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FOCUSSED RESEARCH REVIEW

Monitoring of patients with metastatic melanoma treated with immune checkpoint inhibitors using PET–CT

Antonia Dimitrakopoulou-Strauss[1]

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Abstract

Immune checkpoint inhibitors (ICI) have revolutionized therapy of metastatic melanoma. The first ICI was ipilimumab, a cytotoxic T lymphocyte-associated Ag 4 (CLTA-4) inhibitor with response rates of approximately 11% and disease control of 22%. The programmed cell death 1 (PD-1) inhibitors, such as pembrolizumab and nivolumab, led to longer progression-free survival and overall survival rates with fewer side effects. Molecular imaging techniques, such as positron emission tomography–computed tomography (PET–CT) with 2-deoxy-2-(^{18}F)fluoro-D-glucose (^{18}F-FDG) are in use for staging and therapy monitoring of metastatic melanoma. However, classical radiological imaging criteria such as RECIST and WHO are not appropriate for the assessment of ICI response. New immune-related criteria have been defined such as iRECIST or irRC, which refer to radiological imaging modalities. Until now only a few studies report on immunotherapy response assessment based on ^{18}F-FDG PET–CT. The classical criteria used for therapy monitoring with ^{18}F-FDG PET, such as the EORTC criteria, are not suitable for ICI monitoring. In this focussed review, we present different criteria proposed for ICI monitoring with ^{18}F-FDG and their limitations. One goal is to early identify non-responders to tailor immunotherapy. Another question is pseudoprogression and how to interpret the ^{18}F-FDG images for response assessment. Finally, the definition of ^{18}F-FDG criteria which can be used to identify progress is crucial and discussed in the review. The recent presented PET-based immune-related criteria, the so-called PERCIMT (PET Response Evaluation Criteria for IMmunoTherapy) are presented. Furthermore, new tracers are discussed.

Keywords PET · Melanoma · Immunotherapy monitoring · PIVAC 17

Abbreviations

CB	Clinical benefit
CR	Complete remission
CT	Computed tomography
CTLA-4	Cytotoxic T lymphocyte-associated Ag 4
EORTC	European Organisation for Research and Treatment of Cancer
FD	Fractal dimension
FDA	Food and Drug Administration
^{18}F-FDG	2-Deoxy-2-(^{18}F)fluoro-D-glucose
^{18}F-FLT	^{18}F-3′-Fluoro-3′-deoxythymidine
Ga-68	Gallium-68
GIST	Gastrointestinal stromal tumor
ICI	Immune checkpoint inhibitors
iCPD	Immune-related confirmed progressive disease
irAE	Immune-related adverse events
iRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
irRC	Immune-related response criteria
iUPD	Immune-related unconfirmed progressive disease
LDH	Lactate dehydrogenase
Lu-177	Lutetium-177
MAPK	Mitogen-activated protein kinase
MDSC	Myeloid-derived suppressor cells
MIP	Maximum intensity projection
MRI	Magnetic resonance imaging
mWHO	Modified World Health Organisation

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✉ Antonia Dimitrakopoulou-Strauss
a.dimitrakopoulou-strauss@dkfz.de

[1] Clinical Cooperation Unit Nuclear Medicine, German Cancer Research Center, Im Neuenheimer Feld 280, 69120 Heidelberg, Germany

NK cells	Natural killer cells
No-CB	No clinical benefit
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death 1 receptor
PERCIMT	PET Response Evaluation Criteria for Immunotherapy
PERCIST	PET Response Criteria in Solid Tumors
PET	Positron emission tomography
PFS	Progression-free survival
PMD	Progressive metabolic disease
PMR	Partial metabolic response
PR	Partial remission
RECIST	Response Evaluation Criteria in Solid Tumors
ROI	Region of interest
SD	Stable disease
SMD	Stable metabolic disease
SSTR	Somatostatin receptor
SUL	Standardized uptake value normalized for lean body mass
SUV	Standardized uptake value
TCR	T-cell receptor for Ag
TIL	Tumor-infiltrating lymphocyte
VEGF	Vascular endothelial growth factor
WHO	World Health Organisation
Y-90	Yttrium-90

Introduction

Immunotherapy

Immunotherapy and targeted therapy has dramatically changed treatment and improved overall survival of patients with advanced melanoma. The identification of gene mutations led to the distinction of subsets of patients with melanoma who can profit from dedicated drugs. The introduction of new targeted therapies, such as mitogen-activated protein kinase (MAPK) pathway kinase inhibitors, which block molecular pathways related to cellular proliferation, tumor growth, and tumor invasion revolutionized melanoma treatment. In particular, melanoma patients with BRAF mutations benefit most with a significant improvement of the therapeutic outcome and the overall survival. The combined use of a BRAF and a MEK inhibitor in BRAF mutant melanomas was a great step forward. These changes have significantly improved outcome in metastatic melanomas with an increase of at least 15 months of the median overall survival since 2011 [1]. Besides the kinase inhibitors, immune checkpoint inhibitors (ICI) have further improved therapy of metastatic melanomas (Fig. 1). The first ICI was ipilimumab, a cytotoxic T lymphocyte-associated Ag 4 (CLTA-4) inhibitor with response rates of approximately 11% and control disease of 22%. The programmed cell death 1 (PD-1) inhibitors, such as pembrolizumab and nivolumab, led to longer progression-free survival (PFS) and overall survival (OS) rates. In a phase 3 randomized study with 834 patients, the 6-month PFS for pembrolizumab was 47% vs. 26.5% for ipilimumab. The 12-month survival rates were 74% for pembrolizumab vs. 58% for ipilimumab. Overall, PD-1 inhibitors demonstrate prolonged survival and fewer side effects [2]. However, resistance to these therapies, in particular after initial response limits the long-term effect. The identification of the molecular mechanisms underlying resistance and the development of drugs or drug combinations to overcome resistance is a challenge for future treatment in this disease.

Imaging of response evaluation—general considerations

Radiological and nuclear medicine imaging modalities, such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography–computed tomography (PET–CT) are usually performed to assess the effectiveness of a cancer treatment in patients with advanced melanoma. In the era of immunological therapies, however, the classical imaging response criteria, which had been developed for morphologic imaging modalities such as CT and cytotoxic chemotherapies in solid tumors, seem not to be appropriate due to over- or underestimation of response. The reason is that changes in tumor volume or density of a metastatic lesion and/or the appearance of new metastatic lesions under immunotherapy with immune checkpoint inhibitors do not reflect response in a classical way. This is due to the fact that immunotherapy response demonstrates different response patterns such as pseudoprogression under treatment or response in appearance with new lesions. Wolchok et al. described four distinct response patterns after ipilimumab monotherapy in metastatic melanoma: (1) shrinkage in baseline lesions, without new lesions; (2) durable stable disease (in some patients followed by a slow, steady decline in total tumor burden); (3) response after an increase in total tumor burden; (4) response in the presence of new lesions. All patterns were associated with favorable survival [3].

Therefore, immunotherapy response cannot be correctly evaluated using the known ***R**esponse **E**valuation **C**riteria in Solid **T**umors* (RECIST), which assess single lesions exclusively based on measurements of the longest axial diameter as well as on the appearance of new lesions [4]. Furthermore, they distinguish between target lesions and non-target lesions as well as between new measurable and new, non-measurable lesions (Table 1). Several attempts have been undertaken and are still in progress to define immune-related response criteria. Wolchok et al. proposed a modification of

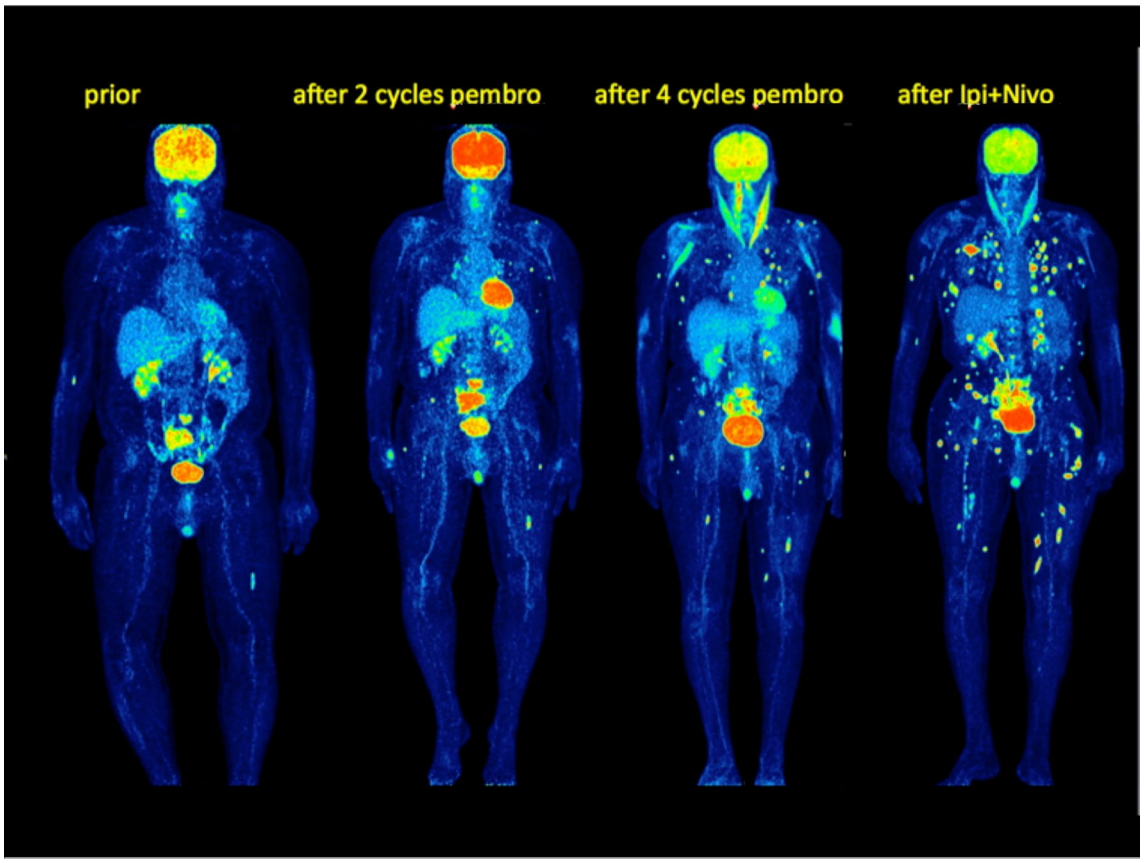

Fig. 1 Maximum Intensity Projection Images (MIP) ^{18}F-FDG PET–CT images in a patient with advanced melanoma prior to ICI, after two and four cycles of pembrolizumab and after a combined ipilimumab/nivolumab therapy. ^{18}F-FDG PET–CT clearly demonstrated progression with new lesions in every follow-up study

the WHO response criteria by introducing the two following new aspects. First, they suggested to evaluate the whole tumor volume, including new lesions and second a follow-up study at least 4 weeks after the first documentation of the tumor volume [3]. The cut-off values for response are the same as for WHO. According to these immune-related (ir) response criteria, the following response categories are defined:

irCR (complete response) is defined as complete disappearance of all lesions and no new lesions.
irPR (partial remission) is defined as decrease in tumor burden $\geq 50\%$.
irSD (stable disease) is defined by exclusion of all other response groups.
irPD (progressive disease) is defined as an increase in tumor burden $\geq 25\%$ to nadir (minimum recorded tumor burden).

In 2013, Nishino et al. published a modified version of the immune-related response criteria (irRC) [5]. These modified criteria, known as irRECIST, are similar to irRC but are based on unidimensional measurements comparable with the widely used RECIST. In contrast, irRC require bidimensional lesion measurements. A comparison between these classification systems is provided in Table 1.

Hodi et al. evaluated the proposed immune-related response criteria in comparison to the RECIST v1.1 in 655 patients with metastatic melanoma treated with pembrolizumab [6]. The authors reported that based on survival analysis, RECIST might underestimate the benefit of pembrolizumab in approximately 15% of the patients. In contrast, immune-related response criteria that permit treatment beyond initial progression per RECIST are more suitable and might prevent premature cessation of immunotherapy treatment.

In a recent publication, Seymour et al. introduced modified RECIST criteria, the so-called iRECIST, which have been defined by the RECIST working group [7]. These criteria have been proposed for radiological assessment of the response of solid tumors after immunotherapy. These newly developed criteria introduce the term unconfirmed progressive disease (iUPD). This term describes the situation, where PD is found after the end of therapy but needs

Table 1 Comparison of different response criteria [3–5, 7, 9, 10, 15]

New, measurable lesions (≥5×5 mm)	
mWHO	Always represent progressive disease
RECIST 1.1	Always represent progressive disease
irRC	Incorporated into tumor burden
irRECIST	Incorporated into tumor burden
iRECIST	iUPD, does not correspond to formal progression, is not incorporated into tumor burden
EORTC	Always represent progressive disease
PERCIST	Always represent progressive disease
PERCIMT	Progressive disease if ≥4 new lesions of less than 1 cm in functional diameter or ≥3 new lesions of more than 1.0 cm in functional diameter or ≥2 new lesions of more than 1.5 cm in functional diameter
New, non-measurable lesions (<5×5 mm)	
mWHO	Always represent progressive disease
RECIST 1.1	Always represent progressive disease
irRC	Do not define progression (but preclude immune-related response)
irRECIST	Do not define progression
iRECIST	iUPD, does not correspond to formal progression, is not incorporated into tumor burden
EORTC	Contribute to overall response classification
PERCIST	Unequivocal progression of FDG avid non-target lesions represents progressive disease
PERCIMT	Contribute to overall response classification
Non-index lesion	
mWHO	Contribute to defining immune-related complete response (complete disappearance required)
RECIST 1.1	Changes contribute to overall response classification
irRC	Incorporated into tumor burden, changes contribute to overall response classification
irRECIST	Incorporated into tumor burden, changes contribute to overall response classification
iRECIST	iUPD, does not correspond to formal progression, is not incorporated into tumor burden
EORTC	Changes contribute to overall response classification
PERCIST	Changes contribute to overall response classification
PERCIMT	Changes contribute to overall response classification
Complete response (CR)	
mWHO	Disappearance of all lesions in two consecutive observations ≥4 weeks apart
RECIST 1.1	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)
irRC	Disappearance of all lesions in two consecutive observations ≥4 weeks apart
irRECIST	Disappearance of all lesions in two consecutive observations up to 12 weeks apart
iRECIST	Disappearance of all lesions in two consecutive observations 4–8 weeks apart
EORTC	Complete resolution of ^{18}F-FDG uptake within the tumor volume. No new, ^{18}F-FDG avid lesions
PERCIST	Complete resolution of ^{18}F-FDG uptake within measurable target lesions (less than the mean liver activity and indistinguishable surrounding blood pool level). No new, ^{18}F-FDG avid lesions
PERCIMT	Complete resolution of all pre-existing ^{18}F-FDG avid lesions. No new, ^{18}F-FDG avid lesions
Partial response (PR)	
mWHO	≥50% decrease in SPD of all index lesion vs. baseline in two observations at least 4 weeks apart, in the absence of new lesions or unequivocal progression of non-index lesions
RECIST 1.1	≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
irRC	≥50% decrease in tumor burden vs. baseline in two observations at least 4 weeks apart
irRECIST	≥30% decrease in tumor burden vs. baseline in two observations up to 12 weeks apart
iRECIST	≥30% decrease in tumor burden vs. baseline in two observations 4–8 weeks apart
EORTC	Decrease in tumor SUV >25% after more than 1 therapeutic cycle or 15–25% decrease in tumor SUV after only one cycle. No new, ^{18}F-FDG avid lesions

Table 1 (continued)

PERCIST	Decrease in tumor peak SUL > 30% in the hottest target lesion. No increase in SUL > 30% in non-target lesions. No new, ^{18}F-FDG avid lesions
PERCIMT	Complete resolution of some pre-existing ^{18}F-FDG avid lesions. No new, ^{18}F-FDG avid lesions
Stable disease (SD)	
mWHO	50% decrease in SPD vs. nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)
RECIST 1.1	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. Persistence of one or more non-target lesions and /or maintenance of tumor marker level above the normal limits
irRC	50% decrease in tumor burden vs. baseline cannot be established nor 25% increase vs. nadir
irRECIST	Neither PR nor PD
iRECIST	Neither PR nor PD
EORTC	< 25% increase of tumor SUV or < 15% decrease of tumor SUV
PERCIST	Neither PMD nor PMR/CMR
PERCIMT	Neither PMD nor PMR/CMR
Progressive disease (PD)	
mWHO	≥ 25% increase in SPD vs. nadir and/or unequivocal progression of non-index lesions and /or appearance of new lesions (at any single time point)
RECIST 1.1	≥ 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Unequivocal progression of existing non-target lesions. The appearance of one or more new lesions is also considered progression
irRC	≥ 25% increase in tumor burden vs. nadir (at any single time point) in two consecutive observations at least 4 weeks apart
irRECIST	≥ 20% increase in tumor burden vs. nadir in two consecutive observations up to 12 weeks apart
iRECIST	≥ 20% increase in tumor burden vs. nadir in two consecutive observations 4–8 weeks apart
EORTC	≥ 25% increase in tumor SUV or appearance of new lesions
PERCIST	> 30% increase of tumor peak SUL in the hottest target lesion. Appearance of new FDG avid lesions.
PERCIMT	Progressive disease if ≥ 4 new lesions of less than 1 cm in functional diameter or ≥ 3 new lesions of more than 1.0 cm in functional diameter or ≥ 2 new lesions of more than 1.5 cm in functional diameter

Non-complete response/non-progressive disease is preferred over stable disease when assessing non-target lesion disease

SUL SUV lean body mass, *iUPD* immune unconfirmed progressive disease, *SPD* sum of products of the two largest perpendicular diameters

to be confirmed by re-scanning after 4–8 weeks. If PD is confirmed in the follow-up scan, the patient is considered as having confirmed progressive disease (iCPD). Most recommendations are unchanged regarding the definition of complete response (CR), stable disease (SD) and progressive disease (PD). The response criteria also distinguish between target lesions, non-target lesions, and new lesions. This guideline will allow consistent interpretation and analysis of trials of immunotherapies.

Assessment of therapeutic response with positron emission tomography–computed tomography (PET–CT)

PET–CT is being increasingly used in melanomas for staging and therapy monitoring. The most common radiopharmaceutical used for melanomas is 2-deoxy-2-(^{18}F)fluoro-D-glucose (^{18}F-FDG). ^{18}F-FDG is a glucose analog, which is transported from plasma to the cell, where it is phosphorylated and trapped, thus reflecting the intracellular glucose metabolism and consumption, and providing information about tissue metabolism. A known limitation of ^{18}F-FDG is the enhanced tracer uptake not only in cancer tissue but also in some benign diseases, such as inflammatory lesions [8]. The combination of ^{18}F-FDG PET with CT allows the comparison of functional and morphological information and is helpful for a better classification of lesions with enhanced uptake by taking into considerations also morphologic criteria. However, the development of more specific tracers is crucial for both diagnosis and therapy management. Some novel radiopharmaceuticals for melanomas are discussed in this review.

Assessment of therapeutic response with ^{18}F-FDG

It is generally accepted that ^{18}F-FDG PET–CT is more sensitive for the assessment of early therapy response than morphologic imaging modalities. Therapy assessment with ^{18}F-FDG PET–CT requires not only standardized imaging protocols but also blood glucose levels within normal range. Another important aspect which should be kept in mind is the performance of a baseline study prior to onset to therapy for comparison with the follow-up studies. The lack of a baseline study is a major limitation for the assessment of therapy response and should be avoided. In an attempt to standardize response assessment for PET studies in particular with ^{18}F-FDG and based on the literature results, response criteria have been proposed first by the European Organisation for Research and Treatment of Cancer (EORTC) in 1999 and by Wahl et al. in 2009. The EORTC criteria are based on changes in the Standardized Uptake Value (SUV), which are related to the time interval after initiation of therapy. Progressive metabolic disease (PMD) is defined as a 25% increase of SUV or the appearance of new metastatic lesions. On the other hand, partial metabolic remission (PMR) is defined as a reduction of SUV of at least 15% after one cycle or more than 25% after more than one cycles [9]. In 2009, Wahl et al. proposed the use of PET Response Criteria in Solid Tumors (PERCIST) criteria for the assessment of therapy response [10]. PERCIST introduced some new parameters for the response evaluation, such as the assessment of normal reference values in the liver as well the assessment of the SUV_{lean} (SUL) peak of a small Region of Interest (ROI) in the hottest tumor area. Furthermore, they recommended a reduction of at least 30% of the SUV_{lean} for a definition of PR, which is higher than the value proposed by the EORTC.

Monitoring of targeted therapy with ^{18}F-FDG

Response after immunotherapy with kinase inhibitors such as BRAF and MEK inhibitors can be successfully monitored with ^{18}F-FDG. A decrease in ^{18}F-FDG uptake is related to longer progression-free survival. Kraeber-Bodere et al. demonstrated a decrease in ^{18}F-FDG uptake even after one cycle of two different MEK inhibitors [11]. McArthur et al. found also an early metabolic response in ^{18}F-FDG on day 15 after vemurafenib and a homogeneous response between metastases in melanoma patients [12]. According to the existing literature data, it seems that ^{18}F-FDG monitoring of BRAF and MEK inhibitors is reliable and allows an early identification of non-responders or resistant lesions [13].

ICI monitoring with PET

Therapy monitoring after ICI treatment is challenging. As mentioned before response after immunotherapy demonstrates different response patterns and requires dedicated ^{18}F-FDG PET–CT criteria for evaluation. Sachpekidis et al. evaluated the response in 22 patients with advanced melanomas after 2 and 4 cycles of ipilimumab to assess the early and late therapeutic effects with ^{18}F-FDG PET–CT [14]. The evaluation was based on the EORTC criteria. Progression-free survival (PFS) and overall survival (OS) served as reference. Early PET predicted 13/15 patients with PMD (progressive metabolic disease), 5/5 with SMD (stable metabolic disease) and none of the two patients with PMR (partial metabolic response) due to pseudoprogression after the second cycle. Patients with late PMD demonstrated a shorter PFS and OS (median PFS 3.6 months, median OS 9.1 months) as compared to SMD (median PFS 9.8 months, median OS 9.8 months). The difference in PFS and OS between two groups was statistically significant for both early and late PET response.

Anwar et al. studied 41 patients with advanced melanomas prior ipilimumab immunotherapy and after the end of four cycles with ^{18}F-FDG PET–CT [15]. The authors found that the absolute number of new lesions is a better parameter for prediction of immunotherapy response than changes in SUV. The patients had been dichotomized into those with clinical benefit (CB) and those without CB (No-CB). The CB group included 31 patients with SD, PR, and CR. The No-CB group included ten patients with PD. The application of a threshold of four newly emerged lesions of any size led to a sensitivity of 84% (correct prediction of CB) and a specificity of 100% (correct prediction of No-CB). The cut-off was lower for the lesions with a larger functional diameter. Three new lesions larger than 1 cm or two new lesions larger than 1.5 cm were associated with No-CB (Table 1). Based on these data, the authors defined criteria for predicting clinical response to immunotherapy for ^{18}F-FDG PET–CT, the so-called PET Response Evaluation Criteria for Immunotherapy, (PERCIMT).

Ribas et al. studied 12 patients with advanced melanoma with ^{18}F-FDG and ^{18}F-FLT at baseline and 2 months after therapy with tremelimumab, a CTLA4-blocking antibody [16]. They found that SUV changes in both ^{18}F-FDG and ^{18}F-FLT in metastases were not significantly different. Significant increase was only noted in ^{18}F-FLT for the spleen. They concluded that changes in SUV were not reliable for response assessment.

Cho et al. evaluated 20 patients before, during and after completion of different therapies with immune checkpoint inhibitors with ^{18}F-FDG PET–CT [17]. Tumor response was evaluated by RECIST 1.1, immune-related response criteria, PERCIST 1.0 and EORTC criteria. Their results

demonstrated that best PERCIST and EORTC threshold values were changes of more than 15.5% and 14.7% in the interim scan, respectively. Their analyses demonstrated that the combination of both morphological and metabolic findings yielded the highest sensitivity (100%), specificity (93%) and overall accuracy (95%). They suggested a cut-off of 15.5% increase in SULpeak of the hottest lesion as a cut-off value to differentiate between patients with CB and those without CB, provided that there were no new developed lesions. A prerequisite for the application of these criteria is a fully diagnostic CT additionally to ^{18}F-FDG and the use of the hottest lesion as an indicator of the whole therapy response.

Overall, the existing data give evidence for a useful role of ^{18}F-FDG PET–CT for ICI monitoring. ^{18}F-FDG may reflect both viable tumor tissue as well as inflammatory reactions and irAE following ICI treatment. However, in particular, the increase of the number of new lesions even early after onset of treatment, e.g., after two cycles seems to correlate with the therapeutic outcome. A late follow-up study, e.g., after four cycles is recommended to exclude pseudoprogression. More studies in larger patient cohorts are needed to validate the role of early ^{18}F-FDG PET–CT imaging in ICI monitoring.

Experimental approaches

Breki et al. used a non-compartmental approach to evaluate the therapeutic outcome in 31 patients with advanced melanoma who received ipilimumab treatment and underwent longitudinal ^{18}F-FDG PET/CT studies [18]. The authors applied a fractal and multifractal analysis based on the box-counting method and calculated the fractal dimension (FD) in follow-up. They could demonstrate that a decrease of FD in follow-up was related to disease progression. The reference in this analysis was the clinical outcome. 20/24 patients could be correctly classified based on the changes of FD. Seven patients with non-tumor-related findings (such as colitis or other unspecific changes) were misclassified. These preliminary results demonstrate a new approach, which is operator independent and may be helpful in a multiparametric evaluation of tumor response.

Visualization of side effects

Therapy with immune checkpoint inhibitors such as CTLA-4 inhibitors as well as PD-1 inhibitors is associated by several side effects, which have to be managed. These are referred to as immune-related adverse events (irAE). They include enterocolitis, hepatitis, pneumonitis, dermatitis, endocrine toxicities (such as thyroiditis, hypophysitis), neuropathies, arthralgia, ocular toxicities and other symptoms [19]. The reported rates of IRAE vary from 10 to 80% for ipilimumab, nivolumab and pembrolizumab. This is related to different classification criteria used across different studies and different terminology, such as "treatment-related" or "immune-mediated" or more than one category. In a review of Yoest, it is stated that irAE rates are higher for CTLA-4 inhibitors, followed by PD-1 inhibitors, followed by a combination of both [20]. Furthermore, it has been hypothesized that the presence of irAE may be a good prognostic sign for the response, but this is still open. Own unpublished data demonstrate a relation between "sarcoid-like lymphadenopathy" in the mediastinum and response to ICI. Some of these side effects can be visualized in ^{18}F-FDG very well (Figs. 2, 3). This is in accordance to Mekki et al., who reported irAE detected by imaging in 74% of patients treated with PD-1 inhibitors [21].

Biomarkers for immune checkpoint inhibitor (ICI) monitoring

Different biomarkers have been used for monitoring ICI therapy. Recently, Jessurun et al. provided a systematic review on this topic and emphasized that blood and genomic biomarkers are in use for CTLA-4 inhibitors, while tumor tissue markers are analyzed for both CTLA-4 and PD-1 inhibitors [22]. Blood cytology markers include myeloid-derived suppressor cells (MDSC), natural killer (NK) cells, whereas soluble blood factors include S100, circulating

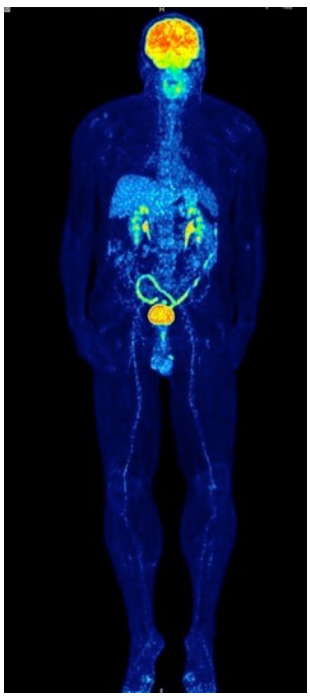

Fig. 2 MIP image of a patient with colitis in ^{18}F-FDG following ipilimumab treatment. Note the enhanced ^{18}F-FDG uptake in the colon descendens, sigmoid and rectum

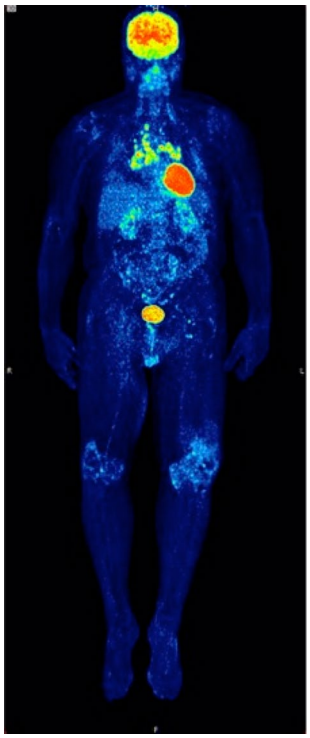

Fig. 3 MIP image of a patient with sarcoidosis (histologically proven) and arthralgia following pembrolizumab therapy. Note the symmetrical enhanced ^{18}F-FDG uptake in mediastinal lymph nodes and the enhanced ^{18}F-FDG uptake in both knees

DNA, vascular endothelial growth factor (VEGF), C-reactive protein as well as lactate dehydrogenase (LDH). Blood cytology factors correlated to overall survival and this may indicate their prognostic value. Other important biomarkers, which require tumor tissue analysis, are mutational load, neoantigen load, immune-related gene expression as well as $CD8^+$ T-cell infiltration at the margins. Interestingly, the predictive value of PD-L1, the best studied biomarker, varied, possibly due to the influence of T-cell infiltration on PD-L1 expression. Overall, the data of this review demonstrate that there is no preference for a single predictive biomarker at the moment. Another explanation for the limited value of PD-L1 as a predictive biomarker may be the abundance of PD-L1 antibodies and assays used as well as the different scoring systems and thresholds as presented in a review paper from Sacher and Gandhi [23]. The heterogeneity in PD-L1 expression between serial section fields of tumor tissue as well as the dynamic nature of PD-L1 expression over time in response to chemotherapy or radiation therapy may be another limiting factor for a reliable use as a biomarker.

Novel imaging biomarkers for PET

More specific tracers than ^{18}F-FDG are necessary to improve ICI monitoring with PET. In an experimental approach, Mayer et al. labeled different PD1 ligands with Cu-64 and Ga-68 [24]. They optimized a high-affinity consensus (HAC) PD1 for in vivo imaging of PD-L1 expression. The authors report that all HAC-PD1 radiolabelled variants enabled detection of human PD-L1 expression in a preclinical model with subcutaneous tumors engineered to be either positive or negative for human PD-L1 expression. Another more experimental approach is the use of T-cell imaging. In experimental studies, labeling of general T-cell markers such as CD4 and CD8 or murine monoclonal T-cell receptors (TCR) have been used. Natarajan et al. presented a new tracer to image human PD-1 expression on tumor-infiltrating lymphocytes (TIL) in a humanized mouse model. They labeled pembrolizumab with Zr-89 and Cu-64 and studied NSG mice bearing A375 human skin melanoma. The authors could demonstrate specific targeting of human PD-1-expressing TIL's homing in tumor and spleen in NSG-not blocked mice as compared to control mice, which indicates successful engraftment [25].

Tavare et al. presented a novel approach to study T-lymphocytes in vivo by anti-CD4 and anti-CD8 cys-diabodies (cDbs) derived from the parenteral hybridomas GK1.5 and 2.43, respectively [26]. The idea is to visualize helper and cytotoxic T-cells after labeling with ^{89}Zr via PET. Experimental studies in mice and biodistribution studies demonstrated targeting and visualization of CD4 and CD8 cDbs in the spleen and lymph nodes of wild-type mice as well as in a murine model of hematopoietic stem cell transplantation. An imaging technology based on T-cell receptor (TCR)—transgenic T-cell tracking is described in another study by Mall et al. [27]. This work supports the translation of such tracers for ICI monitoring in patients.

General considerations and conclusions

Conventional morphological criteria based on changes in tumor size such as RECIST do not seem to be adequate for immunotherapy response assessment. New response criteria, such as immune-related response criteria, iRECIST and irRC, have been proposed for radiological assessment. Similar attempts are undertaken for the evaluation of ^{18}F-FDG PET–CT studies, such as the PERCIMT criteria. Larger studies are necessary to evaluate the impact of these criteria. New imaging biomarkers, more specific than ^{18}F-FDG, are required to improve ICI monitoring in melanoma patients. These biomarkers should allow an early identification of resistance to therapy and ideally even the underlying resistance mechanism. Furthermore, they should provide a better selection of patients by identifying the best drug combination on an individual patient basis.

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Compliance with ethical standards

Conflict of interest The author declares that she has no conflict of interest.

Ethical approval Not applicable. This is a review and not an original paper.

Informed consent Not applicable. This is a review and not an original paper. All patients agreed on the publication of their images.

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