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**Evaluation of response to immune checkpoints inhibitors: Is there a role for positron emission tomography?**

Bauckneht M *et al*. Immune checkpoints inhibitors and PET

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**Abstract**

Strategies targeting intracellular negative regulators such as immune checkpoints inhibitors (ICPIs) have demonstrated significant antitumor activity across a wide range of solid tumors. In the clinical practice, the radiological effect of immunotherapeutic agents has raised several more relevant and complex challenges for the determination of their imaging-based response at single patient level. Accordingly, it has been suggested that the conventional Response Evaluation Criteria in Solid Tumors assessment alone, based on dimensional evaluation provided by computed tomography (CT), tend to underestimate the benefit of ICPIs at least in a subset of patients, supporting the need of immune-related response criteria. Differently from CT, very few data are available for the evaluation of immunotherapy by means of 18F-Fluoro-2-Deoxy-D-Glucose positron emission tomography (FDG-PET). Moreover, being the antineoplastic activity of ICPIs highly related to the activation of T cells against cancer cells, FDG accumulation might cause false positive findings. Yet, discrimination between benign and malignant processes represents a huge challenge for FDG PET in this clinical setting. Consequently, it might be of high interest to test the complex and variegate response to ICPIs by means of PET and thus it is worthwhile to ask if a similar introduction of immune-related PET-based criteria could be proposed in the future. Finally, PET might offer new insight into the biology and pathophysiology of ICPIs thanks to a growing number of non-invasive immune-diagnostic approaches based on non-FDG tracers.

**Key words:** Immune checkpoints inhibitors; Positron emission tomography; Computed tomography; 18F-Fluoro-2-Deoxy-D-Glucose; Non-18F-Fluoro-2-Deoxy-D-Glucose tracers

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**Core tip:** In the clinical practice, the radiological interpretation of immunotherapy effects represents a huge challenge at single patient level. However, if the computed tomography-based response evaluation for immune checkpoints inhibitors (ICPIs) is feasible thanks to the introduction of immune-related response criteria, very few data are available for the potential role of 18F-Fluoro-2-Deoxy-D-Glucose positron emission tomography (FDG-PET). Due to the intrinsic nature of FDG accumulation pathophysiology, it might be central to test the complex and variegated response to ICPIs by means of PET. Finally, PET might offer new insight into the biology of ICPIs thanks to a growing number of non-invasive immune-diagnostic approaches based on non-FDG tracers.

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**TEXT**

Immune system function is characterized by multiple checkpoints aiming to avoid its over-activation against healthy cells (self-tolerance)[1]. Cancer cells may take advantage of these checkpoints to escape detection by the immune system. Some of these checkpoints such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) have been extensively studied as targets in the frame of the so-called cancer immunotherapy[1]. CTLA4 counteracts the activity of the T cell co-stimulatory receptor CD28 and actively delivers inhibitory signals to the T cell[2]. By contrast PD-1 has two ligands, PD1 ligand 1 (PDL1) and PDL2 and its inhibitory effect is accomplished through a dual mechanism of promoting apoptosis in antigen specific T-cells in lymph nodes, while simultaneously reducing apoptosis in regulatory T cells (suppressor T cells)[3]. In the last few years, the blockade of immune checkpoints has disclosed the potential of the antitumor immune response in a fashion that is transforming human cancer therapeutics. CTLA4 antibodies such as ipilimumab and tremelimumab have been tested in the last ten years in different types of cancer, starting with patients with advanced melanoma[4]. Ipilimumab was the first therapy to demonstrate a survival benefit for patients with metastatic melanoma. In the study by Hodi *et al*[5], ipilimumab significantly improved overall survival in patients with previously treated metastatic melanoma and the drug was approved by the United States Food and Drug Administration (FDA) for the treatment of advanced melanoma in 2011[5]. Similarly, Nivolumab, a humanized anti-PD-1 monoclonal antibody, has demonstrated durable responses in the contest of several Phase III trials and has received FDA approval in specific clinical settings in patients with melanoma, renal cell cancer, Hodgkin’s lymphoma, bladder cancer and Non-small cell lung cancer (NSCLC)[6-9]. Figure 1 summarizes the mechanisms of action of the two FDA approved immune checkpoints inhibitors(ICPIs)*.*

***Evaluation of response to ICPIs***

Historically Response Evaluation Criteria in Solid Tumors (RECIST) has been validated and used to evaluate antitumor responses to chemotherapeutic agents[10] (Table 1 for a more detailed description). These criteria are based of dimensional evaluation and rely on the fact that the cytotoxic effect of chemotherapeutic agents tends to translate into measurable effects in terms of tumor shrinkage from baseline. Furthermore published studies indicated that achieving a response according to RECIST criteria is predictive of remission and improved survival in specific settings[11]. Conversely, both RECIST and their revised 1.1 version assumed that an early increase in tumor growth and/or the appearance of new lesions correspond to progressive disease (PD), testifying drug failure and indicating the need ongoing treatment cessation[10].

Some exceptions for the use of these criteria has been already suggested in patients treated with target therapies such as tyrosine kinase inhibitors as in this group of patients the lack of tumor shrinkage in presence of a stable disease has been identified as a potential surrogate end point for improved clinical outcome[12]. However, in the clinical practice, the radiological effect of immunotherapeutic agents has raised several more relevant and complex challenges for the determination of their imaging-based response at single patient level[13]. In published studies, while some patients have responded to ICPIs with the expected tumor shrinkage (chemio-like response) or with a stable disease (target therapy-like response), other distinct immune-related patterns of response have been identified. In particular, initial increase in tumor size, development of new lesions and then a delayed objective response were also observed in patients treated with immunotherapeutic agents[13]. Specifically, in some patients, the initial increase in total tumor burden was proven to be due to inflammatory cell infiltrates by means of biopsy. In these patients the initial pseudo-progression was followed by a decrease in tumor burden or even disease regression.

As RECIST criteria were not suitable to catch these atypical responses, the so-called immune-related response criteria (irRC) have been proposed to provide more rigorous characterization of all patterns of response observed in the phase II development program for ipilimumab in melanoma[13-15] (Table 1). The main differences between RECIST 1.1 and irRC criteria rely on the fact that, according to irRC, appearance of new lesions (PD with RECIST criteria) will only result in progressive disease in case of a significant (≥ 25%) increase in total tumor burden with respect to baseline. Moreover, differently from conventional criteria, if irRC-based PD is evident, it requires further confirmation after one month with the aim of capturing delayed response.

Recently Hodi *et al*[16], evaluated atypical response patterns and reported the overall survival data in correlation with irRC and RECIST criteria in the context of a retrospective analysis of 327 melanoma patients treated with the PD-1 inhibitor pembrolizumab. This study indicated that the conventional RECIST assessment alone tends to underestimate the benefit of PD-1 inhibitor therapy in a subset of patients, supporting a need of immune-related response evaluation[16]. IrRC are thus increasingly proposed but they have not been validated yet in the context of clinical trials and most trials involving ICPIs continue to use RECIST1.1 to obtain standardized endpoints for regulatory approvals[15].

However, despite the irRC seem better than RECIST, the former have some limitations. The irRC use the bidimensional measurements in line with WHO criteria now rarely used in clinical trials because replaced by the unidimensional measurement of the larger axis of target lesions (RECIST 1.0 and 1.1). The bidimensional measurements introduce a greater variability than unidimensional measurements and make it difficult to compare the responses with studies using RECIST criteria.

***Is there a role for 18F-Fluoro-2-Deoxy-D-Glucose positron emission tomography in the evaluation of ICPIs?***

While optimal CT-based response criteria for ICPIs are in the path of their identification, very few data are available for the evaluation of immunotherapy by means of 18F-Fluoro-2-Deoxy-D-Glucose positron emission tomography (FDG-PET), one of the most used imaging techniques in oncology. 18F-FDG PET is currently the most widely used molecular imaging agent in the clinical practice for staging and restaging of several cancer. 18F-FDG PET is clinically indicated before and after treatment in patients with Hodgkin’s lymphoma and NSCLC and it is used in patients with melanoma for specific clinical indications[17-19]. The use of 18F-FDG PET in the post-treatment settings is based on the assumption that tumor size changes are only the final step in a sequence of complex metabolic and functional processes during and after treatment[20]. Two different types of criteria have been proposed for the identification of 18F-FDG PET-based response in solid tumors: the European Organization for Research and Treatment of Cancer (EORTC) and the PET Response Criteria in Solid Tumors (PERCIST) criteria[21,22], Table 1. Both criteria target the most metabolically active part of patient’s tumor burden, which is regarded as the most viable and aggressive disease site. In both case the so-called standardize uptake value (SUV) is measured at baseline and after treatment. However, they differ for some relevant aspects. The EORTC criteria were published in 1999 and are based on the evaluation of a lesion-specific regions of interest (ROIs) chosen as the most 18F-FDG–avid at baseline and followed in the after treatment scans[22]. PERCIST was proposed in 2009 by Wahl *et al*[21] and relies on the use of a 1cm3 ROI on the most 18F-FDG–avid part of the single most metabolically active lesion at each PET/CT scan (which is not necessarily located in the same lesion in all scans).

Relatively few papers have compared the two methods in solid tumors and good agreement, similar responses and survival outcomes have been highlighted in the available studies[23]. However for EORTC criteria, no recommendations on the number of target lesions or on whether computing SUV max or average SUV for response calculation are given while PERCIST recommends the use of lean body mass for SUV normalization (SUL). In this framework, some studies have demonstrated a higher accuracy with respect to RECIST for both metabolic response based criteria in patients treated with target therapies such as Erlotinib. This finding is due to the relative lower tumor-shrinkage characterizing these type of treatment[24]. Similarly, an 18F-FDG PET-based five-point scale (5-PS) the so-called Deauville criteria has been demonstrated superior to CT-based response to score images in the assessment of response at mid- and end of treatment in HD patients[18]. Again these findings testify that functional changes always precede morphological changes in the course of pathological processes. In this line it might be of interest to test the complex and variegated response to ICPIs by means of PET-based criteria. In fact, on one side functional imaging may capture different features of treatment with ICPIs in terms of entity and time course of response. On the other hand, it has been reported that the initial increase in tumor size, later followed by tumor volume reduction in part of the patients treated with ICPIs, is due to inflammatory cell infiltrates. Accordingly, given the well know high metabolic activity characterizing inflammatory cells, this feature may also hamper the evaluation of 18F-FDG PET-based response to ICPIs. Sachpekidis *et al*[20] evaluated the role of 18F-FDG PET/CT after two cycles of ipilimumab in predicting the final response to therapy in 22 patients with metastatic melanoma. Authors evaluated response to treatment by means of EORTC criteria and found that 18F-FDG PET/CT after two cycles of Ipilimumab is predictive of the final treatment outcome in patients with progressive metabolic disease and stable metabolic disease[20]. However, two patients were initially falsely classified as early SMD, but they later demonstrated new metastatic lesions, “upgrading” them to late PMD. Similarly, early evaluation by means of 18F-FDG PET did not identified responders to treatment as the two patients eventually characterized as PMR were initially classified as early PMD due to new lesions[20]. In fact, both RECIST 1.1 and PET-based criteria consider the identification of new (metabolically active) lesions as progressive disease. Therefore, presently proposed PET-based metabolic criteria suffer of at least one of the same limitations that have resulted in the underestimation of response to treatment to ICPIs by means of RECIST 1.1. Similarly, in the phase 2 study by Younes *et al*[9], nivolumab resulted in frequent responses in patients with classical Hodgkin’s lymphoma after failure of ASCT and Brentuximab vedotin. Most of these responses were maintained through the reported follow-up period with an acceptable safety profile. In this study 18F-FDG PET was performed at baseline and at weeks 17 and 25. A negative 18F-FDG PET scan, visually assessed by an independent radiological review committee (IRRC), 19 was required for confirmation of complete remission. The study demonstrated a general reduction of tumor burden. Yet discordance in complete remission between IRRC and investigator assessments was largely based on the interpretation of ¹⁸F-FDG PET scans and standardized uptake values were not collected as part of this study. The vast majority of other available data on the potential utility of 18F-FDG PET after ICPIs are case reports more often describing underlying challenges of monitoring radiologic response in these patients and showing 18F-FDG PET features of inflammatory reactions. PET-highlighted autoimmune pancolitis, splenic sarcoidosis-like lesion and exacerbation of sarcoidosis as a potential confounder in the assessment of tumor response in a melanoma patient treated with ipilimumab have all been described[25-27]. Similarly, Koo *et al*[26] illustrated a series of inflammatory reactions with avid FDG uptake in patients treated with ipilimumab, including thyroiditis, hypophysitis, granulomatous inflammation in the lymph nodes and skin and enterocolitis.

Accordingly, the potential and challenges of 18F-FDG PET imaging in the evaluation of patients treated with ICPIs still need to be clarified and deeply addressed. Given the relatively greater experience of CT-based evaluation in this setting and the fact that irRC CT-based criteria seem to better capture response to ICPIs, it is worthwhile to ask if a similar modification of PET-based criteria could be proposed in the future.

***Potential new PET-based approaches to evaluate the effect of ICPIs***

As mentioned, due to its intrinsic nature, 18F-FDG PET displays not only cancer cell’s metabolic activity but also inflammation. Being the antineoplastic activity of ICPIs highly related to the activation of T cells against cancer cells, 18F-FDG accumulation might cause false positive findings. Yet, discrimination between benign and malignant processes represents a huge challenge for 18F-FDG PET in this clinical setting. Together with the need of the clinicians to discriminate between responders and non-responders, allowing individual therapy optimization and avoiding adverse effects brought about by ineffective therapy, several studies have been recently conducted to explore the possible role of non-FDG radiotracers in the field of ICPIs. These studies, mainly performed with labeled monoclonal antibodies, contributed to open the new era of the so-called “Immuno-PET”. Accordingly, in 2014, Higashikawa *et al*[28] developed a molecular imaging probe able to evaluate CTLA-4 expression prior to CTLA-4-targeted in cancer. This 64Cu labeled radiotracer is basically composed by DOTA protein together with a CTLA-4 specific antibody and is able to display CTLA-4 expression in vivo. Similarly, specific experimental radiotracers were proposed for the visualization of PD-1 and PD-L1 cellular expression[29-32]. Maute *et al*[29] measured PD-L1 expression radiolabeling with 64Cu a PD-L1 high affinity protein (HAC) and tested its feasibility in a living mouse, while Hettich *et al*[30] developed two 64Cu labeled immunoPET tracers for imaging of both PD-1 and PD-L1. Also one SPECT study with radiolabeled anti-murine PD-L1 in mice has been conducted[32]. More recently, a 89Zr labeled CD3 PET imaging agent was proposed by Larimer *et al*[33]. CD3 is a part of the TCR complex that serves as a global T lymphocyte marker. By serving as a marker of total T-Cell infiltration, CD3 may represent a more direct approach than pre-treatment biopsy or genetic screening to monitoring tumor immune response, by directly examining active recruitment of T cells responsible for cancer cell-death. In this study the authors showed that CD3 PET imaging revealed two distinct groups of mice, stratified by PET signal intensity. While high-CD3 PET uptake was correlated with subsequent reduced tumor volume, low uptake was predictive of suboptimal response. Altogether these non-invasive approaches allow simultaneous imaging of the entire cancer mass and associated metastases, which may differ from the primary tumor in CTLA-4, PD-1 or PD-L1 expression status. Immune-imaging can be used for repeated assessment of the same tumor at different time points (*e.g.*, before and after treatment), thereby yielding a richer set of diagnostic information that would be difficult or impossible to achieve with traditional approaches. Furthermore, although further investigations are needed before their potential introduction in the clinical setting, these non-invasive immune-diagnostic approaches might yield novel insights into the biology and pathophysiological importance of ICPIs as cancer therapeutic.

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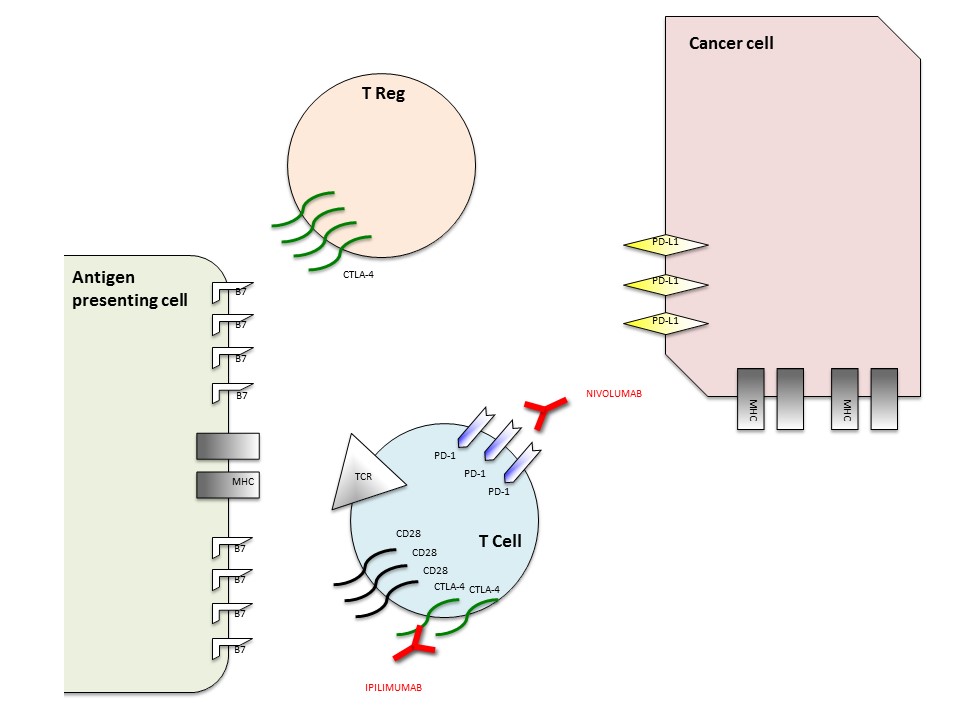
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**Figure 1 Schematic representation of mechanism of action of Nivolumab and Ipilimumab, two Food and Drug Administration approved immune checkpoints inhibitors.** To prevent autoimmunity, numerous checkpoint pathways regulate the activation of T cells at multiple steps (process known as peripheral tolerance). Central in this process are the Cytotoxic T-Limphocyte-Associated Antigen 4 (CTLA-4) and Programmed Death 1 (PD-1) immune checkpoints pathways. CTLA-4 is potentially able to stop autoreactive T cells at the initial stage of naive T-cell activation, typically in lymph nodes, while PD-1 regulates previously actived T cells at the later stages of an immune response in the peripheral tissues. The binding between T-Cell Receptor (TCR), which is expressed on T cell surface, with Major Histocompatibility Complex (MHC) expressed on Antigen Presenting Cells (APC) provide specificity to T-cell activation. However, T cell activation requires more than one stimulatory signals. Among them a central role is played by the binding between B7 molecules (APC) with CD28 (T-Cell). CTLA-4 is a CD28 homolog which does not produce a stimulatory signal but inhibits TCR-MHC binding and thus the T-Cell activation. Differently from T-Cells in which the amount of CTLA-4 is low, T-Regs highly express CTLA-4. In these cells CTLA-4 might play a role in their suppressive functions. PD-1 is a member of the B7/CD38 family of protein, which is able to bind with two different ligands: Programmed Death Ligand 1 (PD-L1) and Programmed Death Ligand 2 (PD-L2). PD-1 activation in a T-Cell prevents the phosphorylation of key TCR signaling intermediates and thus T-Cell activation resulting in suboptimal control of infections and cancers. Therefore, even though they act on different phases of T-Cells activation, the negative effect of PD-1 and CTLA-4 on T-Cell’s activity are similar. Moreover, differently from CTLA-4, PD-1 expression is not peculiar of T-Cells, but can be observed also in B-Cells and myeloid cells. The rationale for immune checkpoint inhibition (represented in red) for cancer treatment is that CTLA-4 and PD1 pathways are strictly related to cancer survival and thus targeting these molecules or their ligands with monoclonal antibodies permits to impact on cancer growth. Therefore, even if the exact mechanism of action of these monoclonal antibodies in the antitumor response remains unclear, several research data suggest that it is at least partially related to an activation and proliferation of T-Cells regardless TCR specificity (due to the inhibition of the inhibitory activity of these checkpoints), which enhances the anti-cancer immune reaction.

**Table 1 Key features of positron emission tomography Response Criteria in Solid Tumors, European Organization for Research and Treatment of Cancer 1999, Response Evaluation Criteria in Solid Tumors 1.1 and immune related Response Criteria**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  |  |  |
| **Category** | **PERCIST** | **EORTC 1999** | **RECIST 1.1** | **irRC** |
| **Target lesions** | The hottest single tumor lesion (SUL peak) at baseline | The most 18F-FDG-avid lesions (SUV BSA). Number of lesions not specified. | Maximum, 5 | Maximum, 15 lesions |
|  | 18F-FDG PET |  |  |  |
| **New lesion** | Results in progressive disease at first appearance | Results in progressive disease at first appearance | Results in progressive disease at first appearance | Up to 10 new visceral and 5 cutaneous lesions |
|  |  |  |  | may be added to the sum of the products of the two largest |
|  |  |  |  | perpendicular diameters of all index lesions at any time point |
| **Complete response** | **CMR**: complete resolution of 18F-FDG uptake within the | **CMR**: complete absence of 18F-FDG uptake | Disappearance of all target and nontarget lesions | |
|  | target lesion (< mean liver activity and indistinguishable from |  | Nodes must regress to < 10 mm short axis | |
|  | background/bloodpool and no new 18F-FDG-avid lesions) |  | No new lesions |  |
|  |  |  | Confirmation required |  |
| **Partial Response** | **PMR**: reduction of a minimum of 30% in the target tumor 18F- | **PMR**: Decrease in SUV > 25% | ≥ 30% decrease in tumor burden compared to baseline | ≥ 50% decrease in tumor burden compared with baseline1 |
|  | FDG SUL peak |  | Confirmation required | Confirmation required |
| **Progressive Disease** | **PMD**: a 30% increase in 18F-FDG SUL peak or advent of new 18F- | **PMD**: increase in SUV > 25 or appearance of new lesions | ≥ 20% + 5 mm absolute increase in tumor burden compared | ≥ 25% increase in tumor burden compared with baseline, |
|  | FDG-avid lesions |  | with nadir | nadir or reset baseline1 |
|  |  |  | Appearance of new lesions or progression of nontarget lesions | New lesions added to tumor burden |
|  |  |  |  | Confirmation required |
| **Stable Disease** | **SMD**: Disease other than CMR, PMR or PMD | **SMD:** Increase in SUV < 25% or decrease in SUV < 15% | Neither partial response nor progressive disease | |
|  |  |  |  |  |

1If an increase in tumor burden is observed at the first scheduled assessment, the baseline is reset to the value observed at the first assessment. PERCIST: PET Response Criteria in Solid Tumors; EORTC: European Organization for Research and Treatment of Cancer; RECIST: Response Evaluation Criteria in Solid Tumors; irRC: Immune related Response Criteria; CMR: Complete metabolic response; PMR: Partial metabolic response; PMD: Progressive metabolic disease; SMD: Stable metabolic disease; SUL: SUV normalized to lean body mass; SUV BSA: SUV normalized for body surface area.