

Prediction of response to immune checkpoint inhibitor therapy using ¹⁸F-FDG PET/CT in patients with melanoma

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Abstract

We aimed to assess serial ¹⁸F-FDG PET/CT imaging according to morphological (RECIST1.1, iRECIST) and functional (PERCIST, PECRIT) criteria to predict clinical response to therapy in patients with advanced melanoma receiving immune checkpoint blocking agents.

Retrospective data collection and analysis was done for 37 patients with unresectable metastatic cutaneous melanoma eligible for immunotherapy (cycles: 4 for ipilimumab and pembrolizumab/ 6 for nivolumab). ¹⁸F-FDG PET/CT imaging was performed prior to (¹⁸F-FDG PET/CT 0) and 14 weeks after ICI onset (¹⁸F-FDG PET/CT 1). Some cases during the follow-up required imaging (¹⁸F-FDG PET/CT 2). Assessment of patient response to treatment was done according to RECIST1.1, iRECIST, PERCIST and PECRIT criteria.

Among 37 assessed patients, 27 had 1 line of ICI, 8 had 2 lines of ICI and 2 patients had 3 lines of ICI: total of 49 PET/CTs. Mean time between initiation of ICI and ¹⁸F-FDG PET/CT (1 or 2) were respectively 13.82 ± 4.32 and 24.73 ± 9.53 weeks. Time between ¹⁸F-FDG PET/CT 1 and ¹⁸F-FDG PET/CT 2 was at mean \pm SD: $11.19w \pm 5.59$. Median PFS was 29.62 months (range 22.52–36.71) ($P = .001$: RECIST 1.1), ($P < .0001$: iRECIST), ($P = .000$: PERCIST), ($P = .072$: PECRIT). Median OS was 36.62 months (30.46–42.78) ($P = .005$: RECIST 1.1), ($P < .0001$: iRECIST), ($P = .001$: PERCIST), ($P = .082$: PECRIT).

¹⁸F-FDG PET/CT could detect eventual ICI-response in patients with metastatic melanoma undergoing ICI using iRECIST and PERCIST criteria

Abbreviations: ¹⁸F-FDG PET/CT = ¹⁸F-FluoroDeoxyGlucose Positron Emission Tomography/Computed Tomography, 3D = three-dimensional, BRAFi = BRAF inhibitor, CMR = complete metabolic response, CR = complete response, CT = computed tomography, ECOG = Eastern Cooperative Oncology Group, EORTC = European Organization for Research and Treatment of Cancer, I = undetermined, ICI = immune checkpoint inhibitors, iCR = immune Complete Response, iPD = immune progressive disease, iPR = immune partial response, irRC = immune-related response criteria, iSD = immune stable disease, iUPD = immune unconfirmed progressive disease, MEKi = MEK inhibitor, MRI = magnetic resonance imaging, NR = non-responder, NSCLC = non-small cell lung cancer, OS = overall survival, PD = progressive disease, PFS = progression free survival, PMD = progressive metabolic disease, PMR = partial metabolic response, PR = partial response, R = responder, SD = stable disease, SMD = stable metabolic disease, TGR = tumor growth rate.

Keywords: criteria, FDG PET/CT, Immune checkpoint inhibitor, melanoma, response assessment

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1. Introduction

The incidence of malignant melanoma has increased over the last decades^[1] with a poor prognosis for patients with advanced tumor.^[2] Immunotherapy, like immune checkpoint inhibitors (ICI) blocking CTLA-4 (e.g., ipilimumab), PD-1 (e.g., nivolumab, pembrolizumab) have demonstrated objective tumor regressions in patients with advanced melanoma and other types of cancer as non-small cell lung cancer (NSCLC) using the activation of the immune system to generate an anti-tumor response.^[3–6] Computed Tomography (CT) assessment of some cancers under (immunotherapy) treatment shows baseline enlarged tumors that seem to fall back over time. Enlarged tumor size could be 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.^[7] Anatomic size measurements do not always appropriately capture a positive tumor response, particularly when the therapeutic agent under investigation stabilizes disease rather than causes tumor shrinkage, or when the study is performed in certain cancer

types. Thus traditional RECIST1.1 morphological criteria may not be reliable to characterize clinical outcomes in cancer patients treated with immune-based anti-neoplastic drugs. Other treatment response criteria such as immune-related response criteria (irRC)^[8] and iRECIST^[9] are increasingly being used. Several studies have investigated the role of ¹⁸F-FluoroDeoxyGlucose Positron Emission Tomography/Computed Tomography (¹⁸F-FDG PET/CT) imaging in early detection of response to immunotherapy using characterization criteria such as PERCIST 1.0 and PECRIT.^[10–12] Many studies have suggested that functional findings obtained from ¹⁸F-FDG PET/CT scans could be used ancillary to anatomic findings obtained by conventional spiral CT and Magnetic Resonance Imaging (MRI).^[13] In the footsteps of the literature, we retrospectively analyzed serial ¹⁸F-FDG PET/CT imaging according to morphological (RECIST 1.1, iRECIST) and functional (PERCIST 1.0, PECRIT) criteria to predict clinical response to therapy (i.e., Progression Free Survival (PFS) and Overall Survival (OS)) in patients with advanced melanoma receiving immune checkpoint blocking agents.

2. Materials and methods

2.1. Patients

Thirty seven consecutive patients with unresectable metastatic cutaneous melanoma were seen at oncology consultation between November 2010 and June 2017 (23 men, 14 women). They were scheduled for ICI blocking CTLA-4 (e.g., ipilimumab) or PD-1 (e.g., nivolumab, pembrolizumab) treatment.

Patients with uveal or mucosal melanoma or with only brain metastasis were excluded from analysis due to the known limitation of ¹⁸F-FDG PET/CT in detecting these lesions. Of the 37 patients, 13 had already been pretreated for metastatic melanoma, and 24 received no treatment while in stage IV. The pretreated patients received therapies containing one or more of the following: dacarbazine or formustine or BRAF inhibitor (BRAFi) or combination of BRAF inhibitor and MEK inhibitor (BRAFi+MEKi). The characteristics of the patients investigated are presented in Table 1.

Ipilimumab was administered intravenously at a dose of 3 mg/kg every 3 weeks for a total of four doses. Nivolumab was administered intravenously at a dose of 3 mg/kg every 2 weeks and pembrolizumab was administered intravenously at a dose of 2 mg/kg every 3 weeks; anti-PD-1 was continued until progression or serious toxicity. Among 37 patients assessed by ¹⁸F-FDG PET/CT, 27 patients had 1 line of ICI, 8 patients had 2 lines of ICI and 2 patients had 3 lines of ICI thus 49 PET/CTs were performed.

Patients gave written informed consent to participate in the study and to have their medical records released. Retrospective collection and analysis of medical data was done from June 2017 to January 2018.

The study was approved by the local Ethics Committee of our institution and was registered on clinicaltrials.gov (ClinicalTrials.gov number NCT 03741231).

2.2. Data acquisition

¹⁸F-FDG PET/CT scans were performed on a Biograph mCT PET/CT 64 scanner system (Siemens, Erlangen, Germany) at baseline, and approximately 14 weeks after the first infusion of

Table 1

Charac.	
Characteristics	No. of patients (%) (n = 37)
Age in years, median (range)	65 (38–90)
Sex — no. (%)	
Male	23 (62%)
Female	14(38%)
ECOG performance status — no. (%)	
0	21 (57%)
1	15 (40%)
2	1 (3%)
Mutations— no. (%)	
BRAF	9/37 (24.32%)
NRAS	7/37 (19%)
KIT	0/37 (0%)
Number of metastatic lesions >3	17/37 (46%)
Brain metastasis	8/37 (22%)
Treatment — no. (%)	
Nivolumab	16/49 (32.65%)
Pembrolizumab	17/49 (34.69%)
Ipilimumab	16/49 (32.65%)
Type of previous systemic therapy — no. (%)	
Chemotherapy	8/37 (21.62%)
BRAF or MEK inhibitor or both	5 /9 (55.55%)
Radiotherapy before start immunotherapy— no. (%)	5/37 (14%)

ECOG=Eastern Cooperative Oncology Group.

immunotherapy. Patients fasted 6 hours before intravenous injection of approximately 3 MBq/kg of ¹⁸F-FDG. Following injection patients remained in a quiet room for approximately 60 minutes before acquisition. Patients were scanned from the top of the skull to the mid-thigh in the arms-down position except for patients with limb melanoma (limbs included).^[14] Patients were allowed to breath normally during the PET and CT acquisitions (2 min per bed position). CT included injection of iodine in the absence of contraindications. PET data were acquired in three-dimensional (3D) mode and, for attenuation correction, were reconstructed using the CT data and followed by reconstruction using an ordered subsets expectation-maximization algorithm (True X PSF+TOF OSEM3D) into 200 × 200 matrices.

¹⁸F-FDG PET/CT imaging was performed prior to initiating immunotherapy (¹⁸F-FDG PET/CT 0), again after 4 or 6 cycles of ICI (4 for ipilimumab and pembrolizumab/ 6 for nivolumab) (¹⁸F-FDG PET/CT 1) (mean±/− SD: 13.82w±4.32), and sometimes during the follow-up especially to confirm an unconfirmed progressive disease (PET/CT 2) (mean delay between ¹⁸F-PET/CT 1 and ¹⁸F-PET/CT 2: ±/− SD 11.19w±5.59). Mean time between initiation of ICI and ¹⁸F-FDG PET/CT 2 was 24.73 ±9.53 weeks.

3. Data analysis

3.1. Response criteria

Datasets were analyzed using Syngo.via software by 2 experienced nuclear medicine physicians.

CT-based responses according to ¹⁸F-FDG PET/CT assessed by one physician were characterized according to RECIST1.1^[15] and iRECIST.^[9] ¹⁸F-FDG PET-based responses were evaluated by a second physician using PERCIST 1.0^[16] and PECRIT^[10] criteria. PERCIST 1.0 was proposed as a new method for the quantitative assessment of metabolic changes in solid tumors and

PECRIT criteria was recently proposed by Cho et al^[10] for early prediction of eventual response to ICI therapy incorporating RECIST-based and PERCIST-based changes (change in peak SUV, normalized by lean body mass within a 1-cm³ spheric volume of interest, of the hottest lesion (SULpeak)) seen 3 to 4 weeks into treatment. Response criteria used in this study are summarized in Table 2.

CT-based anti-tumor responses observed between PET/CT 0 and PET/CT 1 were classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) according to RECIST1.1 and iCR, iPR, iSD, iPD and immune unconfirmed progressive disease (iUPD) according to iRECIST.

¹⁸F-FDG PET-based anti-tumor responses were classified as complete metabolic response (CMR), partial metabolic response (PMR), stable metabolic disease (SMD) or progressive metabolic disease (PMD) according to PERCIST 1.0.

¹⁸F-FDG PET/CT-based responses were classified as clinical or no clinical benefit according to PECRIT criteria.

Based on ¹⁸F-FDG PET/CT results, 3 classes of treatment response were defined according to each criteria: i) Responder (R)

which included respectively for RECIST1.1, iRECIST and PERCIST 1.0 criteria CR, PR, SD, iCR, iPR, iSD and CMR, PMR, SMD and non-PMD. ii) Non-Responder (NR) which included also for these 3 criteria: PD, iPD and PMD. iii) Undetermined (I): iUPD. These 3 classifications were also applied for PFS and OS.

Pseudoprogression was defined as a decrease or stabilization of the tumoral activity (or growth) of an initially evaluated disease progression.^[17,18] Hyperprogression was defined as a RECIST 1.1 progression of ≥ 2 -fold increase in tumor growth rate (TGR) at the first evaluation.^[19]

The duration of observation for each patient is included in Table 3.

3.2. Follow-up

Patients were monitored through standard of care clinical and imaging examinations for assessment of PFS and OS regardless of ¹⁸F-FDG PET/CT data (PET/CT 0, PET/CT 1 and PET/CT 2). PFS was defined as the time from diagnosis to first reported

Table 2
Summary of Treatment Response Criteria.

Responses	CT-based criteria		PET-based criteria	
	RECIST 1.1	iRECIST	PERCIST 1.0	PECRIT
Progression disease (PD)	$\geq 20\%$ increase in sum of diameters of TLs or unequivocal progression of NL or appearance of new lesion	iUPD : $\geq 20\%$ of the sum of longest diameters compared with nadir (minimum 5 mm) or progression of non-target lesions or new lesion Confirmation of progression recommended minimum 4 weeks after the first iUPD assessment iCPD: Increased size of target or non-target lesions Increase in the sum of new target lesions > 5 mm Progression of new non-target lesions Appearance of another new lesion	> 30% RI and >0.8 du SUL peak of HL or unequivocal progression of ¹⁸ F-FDG -avid NL or appearance of new ¹⁸ F-FDG -avid	$\geq 20\%$ increase in sum of diameters of TLs or unequivocal progression of NL or appearance of new lesion →No clinical benefit
Stable disease (SD)	Neither sufficient TR or TG to quality for PR or PD	Neither sufficient TR or TG to quality for PR or PD	Not meeting criteria for CMR, PMR or PMD	Neither sufficient TR or TG to quality for PR or PD Percent change in SUL peak per PERCIST criteria at 3–4 weeks *SUL peak $\leq 15.5\%$ → No clinical benefit *SUL peak >15.5% → Clinical benefit.
Partial response (PR)	$\geq 30\%$ decrease in SoDs of TLs ; NLs may persist but not unequivocally progress	$\geq 30\%$ decrease in SoDs of TLs; NLs may persist but not unequivocally progress	> 30% RD and >0.8 AD in SUL peak of HL	$\geq 30\%$ decrease in SoDs of TLs; NLs may persist but not unequivocally progress → Clinical benefit (CR at 4 months)
Complete response (CR)	Disappearance of all TLs and NLs ; all LNs < 10mm short axis	Disappearance of all TLs and NLs; all LNs < 10 mm short axis	Complete resolution of ¹⁸ F-FDG uptake within measurable TL and disappearance of all other lesions to BBP levels	Disappearance of all TLs and NLs; all LNs < 10 mm short axis → Clinical benefit (CR at 4 months)

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, SULpeak = average SUV corrected by lean body mass within a 1-cm³ spheric volume of interest, HL = hottest lesion, CoT = cycle of therapy, TR = tumor regression, TG = tumor growth, PR = partial response, PD = progressive disease, iCR = immune-related complete response, iPR = immune-related partial response, iPD = 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 SUVmax (maximum voxel value of SUV), iUPD = immune unconfirmed progression disease, iCPD = immune confirmed progression disease.

disease progression or recurrence, or disease-related death. OS was defined as the time from diagnosis to death related to melanoma.

3.3. Clinical and biological data

Other criteria such as Eastern Cooperative Oncology Group (ECOG),^[20] brain metastasis, ≥ 3 metastatic sites were also recorded.

3.4. Statistical analysis

3.4.1. PFS and OS were chosen as endpoints. Univariate analysis was performed to test the significance of the following factors: all response criteria and clinico-biological factors such as ECOG performance status >1 , number of metastatic lesions ≥ 3 , brain metastasis. The Kaplan–Meier method was used to estimate PFS and OS probabilities. A log-rank test was used to estimate survival distributions according to different interpretation criteria.

Significance level of P values was .05. All statistics were determined using XLSTAT-Life software (Addinsoft, Paris, France).

4. Results

4.1. Outcomes

Median PFS was 29.62 months (range 22.52–36.71) and median OS was 36.62 months (range 30.46–42.78). The overall results are summarized in Table 3.

According to RECIST 1.1, assessment of 35 evaluable scans (i.e., 47 imaging reviews) detected 3 CR, 8 PR, 11 SD and 25 PD. According to iRECIST, the conclusions were 3 iCR, 8 iPR, 11 iSD and 25 iUPD. Of these ¹⁸F-FDG PET/CT 2 findings, 14 iUPD were confirmed as iCPD progression (Fig. 1; patient 37 in Table 3). Of the 25 iUPD detected, 7 iUPD remained unchanged, 1 iUPD transformed into iSD, and 3 iUPD were not confirmed due to the change in therapy.

According to PERCIST 1.0 criteria, therapeutic assessment of 36 evaluable scans (i.e., 48 imaging reviews) detected 6 CMR, 6 PMR, 6 SMD, 27 PMD and 3 non-PMD.

According to PECRIT criteria, therapeutic assessment of 35 evaluable scans (i.e., 47 imaging reviews) detected 14 clinical benefit and 33 no-clinical benefit.

4.1.1. Evaluation of criteria for progression-free survival (PFS). According to RECIST 1.1, the median PFS were respectively 15.9, 25.6, 19.8, and 6.2 months for patients with CR, PR, SD, and PD.

According to iRECIST, the median PFS were respectively 15.9, 25.6, 20.2, 10.6 and 6.6 months for patients with iCR, iPR, iSD, iUPD, and iCPD.

According to PERCIST 1.0, the median PFS were respectively 20.9, 21.1, 22.2, 26.4, and 6.1 months for patients with CMR, PMR, SMD, non-PMD, and PMD.

According to PECRIT, median PFS was 20.41 months for patients with clinical benefit and 7.39 months for those with no clinical benefit.

Figure 2 displays Kaplan–Meier PFS results according to different treatment response criteria. Progression free survival estimates were statistically significant according to RECIST 1.1 (P value = .001), iRECIST (P value $< .0001$) and PERCIST 1.0

criteria (P value = .000). The results were statistically non-significant according to PECRIT (P value = .072).

This trend was also observed among responders and non-responders. According to RECIST 1.1, median PFS were respectively 22.24 and 6.18 months for responders and non-responders (P value $< .0001$).

According to iRECIST, median PFS were respectively 23.8, 10.58, and 6.57 months for responders, undetermined and non-responders (P value $< .0001$).

According to PERCIST 1.0, median PFS were respectively 23.80 and 6.14 months with responders and non-responders (P value $< .0001$).

4.1.2. Evaluation of criteria for overall survival (OS). According to RECIST 1.1, the median OS were respectively 15.87, 25.54, 27.51, and 11.27 months for patients with CR, PR, SD, and PD.

According to iRECIST, the median OS were respectively 15.87, 25.54, 28.53, 11.39, and 9.66 months for patients with iCR, iPR, iSD, iUPD, and iCPD.

According to PERCIST 1.0, the median OS were respectively 20.84, 26.44, 28.53, 26.49, and 11.04 months for patients with CMR, PMR, SMD, non-PMD, and PMD.

According to PECRIT, median OS were respectively 24.70 and 17.03 months for patients with clinical benefit and no clinical benefit (P value = .082).

Figure 3 displays Kaplan–Meier OS results according to different treatment response criteria. Overall survival estimates were statistically significant according to RECIST 1.1 (P value = .005), iRECIST (P value $< .0001$), PERCIST 1.0 criteria (P value = .001). The results were statistically non-significant according to PECRIT (P value = .082).

This trend was also observed among responders and non-responders.

According to RECIST 1.1, median OS were respectively 25.8 and 11.27 months for responders and non-responders (P value = .000).

According to iRECIST, median OS were respectively 26.15, 11.39, and 9.66 months for responders, undetermined and non-responders (P value $< .0001$).

According to PERCIST 1.0, median OS were respectively 26.15 and 11.04 months with responders and non-responders (P value $< .0001$).

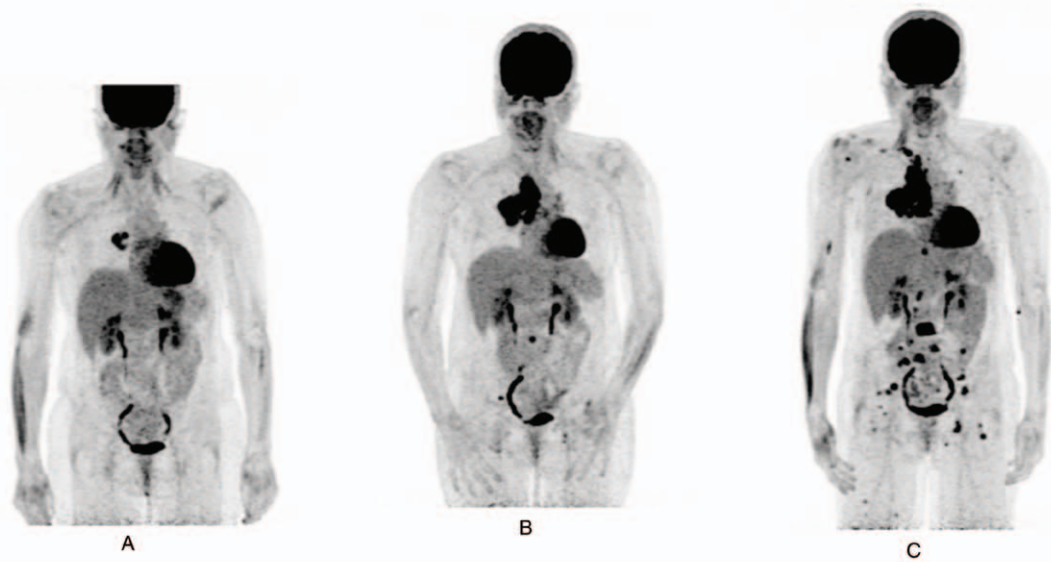
4.1.3. Pseudo-progression and hyperprogression. In this cohort, only 1 patient had a pseudoprogression (patient 33 in Table 3), a 67-year-old male treated with ipilimumab had progression in an initial left lung lesion and a lower diaphragmatic node at the first assessment (¹⁸F-FDG PET/CT 1) according to iRECIST after 15 weeks. No confirmation of disease progression at ¹⁸F-FDG PET/CT 2 after 19 weeks. iUPD observed at the first assessment was transformed into iSD according to iRECIST criteria (Fig. 4). No hyperprogression was reported in this study.

Clinical and biological data with poor prognosis^[21–23] were also tested for PFS and OS with statistically non-significant results. The results are summarized in Table 4.

5. Discussion

Immune checkpoint blockade agents represent a major advancement in cancer therapy and in particular in treatment of melanoma. These agents have demonstrated evidence of benefits

Maximum intensity projection (MIP)18F-FDG PET/CT images during the course of treatment in a 54-year-old woman with metastatic melanoma



A Baseline PET/CT (2 right lung nodules and 1 right hilar node)

B Interim PET/CT (12 weeks) with progression non equivocal (PD according to RECIST 1.1 and PERCIST, iUPD according to iRECIST, no clinical benefit according to PECRIT)

C Final PET/CT (18 weeks) with confirmation of progression disease (iUPD transformed in iCPD according to iRECIST)

Transaxial PET/CT images located in lungs

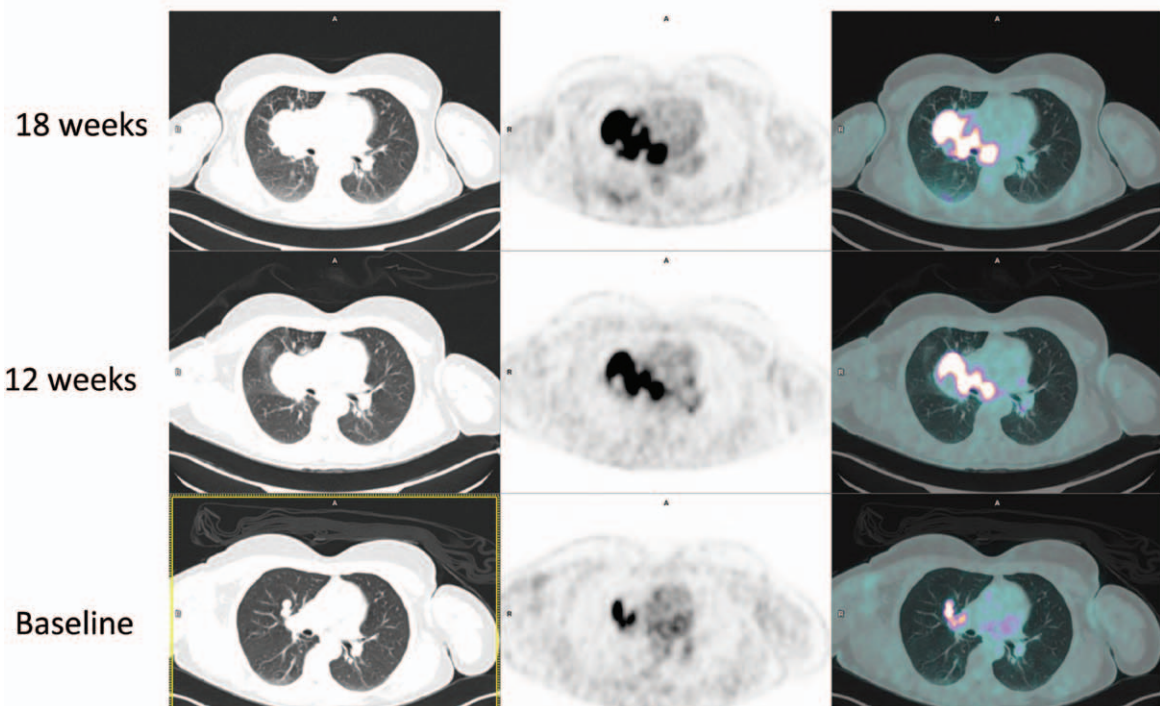


Figure 1. Maximum intensity projection (MIP)18F-FDG PET/CT images during the course of treatment in a 54-year-old woman with metastatic melanoma, A Baseline PET/CT (2 right lung nodules and 1 right hilar node), B Interim PET/CT (12 weeks) with progression non equivocal (PD according to RECIST 1.1 and PERCIST, iUPD according to iRECIST, no clinical benefit according to PECRIT), C Final PET/CT (18 weeks) with confirmation of progression disease (iUPD transformed in iCPD according to iRECIST).

Transaxial PET/CT images located in lungs

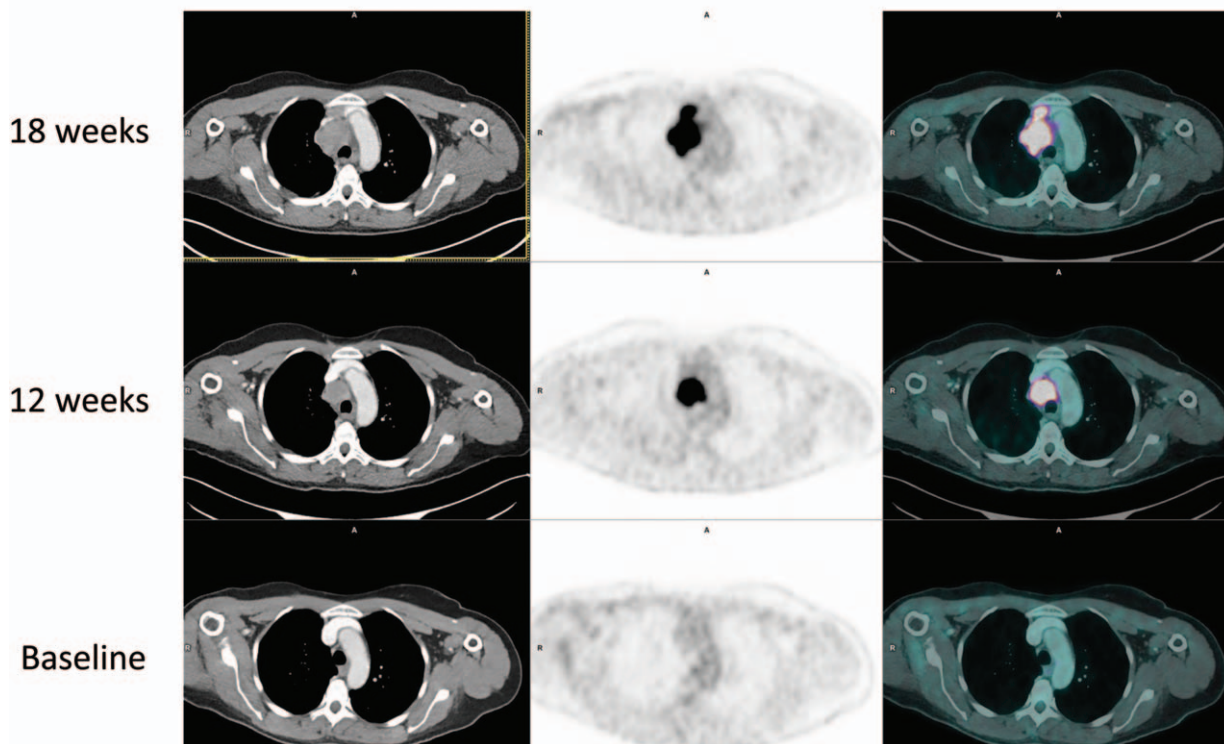


Figure 1. (Continued).

on overall survival and patient safety.^[5,7,24,25] The prognosis of melanoma has improved significantly since the advent of immunotherapy by ICI with survival in 40% of patients after 3 years, and allows prolonged complete responses even after stopping treatment.^[5,26] Most cancer treatment response evaluations are based on CT-changes in tumor size according to morphological criteria such as RECIST 1.1.^[15,27] However, immunotherapy (e.g., ICI) response assessment challenges the conventional measurements and criteria used for changes in tumor response (e.g., size and volume). In addition to the challenges of irregularly shaped or morphologically complex tumors, ICI agents mechanism of action, which depends on host's adaptive immune system,^[28–30] can generate unusual response patterns, for example, pseudoprogression,^[17,18] hyperprogression^[19], atypical and delayed responses. Clinical trials on ICI were developed and conducted in late 2000s for the first time in treatment of melanoma. These clinical trials used RECIST1.1 criteria for assessment of response to treatment. The drawback with conventional criteria such as RECIST1.1, is the incapacity to classify unconventional and additional tumor response patterns to immunotherapeutic agents. Consequently, since 2009, other morphological criteria have been developed such as immune-related response criteria (irRC)^[8], irRECIST^[31–33] and iRECIST.^[9] However, the design and methodology of the studies conducted to develop the above criteria did not provide a high level of evidence to reach consensual criteria for immune-related tumor response assessment. Common language has been reached in prediction of Hodgkin lymphoma and diffuse large B-cell lymphoma response to therapy.^[34,35] In the rise of promising

novel immunotherapeutic agents, it is of high importance to reach consensual criteria for better assessment of ICI agents effectiveness in melanoma.

In an attempt to reach consensual criteria, we retrospectively analyzed serial ¹⁸F-FDG PET/CT imaging according to morphological (RECIST 1.1, iRECIST) and functional (PERCIST 1.0, PECRIT) criteria to predict clinical response to therapy (i.e., Progression Free Survival (PFS) and Overall Survival (OS)) in patients with advanced melanoma receiving immune checkpoint blocking agents.

¹⁸F-FDG PET/CT is particularly interesting as an imaging modality for detection of response to ICI therapy, that is, metabolic changes in melanoma before morphological modifications. Similar to human neoplastic growth, inflammatory/infectious processes have high intracellular glucose metabolism. This could explain in patients with stable disease, ICI-related inflammatory response, that is, increased FDG uptake at an early PET/CT imaging, likely to demonstrate disease regression.^[10,36]

Two morphological (RECIST 1.1 and iRECIST) and 1 functional (PERCIST 1.0) criteria predicted response to ICI therapy. PECRIT clinical benefit vs no-clinical benefit survival results were not significantly different.

In the prospective study of Cho et al, 20 patients with advanced melanoma receiving ICI underwent ¹⁸F-FDG PET/CT at three time points: prior to treatment initiation (SCAN-1), at days 21–28 (SCAN-2), and at 4 months (SCAN-3). Tumor response at post-treatment SCAN-2 and SCAN-3 was assessed according to RECIST 1.1, immune-related response criteria (irRC), PERCIST 1.0 and European Organization for Research and Treatment of

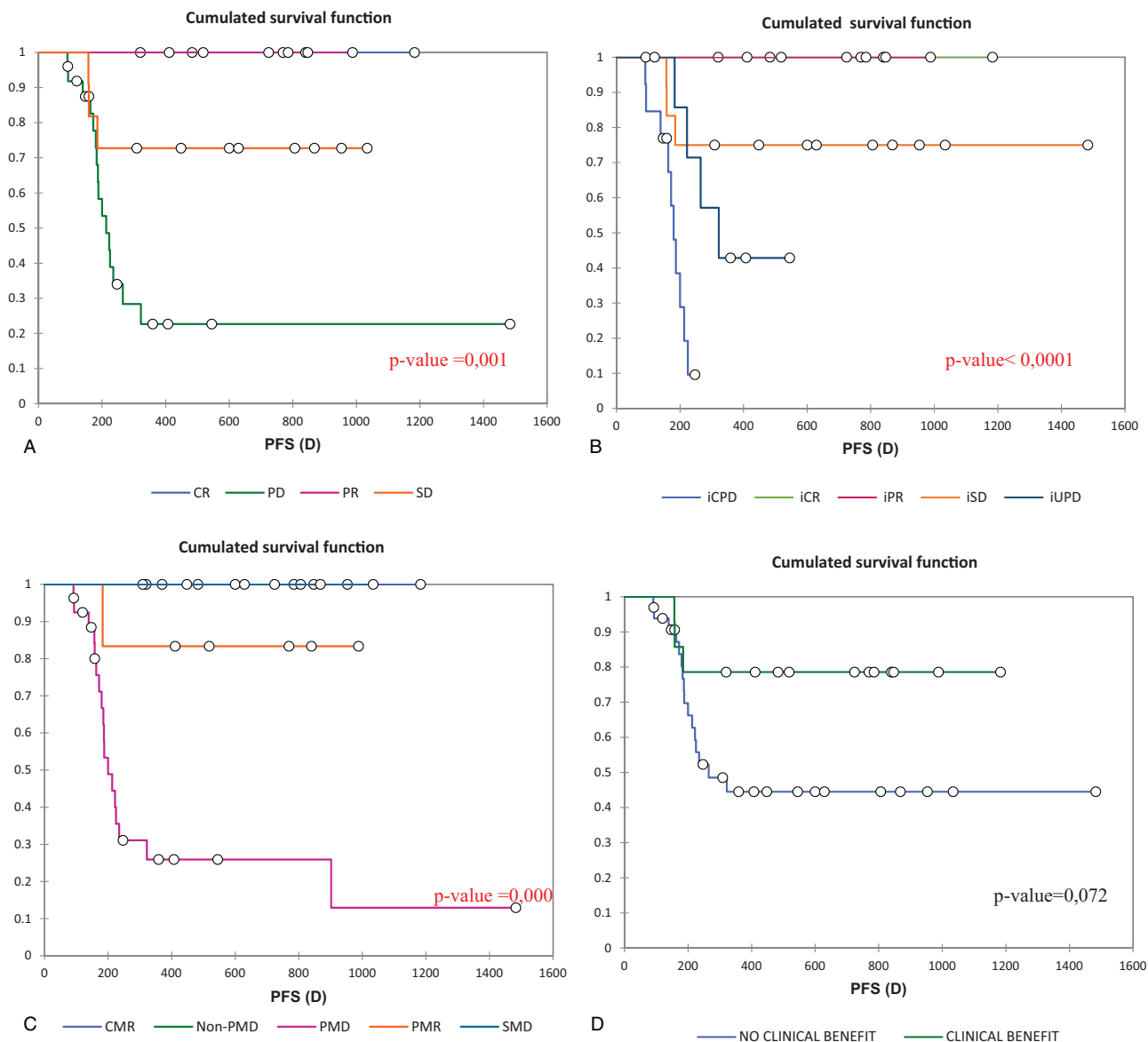


Figure 2. Kaplan–Meier progression free survival (PFS) estimates according to the different criteria, A RECIST 1.1, B iRECIST, C PERCIST 1,0, D PECCRIT, CR= complete response, PR=partial response, SD=stable response, PD=progressive disease, iCPD=immune confirmed progressive disease, iCR=immune complete response iPR=immune partial response, iSD=immune stable disease, iUPD=immune unconfirmed progressive disease, CMR=complete metabolic response, PMR=partial metabolic response, SMD=stable metabolic response PMD=progressive metabolic disease.

Cancer (EORTC). The authors demonstrated that ¹⁸F-FDG-PET/CT scans performed early in ICI therapy could predict eventual response. RECIST 1.1, irRC, PERCIST 1.0 and EORTC criteria demonstrated respective 75%, 70%, 70%, and 65% accuracy in predicting best overall response.^[10] So Cho et al suggested the use of PECCRIT criteria, a combination of functional and anatomical parameters obtained from PET/CT 3 to 4 weeks after therapy onset, for early prediction of eventual response to ICI therapy. According to Cho et al study, patients with stable disease by RECIST1.1 at 3 to 4 weeks, an increase > 15.5% in SUL_{peak} of the hottest lesion by ¹⁸F-FDG PET/CT was associated with eventual clinical benefit (PR or CR at 4 months or SD ≥ 6 months). Their PECCRIT sensitivity, specificity and accuracy to predict response at 4 months were 100%, 93.3%, and 95.0%

respectively. The discrepancy observed for PECCRIT between our study (no significant results for PFS and OS when using PECCRIT) and that of Cho et al may be explained by the delay to perform interim ¹⁸F-FDG PET/CT (3–4 weeks for Cho et al, 14 weeks in our study).

Sachpekidis et al found in 22 patients with metastatic melanoma treated by ipilimumab that assessment by PERCIST 1.0 criteria after 2 cycles of ipilimumab is highly predictive of the final treatment outcome in patients with PMD and SMD. Our PERCIST 1.0 results were consistent with the above literature, that is, predictive of treatment response^[11].

In our study, only 1 pseudo-progression confirmed (2.85%) was described, which is lower compared to the rate reported in Hodi et al study which found 12% of pseudoprogessors among

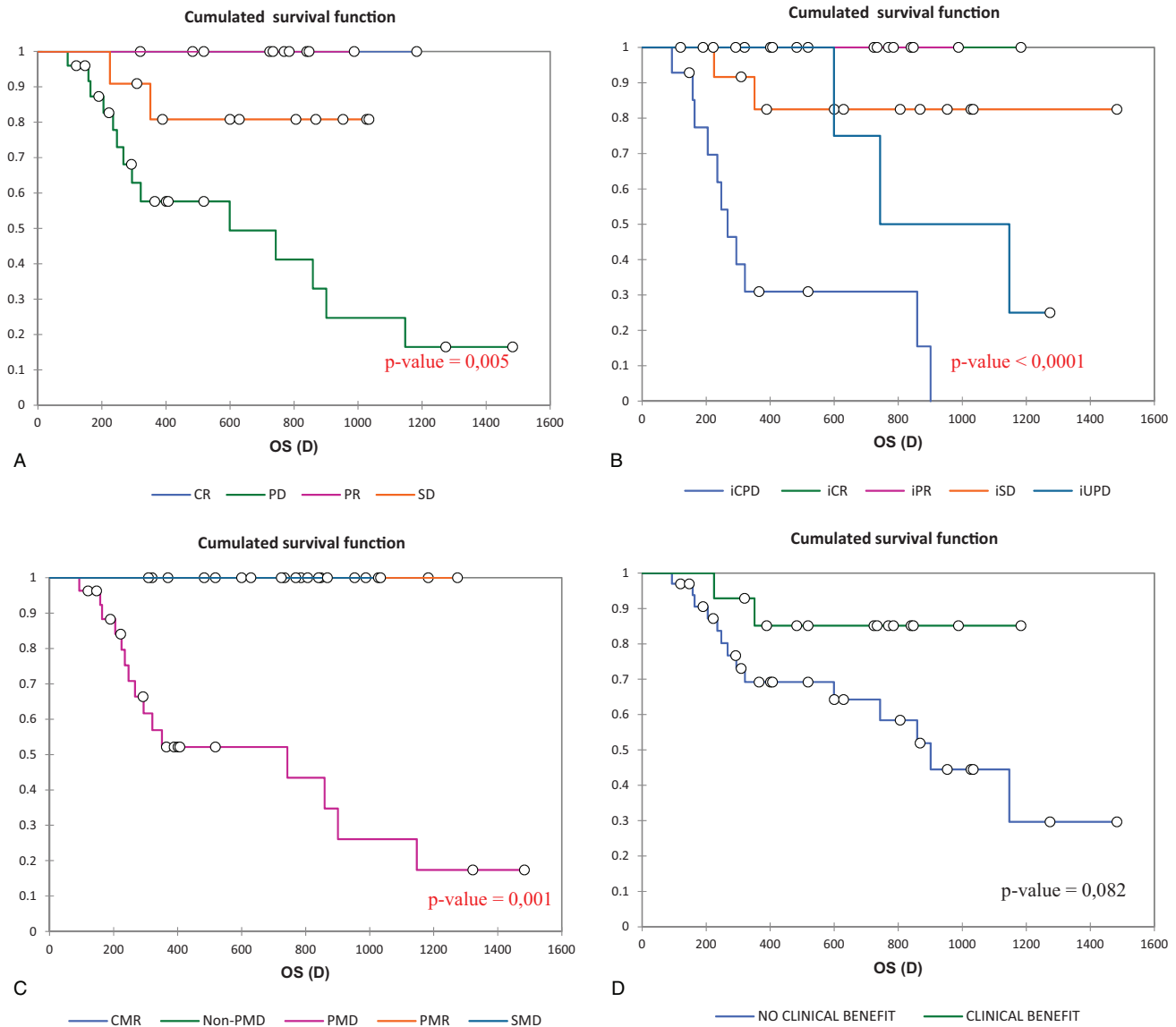


Figure 3. Kaplan-Meier overall survival (OS) estimates according to the different criteria, A RECIST 1.1, B iRECIST, C PERCIST 1.0, D PECRIT.

patients treated by pembrolizumab^[15,18] and a rate of 6.7% in the study of Chiou et al also in a cohort of patients treated by pembrolizumab.^[37] No hyperprogression was diagnosed in our study. Our lower % of pseudo-progression can probably be explained by the fact that 3 of our patients (i.e., classified as iUPD on ¹⁸F-FDG PET/CT1), did not have the ¹⁸F-FDG PET/CT2 due to treatment change and also by the frequency of tumor assessment.

To our knowledge, this is the first study comparing PECRIT a new ¹⁸F-FDG PET/CT criteria, with other validated criteria (PERCIST 1.0, RECIST 1.1, iRECIST) for prediction of ICI treatment response in metastatic melanoma.

Nevertheless, our study has some limitations. First, it was carried out in a single center with relatively small cohort. In addition, morphological criteria RECIST 1.1 and iRECIST were assessed on ¹⁸F-FDG PET/CT not on dedicated CT. Nevertheless, approximately 70% ¹⁸F-FDG PET/CT were performed with iodine injection as CT dedicated but without sequential

acquisition. Response assessment time should be shortened with interim PET/CT performed after 4 to 8 weeks after ICI onset to detect easier atypical responses as pseudo-progression or hyper-progression.

The retrospective nature of the study provides a non-homogeneous methodology.

Our study suggests that ¹⁸F-FDG PET/CT scans could detect eventual ICI-response in patients with metastatic melanoma. According to our study, iRECIST and PERCIST 1.0 may provide the most optimal ICI-related response classification.

6. Conclusion

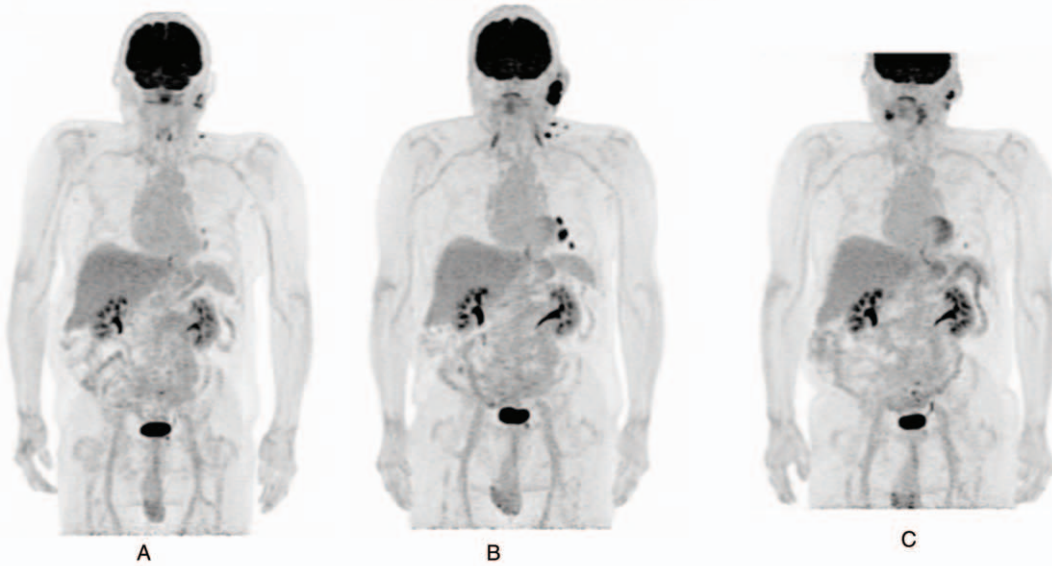
Based on survival analyses, 2 morphological (RECIST 1.1, iRECIST) and 1 functional criteria (PERCIST 1.0) appeared significantly predictive of PFS and OS in patients with unresectable metastatic melanoma treated by ICI. The novel functional PECRIT criteria did not seem to be suitable in late

Table 3
Response assessments in 37 patients with metastatic melanoma receiving ICI therapies.

Patient no	Treatment	1st evaluation ¹⁸ F-FDG PET/CT 1				2nd evaluation ¹⁸ F-FDG PET/CT 2				PFS Time limit (days)	OS limit (days)	OS Time limit (days)	
		RECIST 1.1	iRECIST	PERCIST 1.0	PECRIT	RECIST 1.1	iRECIST	PERCIST 1.0	PECRIT				
1	Pembrolizumab	PD	iUPD	PMD	NO CLINICAL BENEFIT	PD	iCPD	PMD	NO CLINICAL BENEFIT	1	235	1	235
2	Pembrolizumab	PD	iUPD	PMD	NO CLINICAL BENEFIT	PD	iCPD	PMD	NO CLINICAL BENEFIT	1	139	0	518
2'	Ipilimumab	SD	iSD	PMD	CLINICAL BENEFIT	SD	iSD	PMD	CLINICAL BENEFIT	1	158	0	389
2''	Nivolumab	PD	iUPD	PMD	NO CLINICAL BENEFIT								
	PD	iUPD	PMD	NO CLINICAL BENEFIT	0	92	0	190					
3	Nivolumab	PR	iPR	PMR	CLINICAL BENEFIT	PR	iPR	PMR	CLINICAL BENEFIT	0	518	0	518
4	Pembrolizumab	SD	iSD	No PMD	NO CLINICAL BENEFIT	SD	iSD	No PMD	NO CLINICAL BENEFIT	0	806	0	806
5	Pembrolizumab	CR	iCR	CMR	CLINICAL BENEFIT	CR	iCR	CMR	CLINICAL BENEFIT	0	320	0	320
6	Nivolumab	SD	iSD	No PMD	NO CLINICAL BENEFIT	SD	iSD	No PMD	NO CLINICAL BENEFIT	0	953	0	953
7	Pembrolizumab	PR	iPR	CMR	CLINICAL BENEFIT	PR	iPR	CMR	CLINICAL BENEFIT	0	785	0	785
8	Nivolumab	PR	iPR	CMR	CLINICAL BENEFIT	PR	iPR	CMR	CLINICAL BENEFIT	0	847	0	847
9	Nivolumab	PD	iUPD	PMD	NO CLINICAL BENEFIT	PD	iCPD	PMD	NO CLINICAL BENEFIT	1	172	1	205
10	Ipilimumab	PD	iUPD	PMD	NO CLINICAL BENEFIT	PD	iCPD	PMD	NO CLINICAL BENEFIT	1	213	1	294
11	Ipilimumab	PD	iUPD	PMR	NO CLINICAL BENEFIT	PD	NA	PMR	NO CLINICAL BENEFIT	1	183	0	1274
12	Pembrolizumab	PR	iPR	PMR	CLINICAL BENEFIT	PR	iPR	PMR	CLINICAL BENEFIT	0	769	0	769
13	Ipilimumab	PD	iUPD	NA	NO CLINICAL BENEFIT	PD	NA	NA	NO CLINICAL BENEFIT	1	265	1	599
14	Pembrolizumab	PD	iUPD	PMD	NO CLINICAL BENEFIT	PD	iCPD	PMD	NO CLINICAL BENEFIT	1	225	0	365
14'	Ipilimumab	PD	iUPD	PMD	NO CLINICAL BENEFIT	PD	iCPD	PMD	NO CLINICAL BENEFIT	0	147	0	147
15	Pembrolizumab	PD	iUPD	PMD	NO CLINICAL BENEFIT	PD	iCPD	PMD	NO CLINICAL BENEFIT	1	200	1	901
15'	Ipilimumab	PD	iUPD	PMD	NO CLINICAL BENEFIT	PD	iUPD	PMD	NO CLINICAL BENEFIT	0	545	1	743
15''	Nivolumab	PD	iUPD	PMD	NO CLINICAL BENEFIT	PD	iCPD	PMD	NO CLINICAL BENEFIT	0	247	1	247
16	Ipilimumab	SD	iSD	PMD	CLINICAL BENEFIT	SD	iSD	PMD	CLINICAL BENEFIT	1	157	1	351
16'	Nivolumab	SD	iSD	PMD	CLINICAL BENEFIT	SD	iSD	PMD	CLINICAL BENEFIT	1	185	1	225
17	Pembrolizumab	PR	iPR	PMR	CLINICAL BENEFIT	PR	iPR	PMR	CLINICAL BENEFIT	0	988	0	988
18	Pembrolizumab	PR	iPR	PMR	CLINICAL BENEFIT	PR	iPR	PMR	CLINICAL BENEFIT	0	840	0	840
19	Nivolumab	PD	iUPD	PMD	NO CLINICAL BENEFIT	PD	iCPD	PMD	NO CLINICAL BENEFIT	1	163	1	321
19'	Ipilimumab	PD	iUPD	PMD	NO CLINICAL BENEFIT	PD	iCPD	PMD	NO CLINICAL BENEFIT	0	158	1	158
20	Nivolumab	PD	iUPD	PMD	NO CLINICAL BENEFIT	PD	iCPD	PMD	NO CLINICAL BENEFIT	1	91	1	164
21	Ipilimumab	SD	iSD	SMD	NO CLINICAL BENEFIT	SD	iSD	SMD	NO CLINICAL BENEFIT	0	448	0	1027
21'	Nivolumab	SD	iSD	SMD	NO CLINICAL BENEFIT	SD	iSD	SMD	NO CLINICAL BENEFIT	0	600	0	600
22	Nivolumab	SD	iSD	SMD	NO CLINICAL BENEFIT	SD	iSD	SMD	NO CLINICAL BENEFIT	0	629	0	629
23	Pembrolizumab	PR	iPR	SMD	CLINICAL BENEFIT	PR	iPR	SMD	CLINICAL BENEFIT	0	724	0	724
24	Ipilimumab	SD	iSD	SMD	NO CLINICAL BENEFIT	SD	iSD	SMD	NO CLINICAL BENEFIT	0	1034	0	1034
25	Ipilimumab	PD	iUPD	PMD	NO CLINICAL BENEFIT	PD	iUPD	PMD	NO CLINICAL BENEFIT	1	322	1	1147
25'	Nivolumab	PD	iUPD	PMD	NO CLINICAL BENEFIT	PD	iCPD	PMD	NO CLINICAL BENEFIT	1	187	1	859
26	Nivolumab	PR	iPR	PMR	CLINICAL BENEFIT	PR	iPR	PMR	CLINICAL BENEFIT	0	411	0	734
27	Nivolumab	PD	iUPD	PMD	NO CLINICAL BENEFIT	PD	iUPD	PMD	NO CLINICAL BENEFIT	0	359	0	401
27'	Pembrolizumab	PD	iUPD	PMD	NO CLINICAL BENEFIT	PD	iUPD	PMD	NO CLINICAL BENEFIT	0	407	0	407
28	Nivolumab	CR	iCR	CMR	CLINICAL BENEFIT	CR	iCR	CMR	CLINICAL BENEFIT	0	483	0	483
29	Ipilimumab	NA	NA	PMD	NA	NA	NA	PMD	NA	1	902	0	1322
30	Ipilimumab	CR	iCR	CMR	CLINICAL BENEFIT	CR	iCR	CMR	CLINICAL BENEFIT	0	1183	0	1183
31	Pembrolizumab	SD	iSD	No PMD	NO CLINICAL BENEFIT	SD	iSD	No PMD	NO CLINICAL BENEFIT	0	309	0	309
32	Pembrolizumab	PD	iUPD	PMD	NO CLINICAL BENEFIT	PD	iUPD	PMD	NO CLINICAL BENEFIT	1	188	0	292
32'	Ipilimumab	PD	iUPD	PMD	NO CLINICAL BENEFIT	PD	NA	PMD	NO CLINICAL BENEFIT	0	120	0	120
33	Ipilimumab	PD	iUPD	PMD	NO CLINICAL BENEFIT	PD	iSD	PMD	NO CLINICAL BENEFIT	0	1483	0	1483
34	Pembrolizumab	NA	NA	CMR	NA	NA	NA	CMR	NA	0	370	0	370
35	Pembrolizumab	SD	iSD	SMD	NO CLINICAL BENEFIT	SD	iSD	SMD	NO CLINICAL BENEFIT	0	868	0	868
36	Nivolumab	PD	iUPD	PMD	NO CLINICAL BENEFIT	PD	iUPD	PMD	NO CLINICAL BENEFIT	1	222	0	222
37	Pembrolizumab	PD	iUPD	PMD	NO CLINICAL BENEFIT	PD	iCPD	PMD	NO CLINICAL BENEFIT	1	180	1	267
37'	Ipilimumab	PD	iUPD	PMD	NO CLINICAL BENEFIT	PD	iCPD	PMD	NO CLINICAL BENEFIT	1	93	1	93

CR = complete response, PR = partial response, SD = stable response, PD = progressive disease.
 iCR = immune complete response, iPR = immune partial response, iSD = immune stable disease, iCPD = immune confirmed progressive disease, iUPD = immune unconfirmed progressive disease
 CMR = complete metabolic response, PMR = partial metabolic response, SMD = stable metabolic disease, PMD = progressive metabolic disease
 NA = non-available

Maximum intensity projection (MIP) 18F-FDG PET/CT images during the course of treatment in a 67-year-old man with metastatic melanoma



A Baseline PET/CT (2 left lung nodules and 1 lower diaphragmatic node)

B Interim PET/CT (15 weeks) with progression (PD according to RECIST 1.1 and PERCIST, iUPD according to iRECIST, no clinical benefit according to PECRIT)

C Final PET/CT (19 weeks) with no confirmation of progression disease (iUPD transformed in iSD according to iRECIST)

Transaxial PET/CT images located in lungs

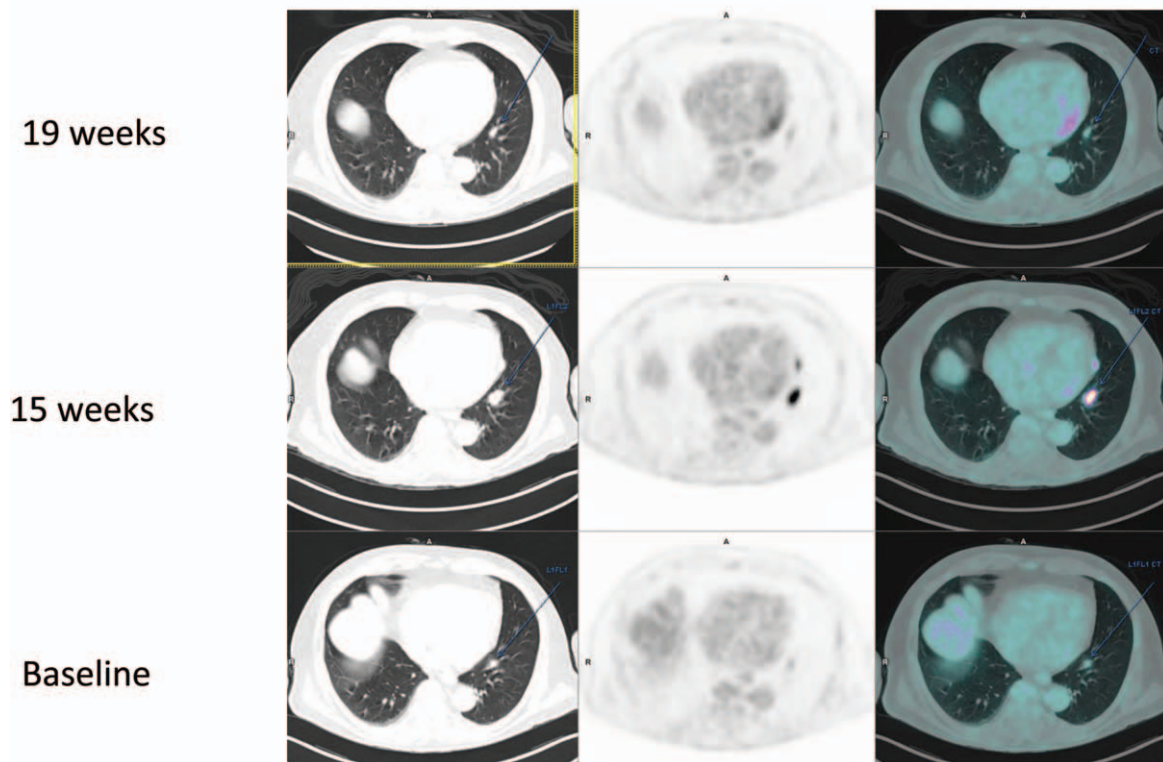


Figure 4. Maximum intensity projection (MIP) 18F-FDG PET/CT images during the course of treatment in a 67-year-old man with metastatic melanoma, A Baseline PET/CT (2 left lung nodules and 1 lower diaphragmatic node), B Interim PET/CT (15 weeks) with progression (PD according to RECIST 1.1 and PERCIST, iUPD according to iRECIST, no clinical benefit according to PECRIT), C Final PET/CT (19 weeks) with no confirmation of progression disease (iUPD transformed in iSD according to iRECIST).

Transaxial PET/CT images located in sub-phrenic node

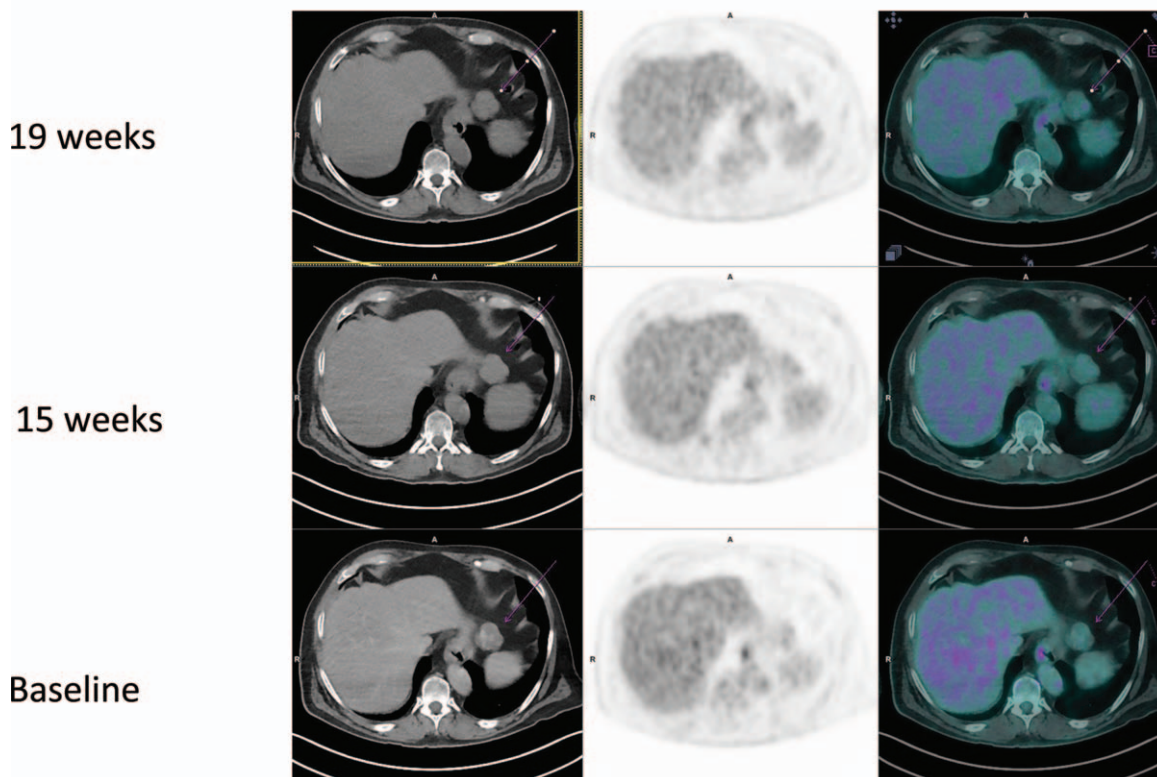


Figure 4. (Continued).

Table 4

Univariate analysis of clinico-biological factors with poor prognosis present before the beginning of treatment.

	ECOG performance status > 1	number of metastatic lesions ≥ 3	Brain metastasis
PFS (P value)	.488	.282	.257
OS (P value)	.598	.169	.094

ECOG=Eastern Cooperative Oncology Group, PFS=progression free survival, OS=overall survival.

(>3–4 weeks) assessment of ICI-response classification. These preliminary results warrant further validation in larger cohort prospective studies using an early (within 3–4 weeks) treatment assessment time-point.

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