was used to evaluate the difference between Kaplan-Meier curves. We realize the potential bias in the comparison of OS by treatment response (*19*). However, treatment response is usually observed in 2 to 4 months, which is a rather short period of time compared to the follow up length in this study. Therefore, we expect the potential bias to be minimal. To calculate the risk ratios and 95% confidence intervals (CIs), univariate analysis was used to identify factors associated with OS. Then, factors found to be significant by univariate analysis (p < 0.05) were entered into a Cox multivariate regression analysis model. For the univariate analysis, we used dummy variables of 1 for the following factors: age ≥75 years, male, 1 or more lines of previous systemic chemotherapies, no cutaneous primary, prior radiotherapy, prior surgery, presence of distant metastasis, presence of active brain metastasis, presence of *BRAF* V600 mutation, receiving 2 or 3 cycles of ipilimumab, elevated lactate dehydrogenase (LDH) level above upper limit of the normal (ULN), and response on ^{18}F-FDG PET/CT. Then, forward stepwise multivariate regression analysis was carried out to identify factors correlated with OS based on calculating hazard ratios (HRs) and 95% CIs. The strength of the concordance between significant prognostic factors in the multivariate model and patient survival was described by Heller-Gönen concordance coefficients (R package clinfun, VE Seshan, MSKCC) (*20*).

Results

Patient characteristics and PET scanning

A flow diagram summarizing the selection of patients is shown in **Figure 2**. Overall, 60 evaluable patients were identified. The last follow-up date for OS calculation was December 31,

2017. Baseline ^{18}F-FDG PET/CT scans were performed at a median of 2.36 weeks (range 0-10 weeks) before initiation of ipilimumab therapy. Follow-up scans were performed 2.9 weeks (median; range 1.0-11.1) after the last dose of ipilimumab. The interval from initiation of ipilimumab to follow-up PET scan was 12.2 weeks (median; range 7.8 - 20.3). Twenty-five baseline scans and 21 follow-up scans were performed outside the PERCIST-recommended window for uptake time (50-70 min p.i.). Moreover, for 16 paired scans, the difference in uptake time (baseline-follow-up) was greater than 15 min. Eleven patients showed a difference of > 0.3 SUL in liver uptake between baseline and follow-up, including five with liver involvement. Patient characteristics are summarized in **Supplemental Table 1**. Ipilimumab was dosed at 3 mg/kg in all patients. Fifty patients received the full course of 4 cycles of ipilimumab. Ten patients received only 2 (n=5) or 3 (n=5) cycles of therapy due to immune-related colitis (n=9) or immune-related aseptic meningitis (n=1), respectively.

^{18}F-FDG PET/CT results

Median changes of SULpeak (%) for PERCIST5, PERCIST1, and imPERCIST5 were -3.60% (range: -100% to +227.02%), +4.46% (range: -100% to +287.57%), and +30.32% (range: -100% to +779.90%), respectively (**Figure 3**). Response rates (CMR and PMR) by PERCIST5, PERCIST1, and imPERCIST5 were 18%, 16.7%, and 25%, respectively. Disease control rates (CMR, PMR, and SMD) for the two approaches to response assessment were 33%, 32%, and 48%, respectively. In 35 patients, new lesions became apparent on the follow-up scan. Most of these new lesions occurred in patients classified as PMD (n=24) by imPERCIST5 (with an increase in the sum of SULpeak, and therefore not causing any difference in response classifications by imPERCIST5 vs. PERCIST5). However, in 4 patients, response was classified as PMR by imPERCIST5, but as PMD by PERCIST5 due to the appearance of new lesions. Because of these cases, the response rate by PERCIST5 (18%) was lower than the response rate by imPERCIST5 (25%). In two of the four patients, the lesions resolved spontaneously, without significantly increasing FDG uptake or tumor diameter during the follow-up period, indicating a benign etiology.

In the other two patients, new metastatic disease was confirmed during follow-up (**Table 1**).

A total of 7 patients with a decrease in the sum of SULpeak of target lesions by at least 30% by PERCIST5 showed new suspicious lesions on follow-up imaging. However, 4 of these patients were considered as PMR by imPERCIST5 because the %change of the sum of SULpeak including new suspicious lesions was > -30%; in the other 3 patients, the new lesions included in the sum of SULpeak led to response classification as SMD (n = 2) or PMD (n = 1).

In addition, new lesions were seen in 6 of the 14 patients with SMD by imPERCIST5. Thus, the disease control rate of PERCIST5 was only 33% as compared to 48% for imPERCIST5. In three of these patients, metastatic disease was confirmed during follow-up, in 2 patients the lesions resolved without specific treatment, and in 1 patient no definitive decision could be made. The correlations between the response patterns according to imPERCIST5 and other response criteria are shown in **Table 2.** Discordance in response assessment among PERCIST5, PERCIST1, and imPERCIST5 was observed in 13 and 17 patients (Cohen's kappa; κ= 0.637 and 0.521), respectively.

Treatment outcome

The median duration of follow-up was 14.9 months (range: 2.6 - 68.0 months). At the time of data cutoff for the analysis, 39 patients had died. Median OS for all patients was 17.31 months (95% CI, 9.45-25.18 months). The two-year OS for responders vs. non- responders according to PERCIST5, PERCIST1, and imPERCIST5 were 61% vs. 33% (p = 0.028), 69% vs. 33% (p = 0.021), and 66% vs. 29% (p = 0.003), respectively. In the non- responder groups of PERCIST5, PERCIST1, and imPERCIST5, median OS was 14.5 months, 14.7 months, and 14.5 months, respectively. In the responder groups, median survival was not reached (**Figure 4**). Survival was better in patients with CMR than in those with PMR by imPERCIST5. On the other hand, survival was similar for patients with SMD and PMD (**Figure 4**). The Gönen-Heller concordance index was highest for the correlation of response by imPERCIST5 and OS (0.61, 95% CI: 0.541-0.679), followed by PERCIST1 (0.57, 95% CI: 0.507-0.645) and PERCIST5 (0.57, 95% CI: 0.501-0.639).

In a univariate Cox proportional hazards model, lines of prior chemotherapy, prior radiotherapy, active brain metastases, and response on ^{18}F-FDG-PET/CT were significantly associated with OS (**Supplemental Table 2**). In the multivariate analysis, imPERCIST5 (HR 3.853, 95%CI 1.498-9.911, p = 0.005) was the only independent factor associated with OS.

Discussion

The results of this study indicate that tumor response on ^{18}F-FDG PET/CT as classified by PERCIST is significantly correlated with OS in patients with advanced melanoma treated with ipilimumab. As in previous case reports, we observed a few cases with "pseudo-progression," i.e., the appearance of new lesions that resolved spontaneously and were probably inflammatory in nature. However, in most patients, the appearance of new lesions was associated with progression of known metastases and poor prognosis.

The correlation between response on ^{18}F-FDG PET/CT and patient survival was improved by using modified response criteria ("immunotherapy-modified PERCIST," imPERCIST). The key difference between imPERCIST and PERCIST lies in the interpretation of new lesions on the post-treatment scan. In PERCIST, new lesions always indicate PMD. In contrast, imPERCIST includes new lesions in the quantification of tumor FDG uptake, and a patient is only classified as PMD if the intensity of FDG uptake for measured lesions increases by at least 30%. In imPERCIST5, the sum of SULpeak for up to 5 lesions is measured to assess response. These modified response criteria use an approach similar to that of the immune-related response criteria for morphologic imaging (*12*), which include new lesions in the sum of tumor diameters used to quantify overall tumor burden. New lesions do not necessarily result in a scan to be classified as PMD. Of note, while imPERCIST5 reduces overdiagnosis of progressive disease, new lesions in patients with PMR or SMD by imPERICST5 were eventually found to be metastases in 55% of the cases (6 of 11, Table 1). Thus, the prognosis of patients with decreasing or stable target lesions but appearance of new lesions appears indeterminate, and biopsy should be considered before any change in treatment.

To date, only a few reports have been published on the use of FDG PET/CT to monitor

tumor response to ipilimumab and other checkpoint inhibitors. The first results were presented by Sachpekidis et al. (*16*), who studied a group of 22 patients receiving ipilimumab. Tumor response on ^{18}F-FDG PET/CT was classified by EORTC criteria (*21*). Only two of the patients achieved a PMR at the end of therapy. Therefore, the authors compared the prognosis of patients with PMD and SMD (and not responders with non-responders). Progression-free survival was significantly longer for patients with disease stabilization (9.8 months vs. 3.6 months, p < 0.001). Median OS was slightly longer in the group of patients with SMD than in that of patients with PMD (9.8 vs. 9.1 months). Here we confirm the prognostic value of FDG PET/CT in an almost three-fold larger patient population. The longer OS for the whole patient group in our study is probably related to different baseline patient characteristics and the availability of second-generation immunotherapies in patients progressing after ipilimumab.

In a follow-up publication (*22*), the same group showed in 41 patients that the number of new FDG-avid lesions on a post-treatment FDG-PET/CT scan is closely correlated with the "clinical benefit" of the therapy. Clinical benefit was defined by clinical follow-up, ^{18}F-FDG PET/CT, brain MRI, and laboratory tests. All patients without clinical benefit from ipilimumab therapy demonstrated 4 or more new lesions at the end of therapy, whereas 84% of the patients with clinical benefit demonstrated fewer than 4 new lesions. Unexpectedly, changes in SUVs showed no correlation with clinical benefit, although the previous analysis of 21 patients had demonstrated a correlation with tumor response by EORTC criteria (which define response and progression by changes of SUV) and progression-free survival (*22*).

In contrast, we observed a significant association between changes in tumor SUV and OS for all three approaches for response assessment (PERCIST5, imPERCIST5, and PERCIST1). We used OS, rather than best overall response, as the outcome parameter since best overall response is largely defined by imaging studies, i.e., is not an independent reference standard.

As shown in Figure 4, patients with CMR showed longer survival than those with PMR. However, patients with SMD showed almost the same poor survival as patients with PMD. A similar observation has been made in patients with breast cancer treated with chemotherapy (*23*). This

contrasts with response assessment by CT and RECIST, because stable disease on CT is generally associated with better prognosis than progressive disease. The difference may be explained by the fact that at the end of therapy a residual mass on CT may be fibrotic tissue, whereas persistent FDG uptake usually indicates the presence of viable tumor cells.

Our study has some limitations: while we report on the largest patient population treated with ipilimumab, the results may be affected by selection bias because PET/CT imaging was used at the discretion of the referring physicians. Further, the time between completion of ipilimumab therapy and follow-up imaging was not standardized, which may have affected changes in tumor FDG uptake and the number of lesions detected. Moreover, timing of scans (uptake time, differences between baseline and follow-up) did not always adhere to PERCIST specifications. Another consequence of the retrospective study design is the use of different PET/CT scanners, which, despite our efforts at standardization, may have caused variability in SUV measurements and insensitivity to detection of new metastases. Despite this variability, which reflects the typical use of ^{18}F-FDG PET/CT in clinical practice, we observed a clear correlation between PET responses and OS, suggesting that response assessment by PERCIST or imPERCIST is robust for clinical use.

Conclusion

In this retrospective study, assessment of tumor response to ipilimumab by PERCIST after completion of treatment was significantly correlated with survival of patients with advanced melanoma. Slight modifications of PERCIST (imPERCIST5), changing the definition of PMD, further improved the prognostic value of ^{18}F-FDG PET/CT. These findings are encouraging for the use of FDG PET/CT to assess tumor response to ipilimumab in research and clinical practice.

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Figure legends
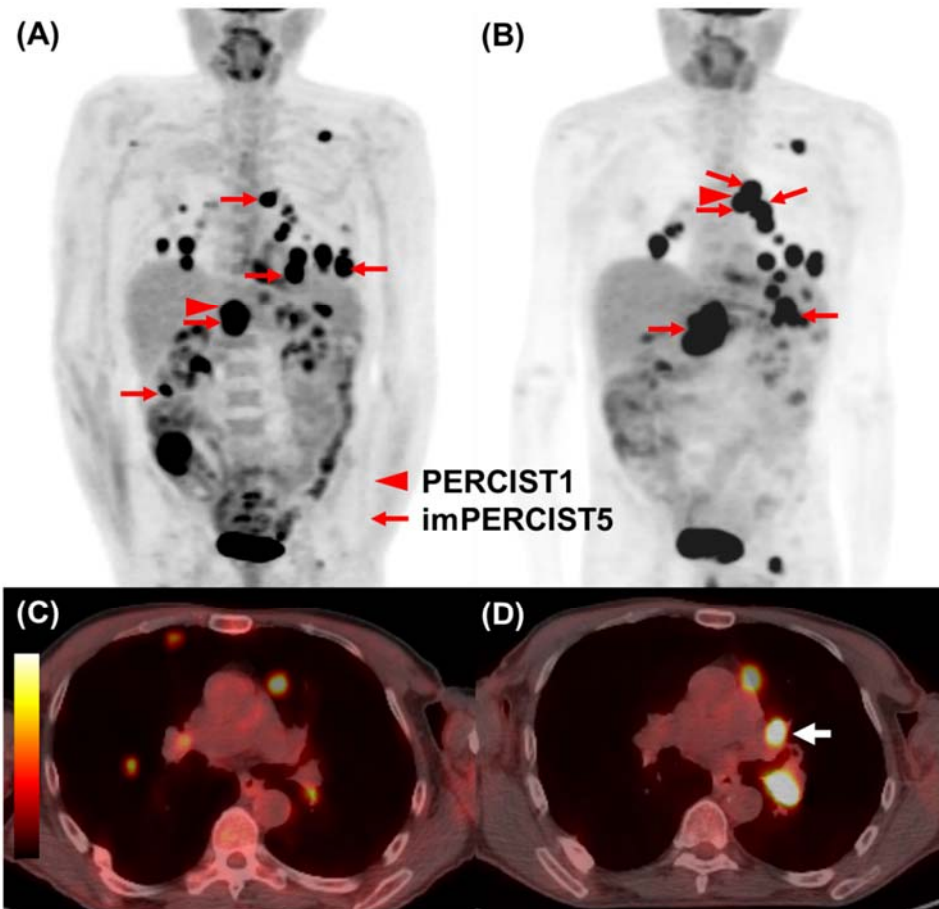
Figure 1. Representative case for the differences between response classifications. Sixty-six-year-old man classified as progressive disease by PERCIST5 and PERCIST1 (due to the appearance of a new lesion), but SMD by imPERCIST5. Maximum-intensity projection (MIP) images at baseline (A) and follow-up (B). Target lesions for PERCIST5 and imPERCIST5 are indicated by red arrows (sum of SULpeak 47.61 at baseline). The target lesions for PERCIST1 at baseline is an abdominal lymph node (SULpeak 15.07, red arrow head). On the follow-up scan (B) the target lesion for PERCIST1 is a thoracic lymph node (SULpeak 10.05) because the SULpeak of the abdominal lymph node had decreased to 8.86. Comparison of axial images of the chest at baseline (C) and follow-up (D) show the development of a new hypermetabolic left hilar lymph node (red arrow). This lesion (SULpeak 9.29) was included in the target lesions for imPERCIST5.

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│                  Eligible patients (n = 93)                │
│  Patients treated with ipilimumab monotherapy undergoing   │
│       pre- and post-treatment 18F-FDG PET/CT scans         │
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Excluded patients (n = 33)
-Baseline PET/CT beyond 10 weeks from ipilimumab therapy (n = 11)
-No target lesion over the liver threshold at baseline PET (n = 11)
-No lesion at baseline PET/CT (n = 4)
-Technical problems of PET/CT data (n = 2)
-Coexistence of other advanced cancer (n = 2)
-Receiving previous chemotherapy at baseline PET/CT (n = 2)
-Censored case within 3 months without prognostic information (n=1)

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│                 Study population (n = 60)                  │
│  Patients treated with ipilimumab who underwent both       │
│       baseline and follow-up 18F-FDG PET scans             │
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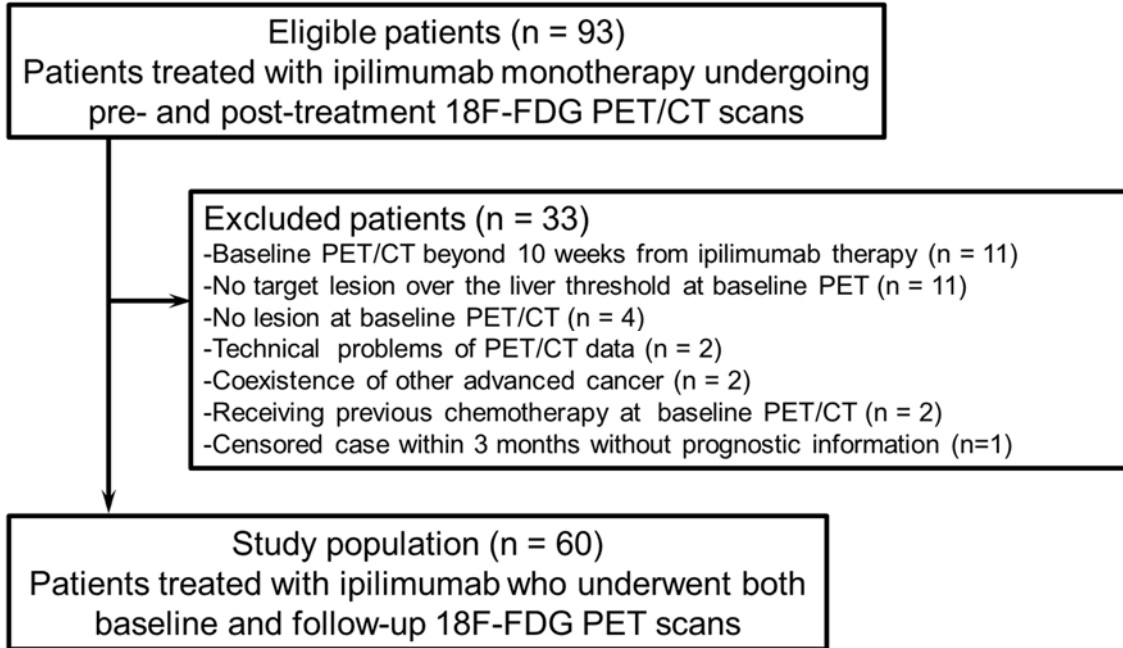
Figure 2. Flow diagram of study patients.
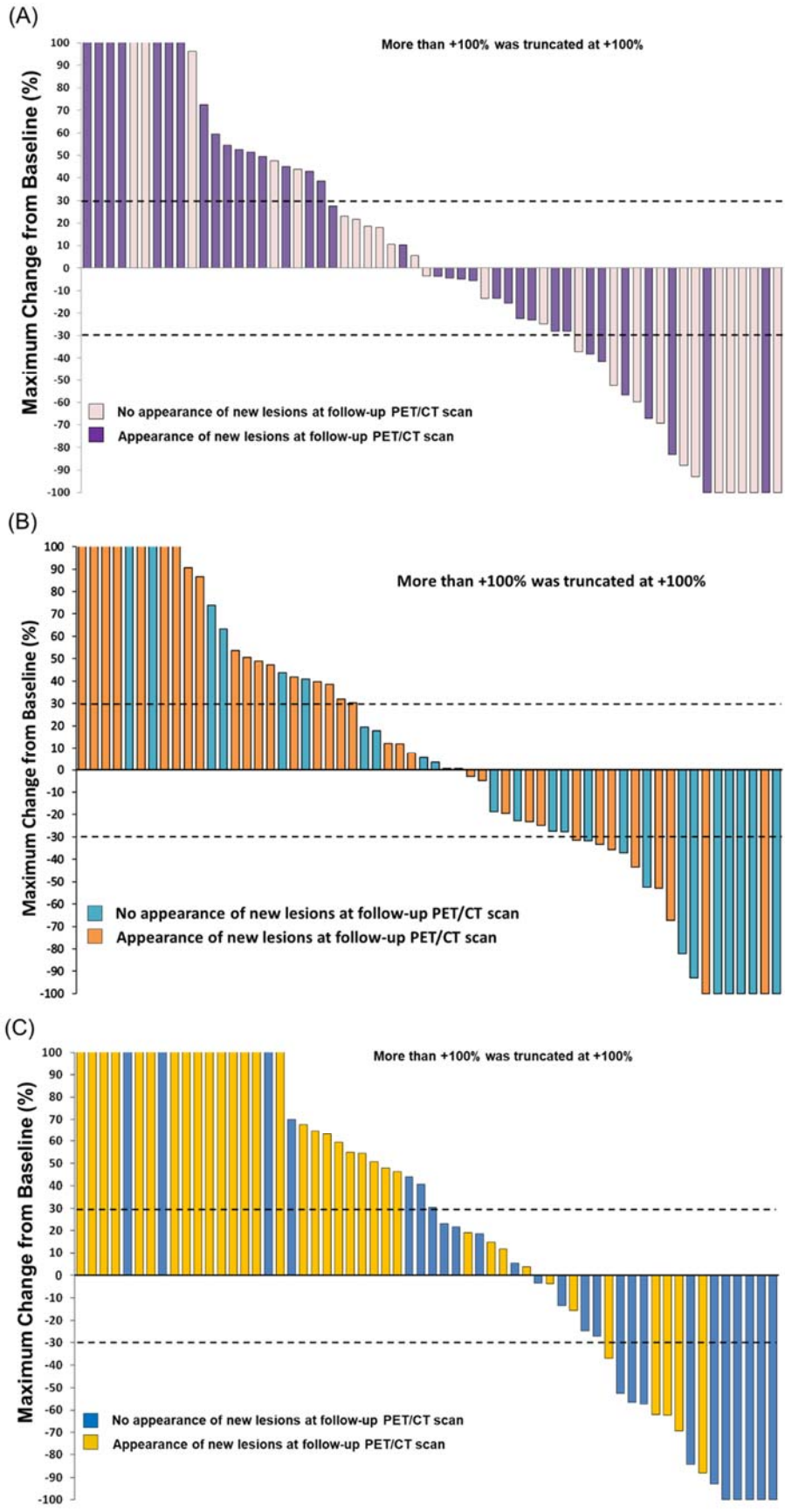
Figure 3. Waterfall plot of maximum changes in SULpeak for (A) PERCIST5, (B) PERCIST1, and (C) imPERCIST5. Upper short dashed line indicates separation of PMD from SMD. Lower short dashed line indicates separation of SMD from PMR.
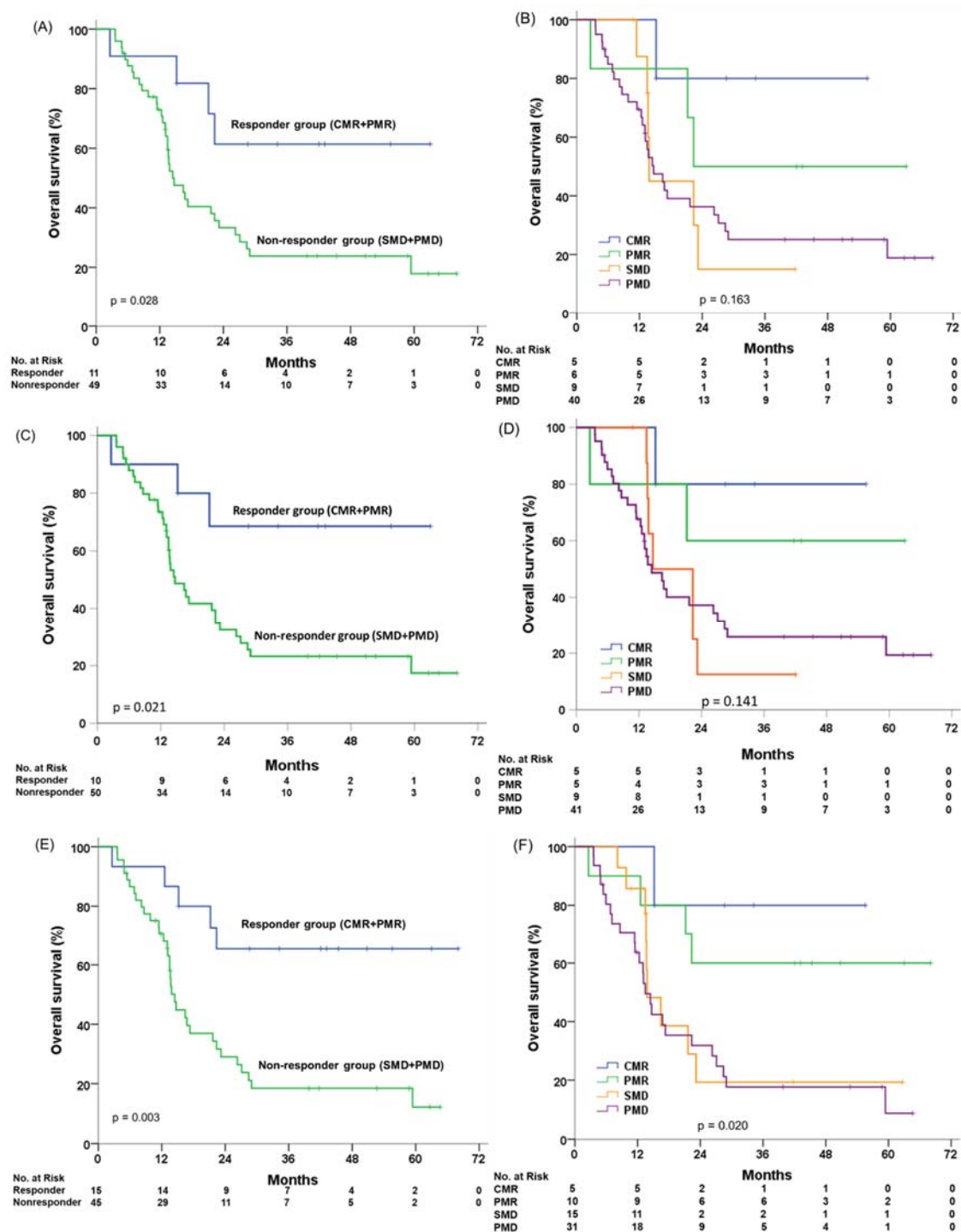
Figure 4. Kaplan-Meier estimates of overall survival for responders and non- responders (left), and survival rates by response category (right). (A) and (B): PERCIST5, (C) and (D) PERCIST1, and (E) and (F) imPERCIST5.

Tables

No.	Response in imPERCIST5	Completed ipilimumab cycles	Follow-up PET/CT duration from initial ipilimumab (weeks)	%Change of imPERCIST5	New lesion site	SULpeak	Clinical course and diagnosis
					Table 1. Cases with appearance of new lesions in PMR and SMD in imPERCIST5		
1	PMR	4	12	-57.2	Pancreas body	2.24	Metastasis
2	PMR	4	11	-84.4	Skin at right thigh	0.95	SR 4 months later
3	PMR	4	12	-61.9	Left serratus anterior muscle	1.49	SR 2 months later
4	PMR	4	11	-62.2	Paraaortic lymph node	4.73	Metastasis
5	SMD	4	17	3.9	Abdomen lymph node	2.89	Metastasis
6	SMD	4	11	-3.4	Left hilar lymph node	9.29	Metastasis
7	SMD	4	11	-27	Left hilar lymph node	3.54	SR 2 months later
					Right hilar lymph node	3.36	SR 2 months later
8	SMD	4	10	-15.7	Left gluteus maximus muscle	5.69	Metastasis
					Right intra-iliac lymph mode	2.98	Metastasis
9	SMD	4	15	19.1	Left hilar lymph node	2.7	SR 2 months later
					Right hilar lymph node	2.34	SR 2 months later
10	SMD	4	11	11.8	Left cervical lymph node	2.3	Unknown
					Right cervical lymph node	1.68	Unknown
11	SMD	4	11	14.8	Right neck lymph node	3.79	Metastasis
					Transverse colon	3.67	SR 2 months later
					Soft tissue at right elbow	1.94	SR 2 months later

PMR: partial metabolic response; SMD: stable metabolic disease; SR: spontaneous remission.

Table 2. Correlation between response assessments

imPERCIST5	PERCIST5				
	CMR	PMR	SMD	PMD	Total
CMR	5	0	0	0	5
PMR	0	6	0	4	10
SMD	0	0	7	7	14
PMD	0	0	2	29	31
Total	5	6	9	40	60

imPERCIST5	PERCIST1				
	CMR	PMR	SMD	PMD	Total
CMR	5	0	0	0	5
PMR	0	4	2	4	10
SMD	0	1	5	8	14
PMD	0	0	2	29	31
Total	5	5	9	41	60

CMR: complete metabolic response; PMR: partial metabolic response; SMD: stable metabolic disease; PMD: progressive metabolic disease.

Supplemental Table 1. Demographic and disease characteristics of patients receiving ipilimumab therapy	
Characteristic	**Ipilimumab (n = 60)**
Median age (range)	65 (35-88)
Male sex (%)	32 (53.3)
Primary site (%)	
Cutaneous	34 (53.7)
Mucosal*	12 (20.0)
Uveal	2 (3.3)
Unknown**	12 (20.0)
Elevated LDH level over ULN (%)	9 (15.0)
***BRAF V600* mutation (%)**	
Positive	15 (25.0)
Negative	41 (68.3)
Unknown	4 (6.7)
Active brain metastases (%)	9 (15.0)
Prior radiotherapy (%)	16 (26.7)
Prior surgery for tumor lesions (%)	51 (85.0)
Number of cycles with ipilimumab therapy (%)[†]	
2	5 (8.3)
3	5 (8.3)
4	50 (83.3)
Line of previous systemic therapy (%)	
0	40 (66.7)
1	18 (60.0)
2	2 (3.3)
Type of previous systemic therapy[‡]	
Chemotherapy	16
BRAF or MEK inhibitors or both	3
Others	1

LDH, lactate dehydrogenase; ULN, upper limit of the normal range

*Vagina 5, Maxillary sinus 2, Oral mucosa 1, GI tract 1, Esophagus 1, Cervix 1, Anus 1

**Most cases were presumed as cutaneous primary.

[†]All cases with 2 or 3 cycles withdrew due to severe immune-related adverse events.

[‡]Only therapy administered for advanced or metastatic disease is listed.

Supplemental Table 2. Results of univariate and multivariate analyses

	HR	95% CI	P value
Univariate analysis			
Age			
≥ 75 years	1.433	0.723-2.841	0.302
< 75 years	1.000 (ref)		
Sex			
Man	0.953	0.507-1.790	0.881
Woman	1.000 (ref)		
Line of previous chemotherapy status			
≥ 1	1.894	1.180-3.041	0.008
0	1.000 (ref)		
Primary site of melanoma			
Others and unknown	1.060	0.558-2.011	0.859
Cutaneous	1.000 (ref)		
Prior radiotherapy			
Yes	2.227	1.123-4.418	0.022
No	1.000 (ref)		
Prior surgery			
Yes	0.603	0.252-1.445	0.256
No	1.000 (ref)		
Elevated LDH level over ULN			
Yes	2.037	0.879-4.724	0.097
No	1.000 (ref)		
Active brain metastases			
Present	2.600	1.129-5.987	0.025
Absent	1.000 (ref)		
Receiving ipilimumab cycles			
< 4	1.017	0.433-2.484	0.936
4	1.000 (ref)		
PERCIST5			
Non-responder	1.530	1.031-2.269	0.035
Responder	1.000 (ref)		
imPERCIST1			
Non-responder	2.543	1.202-5.379	0.015
Responder	1.000 (ref)		
imPERCIST5			
Non-responder	3.853	1.498-9.911	0.005
Responder	1.000 (ref)		
BRAF V600 mutate			
Present	1.061	0.510-2.205	0.875
Absent	1.000 (ref)		
Multivariate analysis			
imPERCIST5			
Non-responder	3.853	1.498-9.911	0.005
Responder	1.000 (ref)		

Supplemental Table 3. Summary of comparison of imPERCIST and PERCIST

Characteristic	Immunotherapy-modified PERCIST (imPERCIST, draft definition)	PERCIST1.0
Measurability of lesions at baseline	Same as PERCIST1.0.	1. Measurable target lesion is hottest single tumor lesion SUL of "maximal 1.2-cm diameter volume ROI in tumor" (SUL peak). SUL peak is at least 1.5-fold greater than liver SUL mean + 2 SDs (in 3-cm spherical ROI in normal right lobe of liver). If liver is abnormal, primary tumor should have uptake > 2.0 × SUL mean of blood pool in 1-cm-diameter ROI in descending thoracic aorta extended over 2-cm z-axis. 2. Tumor with maximal SUL peak is assessed after treatment. Although typically this is in same region of tumor as that with highest SUL peak at baseline, it need not be. 3. Uptake measurements should be made for peak and maximal single-voxel tumor SUL. Other SUV metrics, including SUL mean at 50% or 70% of SUV peak, can be collected as exploratory data; TLG can be collected ideally on basis of voxels more intense than 2 SDs above liver mean SUL. 4. These parameters can be recorded as exploratory data on up to 5 measurable target lesions, typically the 5 hottest lesions, which are typically the largest, and no more than 2 per organ. Tumor size of these lesions can be determined per RECIST 1.1.
Normalization of uptake	Same as PERCIST1.0	Normal liver SUL must be within 20% (and <0.3 SUL mean units) for baseline and follow-up study to be assessable. If liver is abnormal, blood-pool SUL must be within 20% (and <0.3 SUL mean units) for baseline and follow-up study to be assessable. Uptake time of baseline study and follow-up study 2 must be within 15 min of each other to be assessable. Typically, these are at mean of 60 min after injection but no less than 50 min after injection. Same scanner, or same scanner model at same site, injected dose, acquisition protocol (2- vs. 3-dimensional), and software for reconstruction, should be used. Scanners should provide reproducible data and be properly calibrated.

Selection of target lesions at follow-up scan	Up to 5 measurable target lesions, typically the 5 hottest lesions among ALL lesions including NEW lesions, and no more than 2 per organ. Tumor size of these lesions can be determined per RECIST 1.1. The threshold of SUL is not defined in this version.	If 5 lesions are used as exploratory approach, it is suggested that sum of SULs of baseline 5 lesions serve as baseline for study. After treatment, sum of same 5 lesions should be used. Percentage change in SUL is based on change in these sums from study 1 to study 2. Exploratory analysis can include calculating percentage change in SUL in individual lesions and averaging them. This may produce different result. We believe summed SUL approach will be less prone to minor errors in measurements. Same to baseline target lesions or, highest 5 lesions (SULpeak) among baseline lesions.
Evaluation for non-target lesion	Not defined in this version	Nontarget lesions: CMR, disappearance of all 18F-FDG–avid lesions: PMD, unequivocal progression of 18F-FDG–avid nontarget lesions or appearance of new 18F-FDG–avid lesions typical of cancer; non-PMD: persistence of one or more nontarget lesions or tumor markers above normal limits.
Approach for appearance of new lesions	Measure the FDG uptake (SULpeak) of ALL NEW suspicious sites as well as the original sites, then select the 'hottest' (up to 5) lesions from this pool of lesions and compare their summed SULpeak to the summed SULpeak of baseline lesions. PMD is only called when the summed SULpeak on follow-up scan is > 30% higher than the summed SULpeak at baseline. Again, no more than 2 lesions/organ will be picked. Presence of new lesions, per se, does NOT constitute PMD.	Categorized as PMD
Objective response		

Complete metabolic response (CMR)	Same as PERCIST	Complete resolution of 18F-FDG uptake within measurable target lesion so that it is less than mean liver activity and indistinguishable from surrounding background blood-pool levels. Disappearance of all other lesions to background blood-pool levels. Percentage decline in SUL should be recorded from measurable region. No new 18F-FDG–avid lesions in pattern typical of cancer. If progression by RECIST, must verify with follow-up.
Partial metabolic response (PMR)	Reduction of SULpeak in target lesions by a at least 30%, and absolute drop in SUL by at least 0.8 SUL units.	Reduction of minimum of 30% in target measurable tumor 18F-FDG SUL peak. Absolute drop in SUL must be at least 0.8 SUL units, as well. Measurement is commonly in same lesion as baseline but can be another lesion if that lesion was previously present and is the most active lesion after treatment. ROI does not have to be in precisely same area as baseline scan, though typically it is. No increase, >30% in SUL. Reduction in extent of tumor 18F-FDG uptake is not requirement for PMR. Percentage decline in SUL should be recorded. No new lesions.
Stable metabolic disease (SMD)	SMD: not CMR, PMR, or PMD.	SMD: not CMR, PMR, or PMD. SUL peak in metabolic target lesion should be recorded.
Progressive metabolic disease (PMD)	>30% increase in SUL peak, with >0.8 SUL unit increase in tumor SUVpeak, from baseline scan in a pattern typical of tumor and not of infection/treatment effect.	>30% increase in 18F-FDG SUL peak, with >0.8 SUL unit increase in tumor SUV peak from baseline scan in pattern typical of tumor and not of infection/treatment effect. OR: New 18F-FDG–avid lesions that are typical of cancer and not related to treatment effect or infection. PMD other than new visceral lesions should be confirmed on follow-up study within 1 mo unless PMD also is clearly associated with progressive disease by RECIST 1.1.
Overall response	Same as PERCIST1.0	1. Best response recorded in measurable disease from treatment start to disease progression or recurrence. 2. Non-PMD in measurable or non-measurable nontarget lesions will reduce CR in target lesion to overall PMR. 3. Non-PMD in nontarget lesions will not reduce PR in target lesions.

Duration of response	Same as PERCIST1.0	1. Overall CMR: from date CMR criteria are first met; to date recurrent disease is first noted. 2. Overall response: from date CMR or PMR criteria are first met (whichever status came first); to date recurrent disease is first noted. 3. SMD: from date of treatment start to date PMD is first noted.

CMR = complete metabolic response; PMR = partial metabolic response; PD = progressive disease; SMD = stable metabolic disease; PMD = progressive metabolic disease; CR = complete remission; PR = partial remission; NC = no change.