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► To cite this version:

Guillaume Manson, Amaeshi Chukwunonye Lemchukwu, Fatima-Zohra Mokrane, Egesta Lopci, Nicolas Aide, et al.. Interpretation of 2-[F-18]FDG PET/CT in Hodgkin lymphoma patients treated with immune checkpoint inhibitors. *European Radiology*, 2022, 32, pp.6536-6544. 10.1007/s00330-022-08669-8 . hal-03665222

HAL Id: hal-03665222

<https://hal.science/hal-03665222>

Submitted on 30 Sep 2022

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Interpretation of 2-[F-18]FDG PET/CT in Hodgkin lymphoma patients treated with immune checkpoint inhibitors

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Abstract:

The development of immunotherapy has revolutionized cancer treatment, improving the outcome and survival of many patients. Immune checkpoint inhibitors (ICI), the most common form of immunotherapy, use antibodies to restore T-cells' anti-tumor activity. Immune checkpoint inhibitors are gaining ground in the therapeutic strategy across various cancers. Although widely used in solid tumors, ICIs have shown remarkable efficacy in patients with Hodgkin lymphoma. $2\text{-}^{18}\text{F}$ -Fluoro- 2-deoxy-D- glucose (FDG)-positron emission tomography (PET) /CT is the gold standard to stage and monitor responses in Hodgkin lymphoma. This article reviewed the use of $2\text{-}^{18}\text{F}$ -FDG-PET/CT in patients with Hodgkin lymphoma treated with ICI, focusing on image interpretation for response monitoring and detecting adverse events.

Keywords: Hodgkin lymphoma, immunotherapy, immune checkpoint inhibitors, PET, pseudoprogression, indeterminate response

Key points:

1/ Immune checkpoint inhibitors have dramatically improved the outcome of patients with cancer. Their mechanisms of action induce inflammatory processes that might translate into a high ~~2-[¹⁸F]FDG~~ ~~[¹⁸F]-FDG~~ uptake visible on ~~2-[¹⁸F]FDG-PET/CT~~ ~~[¹⁸F]-FDG-PET/CT~~, requiring an adaptation of the evaluation criteria,

2/PET readers should be aware of new patterns of response observed with immunotherapy in assessing treatment response in HL patients.

3/ Non-tumoral inflammatory events require more interaction between physicians and PET readers, through multi-disciplinary meetings

4/ ~~2-[¹⁸F]FDG-PET/CT~~ ~~[¹⁸F]-FDG-PET/CT~~ has an unparalleled ability of assessing tumour response, visualizing signs of immune activation as well as immune-related adverse events in a one-stop-shop examination

List of abbreviations and acronyms

Abs: Antibodies

BLR: Bone marrow to liver ratio

CR: complete response

CTLA4: Cytotoxic T-lymphocyte-associated protein 4

HL: Hodgkin lymphoma

HPD: Hyperprogressive disease

ICI: Immune checkpoint inhibitor

IR: Indeterminate response

IRAEs: Immune-related adverse events

LYRIC: Lymphoma Response to Immunomodulatory therapy Criteria

PD: Progressive disease

PD1: Programmed cell death 1

PR: Partial response

R/R: Relapsing/refractory

SD: Stable disease

SLR: Spleen to liver ratio

SUV: Standardized uptake value

TBP: Treatment beyond progression

Introduction

Immune checkpoint inhibitors (ICI), namely anti-PD1 antibodies, have shown great effectiveness in patients with relapsed or refractory classical Hodgkin Lymphoma (R/R HL). Presently, the FDA approved two anti-PD1 antibodies, nivolumab, and pembrolizumab to treat patients with refractory HL or who have relapsed after three or more prior lines of therapy. Despite the high response rate, most patients treated with ICI will eventually relapse [1–4], especially those who do not achieve complete remission. There is limited data about the optimal management of these patients (including treatment duration and the need for consolidation with allogeneic hematopoietic stem cell transplantation). Thus, prognostic factors are needed to guide their management better. Classical clinical and biological factors usually associated with prognosis in HL patients have poorly predicted the outcome of patients treated with anti-PD1 therapy thus far [1–3, 5]. Collaboration between haematologists and nuclear medicine physicians is needed to understand better the patterns of response observed in patients treated with immunotherapy. In this review, we described the new role of $2\text{-}^{18}\text{F}$ -Fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography ($2\text{-}^{18}\text{F}$ FDG-PET/CT/ ^{18}F FDG-PET/CT) to guide and assess treatment response in HL patients treated with ICI. We also discussed the challenges in interpreting imaging findings.

1) $2\text{-}^{18}\text{F}$ Fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography ~~Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET)/CT Imaging in Hodgkin Lymphoma~~

Hodgkin lymphoma presents a unique tumor microenvironment. It is characterized by the pathognomonic Reed-Sternberg cells (RSC), representing just less than one percent of the tumor microenvironment, composed of numerous inflammatory cells [6]. This interaction between RSC and the inflammatory cells in the microenvironment leads to an increase in anaerobic glycolysis from increased glucose uptake by the proliferative tumor compared to a normal differentiated tissue: the Warburg effect [7]. This high avidity translates into a high $2\text{-}^{18}\text{F}$ -FDG uptake visible on $2\text{-}^{18}\text{F}$ FDG-PET/CT ~~FDG-PET/CT~~ [8]. An accurate assessment of the stage of the disease in patients with HL is essential for selecting the appropriate therapy. Risk stratification with initial staging permits most patients to be treated with ~~frontline~~with frontline therapy with minimal risk of long-term complications. The imaging staging system is based on whether the involved lymph nodes are on one or both sides of the diaphragm, the number of involved sites, bulky nature of the disease, and the presence of extranodal involvement [9]. $2\text{-}^{18}\text{F}$ FDG-PET/CT ~~^{18}F FDG-PET/CT~~ has surpassed bone marrow biopsy as it has an extremely high specificity for detecting bone marrow involvement [10]. $2\text{-}^{18}\text{F}$ FDG-PET/CT ~~^{18}F FDG-PET/CT~~ is recognized as an important tool as it provides more diagnostic and therapeutic information than standard radiographic methods [11] and is now recommended for initial staging [12]. Furthermore, response-adapted strategy using $2\text{-}^{18}\text{F}$ FDG-PET/CT ~~^{18}F FDG-PET/CT~~ imaging has become the standard of care for patients with early or advanced-stage HL [13]. It is also the imaging of choice in disease relapse, permitting a new staging and guiding a possible biopsy.

2) Imaging during anti-PD1 therapy: response assessment and atypical patterns of response

Classical response criteria were designed for chemotherapy, radiotherapy, and targeted therapies, whose mechanisms of action can induce rapid tumor shrinkage or decrease in ~~2-[¹⁸F]FDG-PET/CT~~ ~~[¹⁸F]-FDG-PET/CT~~ avidity [12, 14]. Anti-PD1 antibodies work by activating anti-tumor immune cells that can translate into an increased glucose consumption and enhanced ~~2-[¹⁸F]-FDG~~ uptake (as seen in infectious and autoimmune diseases). Theoretically, this could have conflicting effects on response assessment of HL patients treated with anti-PD1 by decreasing ~~2-[¹⁸F]-FDG~~-uptake in tumor cells but increasing it in immune cells. This immune activation upon checkpoint inhibition might induce atypical response patterns in patients with HL, such as pseudoprogression and hyper-progression.

a) Response assessment and prognostic value

In patients with HL treated with non-immune therapies, ~~2-[¹⁸F]FDG-PET/CT~~ ~~[¹⁸F]-FDG-PET/CT~~ is considered the standard imaging of choice [12]. Recent data recommend it in the assessment of treatment response in patients on ICI therapy, as it is more accurate in assessing complete response compared to CT scan [15, 16]. However, the prognostic value of complete response (CR) versus partial response (PR) achieved by a patient undergoing ICI therapy remains controversial. Some authors argue that metabolic CR might not be the best endpoint [17], notably because some patients with partial response can experience prolonged progression-free survival [2].

Moreover, there are significant differences between response assessment by the investigators vs central review in clinical trials [18], probably because ICI therapy often can cause non-tumoral inflammatory lesions in minor areas not previously known to be involved. In the clinical practice, patients with minor residual/new inflammatory lesion who benefit from the therapy (i.e. without clinical signs of progression) might continue the treatment and be considered as a persistent responder. Ignoring these areas of ~~2-[¹⁸F]-FDG~~ uptake can therefore lead to differences with central review assessment.

In a retrospective study, patients who did not achieve a CR and were not consolidated with allogeneic stem cell transplantation experienced a worse outcome [3]. Complete responders had a significantly better clinical outcome and some of them (between 10 and 20%) may be cured of the cancer [3, 19].

Another retrospective study found that early complete metabolic responses, evaluated by triple blinded centralized review, predicted a better overall survival [15, 20].

In the analysis of a cohort of HL patients treated with ICI who discontinued treatment after achieving an objective response, for other reasons such as toxicity or prolonged remission, and without subsequent antitumor treatment, younger patients, with earlier and deeper responses (i.e. CR) had a greater probability to be relapse-free up to 12 months after treatment discontinuation [5].

These data suggest that ~~2-¹⁸F]FDG-PET/CT~~ ~~[¹⁸F] FDG-PET/CT~~ can identify early responders who will experience a favorable outcome. We suggest further studies to be done to validate and develop risk-adapted strategies. Discussion between hematologists and nuclear medicine physicians, for instance as part of multidisciplinary meeting, are important to distinguish, based on clinical examination, good responders who will benefit from the therapy (despite any residual inflammatory uptake), from true progressors. Furthermore, new biopsy might be necessary in certain situations.

Finally, CT measurement of anthropometric parameters such as sarcopenia may also correlate with treatment efficacy. In patients with HL treated with ICI, improvement of skeletal muscle index across the treatment sequence was observed in 62% of responders. Therefore, skeletal muscle index can be envisioned as a dynamic biomarker where an increase is associated with a favorable outcome. This should be validated in prospective studies [21].

b) Atypical patterns of response

Pseudoprogression

Pseudoprogression is due to an ICI-mediated immune infiltration of the tumor. This inflammation is responsible for a non-malignant increase in tumor size or the appearance of new lesions that can be followed by tumor shrinkage or stable disease. Pseudoprogression was first described in patients with melanoma treated with anti-CTLA4 antibodies [22] and was later reported with anti-PD1 therapy as well. In solid tumors [23], ICI treatment leads to pseudoprogression in 5-10% of patients [23, 24].

Interim and final ~~2-¹⁸F]FDG-PET/CT~~ ~~[¹⁸F] FDG-PET/CT~~ assessment is conventionally based on the five-point scale Deauville criteria which was defined in the pre-immunotherapy era [25]. The term “Deauville X” was added to address new areas of uptake unlikely to be related to lymphoma [**Supplementary table 1**]. The Lymphoma Response to Immunomodulatory therapy Criteria (LYRIC), an adaptation of the Lugano criteria for evaluating lymphoma after an immune-based therapy, introduced the term *indeterminate response* for patients with progressive disease on PET without clinical deterioration. Therefore, the term *indeterminate response* was added to address such lesions until confirmed as being true disease progression or not [**Figure 1**] [26].

Unlike in solid tumors, pseudoprogression seems to be a rare, but probably under-reported, phenomenon in haematological malignancies. In a cohort of 45 HL patients treated with nivolumab [15], pseudo-progressive lesions were identified in 2 patients (4.4%) with unequivocal radiographic progression, but without clinical manifestation of this radiological pseudoprogression. In other words, there were two cases of patients with pseudo-progressive lesions that involved only one anatomic site. These lesions did not modify response assessment as they were found in patients with unequivocally progressive disease on imaging [15]. In another

study, 2 out of 16 HL patients (12.5%) treated with anti-PD1 antibodies experienced indeterminate response and proved thereafter to be in transient progression according to the LYRIC criteria [21].

In phase II checkmate 205 trial [2], 243 relapsing/refractory (R/R) HL patients were treated with nivolumab. Progressive patients were allowed to continue treatment for clinical benefit despite radiological progressive disease. Patients treated beyond progression (TBP) seemed to experience a favorable outcome as 31 of 51 TBP patients with evaluable post-progression data had a stable or reduced tumor burden. The criteria used in this study were the 2007 consensus of the international working group [14] and not the LYRIC criteria but this observation suggests that some patients experienced pseudoprogression. A recent retrospective study reported that out of 20 patients who were TBP (ICI received were mostly nivolumab and pembrolizumab), only one achieved an objective response, even though many patients experienced durable disease control (some of them beyond 1 year) [27].

Overall, further studies are warranted to confirm the existence of pseudoprogression, as defined in solid tumors and in patients with HL treated with ICI. However, preliminary data suggest that anti-PD1 treatment might be continued even in patients with “progressive disease” (according to the 2007 consensus and Lugano criteria) who experience clinical benefit. Nonetheless, clinicians should be aware that progression on medical imaging is associated with a true progression and a poorer prognosis in most cases [Figure 2a].

Hyperprogressive disease

Hyperprogressive disease (HPD) is defined by an acceleration of the tumor growth shortly after a patient has started ICI therapy [28]. This concept has emerged in the solid tumor setting as following i) rapid deterioration of patients’ clinical status after anti-PD 1 initiation and ii) multiple randomized clinical trials observed an early crossing over of survival curves, suggesting that some patients might worsen with the treatment. This phenomenon was observed in 6 – 29% of patients treated with anti-PD(L)1 antibody for solid tumors [29]. The mechanisms responsible for HPD remain poorly understood despite numerous suggested hypothesis (e.g., stimulation of regulatory T cells, increased T-cell exhaustion).

The diagnosis of HPD is calculated by comparing the kinetics of tumor growth before and after initiation of immunotherapy [29]. Hyperprogressive disease, which has been described so far in several tumor types [28], could affect up to 15% of patients with lung cancer [30], and is associated with a poor prognosis. Several measures may need to be undertaken to prevent hyperprogression, including identifying predictive factors of HPD or the combination with cytotoxic agents (i.e., chemotherapy) to prevent the initial worsening of tumor growth. In contrast with solid tumors, HPD has been described only in patients with T-cell lymphoma as the tumor cell itself is a T cell. PD-1 is a central tumor suppressor gene that is frequently inactivated in human T-cell lymphoma, and whose inhibition can accelerate tumor growth [31, 32]. Only one case of HL patient treated with nivolumab has been recently reported and is consistent with HPD classical definition [33]. In another

series, there was no case of hyperprogression [21]. The role of ~~2-[¹⁸F]FDG-PET/CT~~ ~~[¹⁸F]FDG-PET/CT~~ for diagnosing hyperprogressive disease remains an area of active investigation [34].

Abscopal effect

The abscopal effect is a rare phenomenon that occurs during radiation therapy with tumor regression occurring at a distant site from the irradiation. Immune activation with checkpoint inhibition may potentiate the effector T-cell response generated after radiation-induced cell damages [35]. To date, few clinical observations have suggested that an abscopal effect could occur in HL patients treated with anti-PD1 and concomitant radiotherapy [36–38].

Mixed responses

Dissociated response, also referred to as a mixed or disproportional response, defines the concomitant decrease or stabilization of the tumor at sites with a simultaneous increase in other sites. Mixed responses can be misinterpreted and there is no clear consensus-based definition or guidelines for mixed metabolic response. It requires accurate assessment of metabolic and morphological diagnosis dataset, and careful anatomical measurements on contrast CT. There are numerous phenomena that mimic mixed response including synchronous neoplasms, other inflammatory processes, and treatment-related events.

This phenomenon has been reported in less than 10% of patients with solid tumors treated with ICI and has been associated with a better outcome compared to “progression with no dissociated response” in retrospective cohorts [39, 40] [Figure 2b]. These heterogeneous responses are challenging and clinical decisions for these situations are made on a case-by-case basis.

Immune-related adverse events detected on ~~2-[¹⁸F]FDG-PET/CT~~ [¹⁸F]FDG-PET/CT

The Warburg effect is a non-specific increase in glucose consumption by tumor cells. However, we also see this in non-tumoral inflammatory events such as infectious states, recent surgery, bone marrow regeneration, which may interfere with the assessment of treatment efficacy. In addition to inflammatory events as discussed above (i.e, pseudoprogression), immune activation leads to particular adverse events during ICI therapy, named immune-related adverse events (IRAEs) [Figure 3]. Those adverse events can involve any organ. In most cases, they involve the skin, the gastrointestinal tract, the endocrine glands, the liver, the lungs, or the joints [41]. In a cohort of 53 patients with solid tumors, medical imaging detected 74% of IRAEs [42], emphasizing the need for clinical information to optimize response assessment. Inflammatory lesions detected with ~~2-[¹⁸F]FDG-PET/CT~~ [¹⁸F]FDG-PET/CT were a thoracic sarcoid-like reaction, enterocolitis, thyroiditis, hypophysitis, and pancreatitis. Our group also reported patients with HL for whom imaging findings were consistent with IRAE, such as gastritis and haemolytic anemia (increased spleen uptake) [43].

Several studies suggested a possible association between IRAE occurrence and treatment efficacy, primarily for solid tumors such as lung cancers [44, 45] and melanomas [46, 47]. A recent meta-analysis even found a strong

association between IRAE occurrence and reduced risk of death (HR = 0.49, $p < 0.001$), in patients treated with ICI therapy [48]. In the meta-analysis, most patients had lung or skin cancers; and haematological malignancies were excluded.

Since IRAEs may be associated with disease prognosis and are detected most times with ~~$2\text{-}^{18}\text{F}$ FDG-PET/CT~~ ^{18}F FDG-PET/CT, they may be a useful radiological bio-marker of disease prognostication. Indeed, retrospective studies suggested a positive association between PET-detectable IRAE and outcome, including progression-free survival [49, 50] in patients with solid tumors, and response rate in 40 patients, some of whom have lymphoma [51].

Signs of immune activation detected on ~~$2\text{-}^{18}\text{F}$ FDG-PET/CT~~ ^{18}F FDG-PET/CT

The first sign of immune activity to be evaluated is spleen enlargement or increased uptake leading to equalization or an inversion of the spleen to liver ratio (SLR) [52, 53]. Some groups also proposed other signs, such as the bone marrow to liver ratio (BLR) [54] and uptake in the ileocecal valve [21]. In the first place, we thought that SLR was able to predict immune activation [53], as an increased spleen uptake would reflect “unleashed” T lymphocytes with an expected better outcome. However, several studies showed that an increase in SLR on baseline or follow-up ~~$2\text{-}^{18}\text{F}$ FDG-PET/CT~~ ^{18}F FDG-PET in solid tumors was an adverse finding, likely related to inflammation and tumor [55, 56]. Strong reproducibility studies were reported for spleen and bone marrow measurements [57].

Most of the published data on signs of immune activation are focused on solid tumors but Derclé et al reported in a series of 16 HL patients that a decrease in tumor metabolism and volume (SUV mean, metabolic tumor volume) and an increase in healthy splenic metabolism at three months after antiPD1 treatment were observed in responders as per LYRIC criteria [21].

The beneficial or detrimental significance of an increased ~~$2\text{-}^{18}\text{F}$ FDG splenic uptake~~ remains controversial and should be further investigated.

Conclusions

Immune checkpoint inhibitors have dramatically improved the outcome of patients with cancer. Their mechanisms of action induce inflammatory processes that might translate into a high ~~$2\text{-}^{18}\text{F}$ FDG uptake~~ visible on ~~$2\text{-}^{18}\text{F}$ FDG-PET/CT~~ ^{18}F FDG-PET/CT. These phenomena require an adaptation of the evaluation criteria and new patterns of response observed with immunotherapy in assessing treatment response in HL patients. Collaboration between physicians and PET readers is more than ever necessary to discriminate non-tumoral inflammatory events from (hyper-) progression. On the other hand, PET imaging might identify asymptomatic IRAEs, which might be associated with a better prognosis in some patients. We recommend discussing equivocal cases during multidisciplinary meetings. A new biopsy might be necessary in some patients whenever possible as it is the only way to confirm a CR in case of persistent ~~$2\text{-}^{18}\text{F}$ FDG uptake.~~

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Figure 1

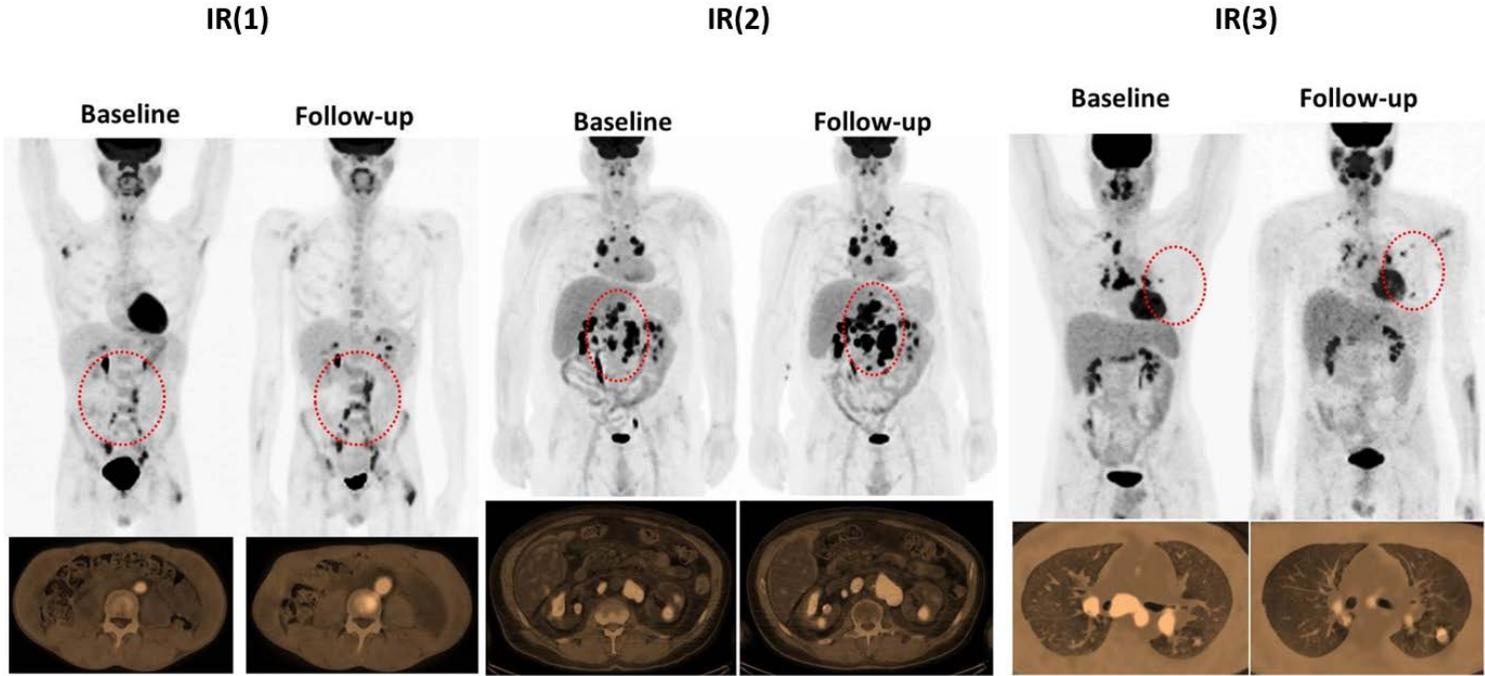
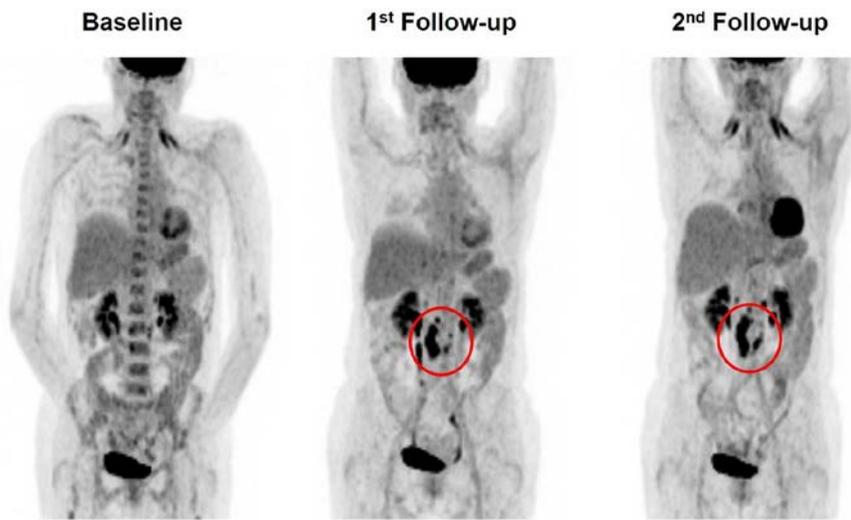


Figure 2. Progressive disease (a) and dissociated response (b)

a

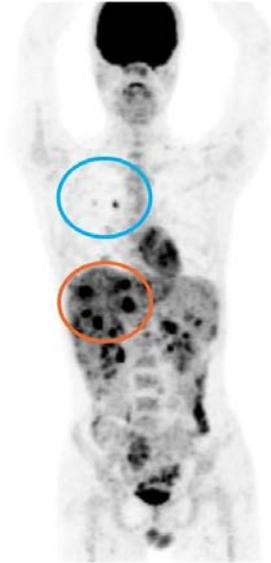


b

Baseline



1st Follow-up



2nd Follow-up

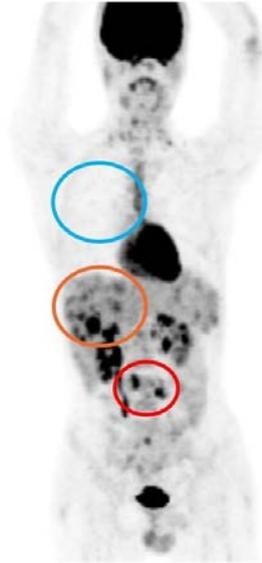
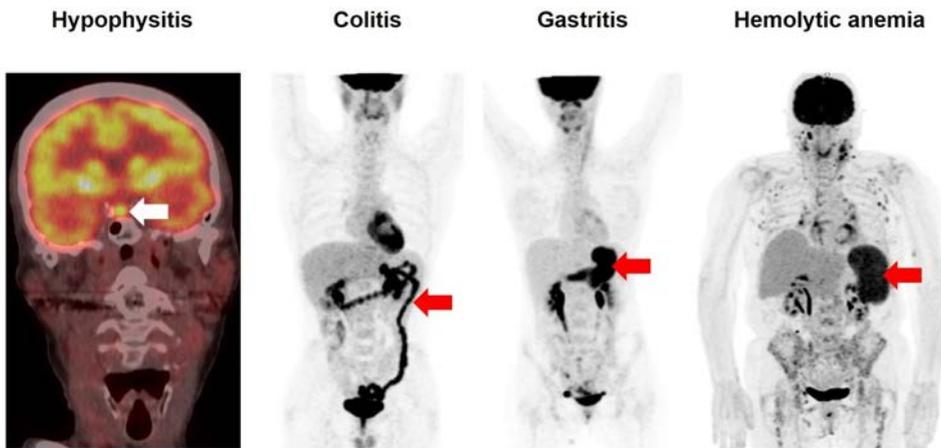


Figure 3. Immune related adverse events detected on ~~2-¹⁸F-FDG-PET/CT~~ ~~[¹⁸F]-FDG-PET/CT~~ (a), and magnetic resonance imaging (b)

a



b

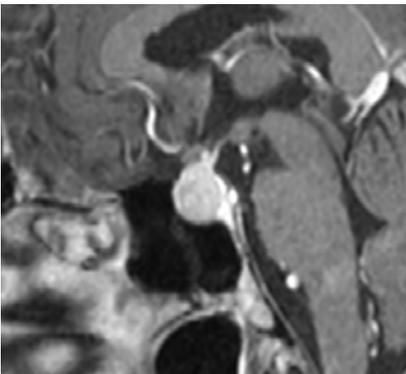


Figure 1 legend.

IR (1): $\geq 50\%$ increase in overall tumor burden (sum of the product of the perpendicular diameters of up to six target measurable nodes and extranodal sites) occurred in the first 12 weeks of therapy and without clinical deterioration.

IR (2): New lesions or $\geq 50\%$ increase of existing lesion(s) without a $\geq 50\%$ increase of overall tumor burden at any time during treatment.

IR (3): Increased ~~$2\text{-}^{18}\text{F}$~~ ~~FDG~~ uptake of one or more lesions without any increase in size or number of those lesions.

Figure 2 legend.

a. progressive disease: ~~$2\text{-}^{18}\text{F}$~~ ~~FDG-PET/CT~~ ~~^{18}F~~ ~~FDG-PET/CT~~ shows progressive disease of retroperitoneal lymph nodes on 1st assessment that is confirmed 1 month later by second follow-up (red circle)

b. Dissociated response: ~~$2\text{-}^{18}\text{F}$~~ ~~FDG-PET/CT~~ ~~^{18}F~~ ~~FDG-PET/CT~~ shows complete response of pulmonary lesion after 2nd follow up (blue circle) while there was hepatic pseudoprogressive disease (orange circle) and objective progression of retroperitoneal lymph nodes (red circle)

Figure 3 legend.

~~$2\text{-}^{18}\text{F}$~~ ~~FDG-PET/CT~~ ~~^{18}F~~ ~~FDG-PET/CT~~ detects immune-related adverse events. These new $2\text{-}^{18}\text{F}$ -FDG avid lesions should be differentiated from progressive disease since they require a specific management and are typically associated with response to treatment. We also show here an MRI image (b) for the case of hypophysitis as it remains the imaging of choice.

Supplementary table 1. Five-point scale Deauville Score (DS) [25]

DS = 1	No uptake above background
DS = 2	Uptake \leq mediastinum
DS = 3	Uptake $>$ mediastinum but \leq liver
DS = 4	Uptake moderately $>$ liver
DS = 5	Uptake markedly higher than liver and/or new lesions
DS = X	New areas of uptake unlikely to be related to lymphoma