



# <sup>18</sup>F FDG PET/CT in the early assessment of non-small cell lung cancer response to immunotherapy: frequency and clinical significance of atypical evolutive patterns

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## Abstract

**Purpose** This prospective study aimed (1) to assess the non-small cell lung cancer (NSCLC) evolutive patterns to immunotherapy using FDG-PET and (2) to describe their association with clinical outcome.

**Design** Fifty patients with metastatic NSCLC were included before pembrolizumab or nivolumab initiation. FDG-PET scan was performed at baseline and after 7 weeks of treatment (PET<sub>interim1</sub>) and different criteria/parameters of tumor response were assessed, including PET response criteria in solid tumors (PERCIST). If a first PERCIST progressive disease (PD) without clinical worsening was observed, treatment was continued and a subsequent FDG-PET (PET<sub>interim2</sub>) was performed at 3 months of treatment. Pseudo-progression (PsPD) was defined as a PERCIST response/stability on PET<sub>interim2</sub> after an initial PD. If a second PERCIST PD was assessed on PET<sub>interim2</sub>, a homogeneous progression of lesions (termed immune homogeneous progressive-disease: iPD<sub>homogeneous</sub>) was distinguished from a heterogeneous evolution (termed immune dissociated-response: iDR). A durable clinical benefit (DCB) of immunotherapy was defined as treatment continuation over a 6-month period. The association between PET evolutive profiles and DCB was assessed.

**Results** Using PERCIST on PET<sub>interim1</sub>, 42% (21/50) of patients showed a response or stable disease, most of them (18/21) reached a DCB. In contrast, 58% (29/50) showed a PD, but more than one-third (11/29) were misclassified as they finally reached a DCB. No standard PET<sub>interim1</sub> criteria could accurately distinguished responding from non-responding patients. Treatment was continued in 19/29 of patients with a first PERCIST PD; the subsequent PET<sub>interim2</sub> demonstrated iPD<sub>homogeneous</sub>, iDR and PsPD in 42% (8/19), 26% (5/19), and 32% (6/19), respectively. Whereas no patients with iPD<sub>homogeneous</sub> experienced a DCB, all patients with iDR and PsPD reached a clinical benefit to immunotherapy.

**Conclusion** In patients with a first PD on PERCIST and treatment continuation, a subsequent PET identifies more than half of them with iDR and PsPD, both patterns being strongly associated with a clinical benefit of immunotherapy.

**Keywords** FDG PET · Immunotherapy · Lung cancer · Monitoring · Response

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## Introduction

Immune checkpoint inhibitors (immunotherapy) targeting programmed cell death-1 (PD-1) have been recently approved in locally advanced and metastatic non-small cell lung cancer (NSCLC), irrespectively of the histologic subtype [1].

One unresolved issue is how to identify patients that are more likely to benefit from immunotherapy, as early as possible [2, 3]. Although PD-L1 positivity enriches for populations with clinical benefit, PD-L1 testing alone appears to be insufficient for patient selection [4]. As there are currently no reliable biological markers for prediction or early identification of tumor response to immunotherapy, the therapeutic decision currently relies on imaging combined with a clinical evaluation [4]. But new challenges have been raised with the radiological assessment of immunotherapy efficiency. Conventional imaging criteria such response evaluation criteria in solid tumors (RECIST) v1.1, based on morphologic measurements on computed tomography (CT), or PET response criteria in solid tumors (PERCIST V1.0), based on glucose metabolic changes on  $^{18}\text{F}$ -fluorodeoxy-glucose positron-emission tomography ( $^{18}\text{F}$ FDG PET), rely on the paradigm that the cytotoxic effect of chemotherapy translates into measurable tumor shrinkage and metabolism decrease, respectively [5, 6]. Yet, the mechanisms of action of immunotherapy are different from conventional chemotherapy; the lifting of the inhibition of the lymphocyte system induces a tumor infiltration and proliferation of immune cells that can lead to a transient increase in tumor burden on CT and metabolic activity on  $^{18}\text{F}$ FDG PET [7–9]. Consequently, when using immunotherapy, new response patterns have been described such as a transient tumor increase in size and metabolism, or appearance of new lesions, followed by a delayed response or stability [7, 9]. This challenging and specific immune-related response pattern is termed “pseudo-progression” (PsPD) and may lead to misinterpretation of clinical images.

The limits of the RECIST criteria to assess tumor response in the setting of immunotherapy have led to new immunotherapy-adapted criteria: the iRECIST [9, 10]. Their key point is that because of a potentially delayed response to immunotherapy treatment, imaging assessment of disease progression should be made with two consecutive follow-up imaging studies performed at least 4 weeks apart, especially when a pseudo-progressive disease is suspected. When using FDG PET, no specific immune-related response criteria for solid tumors have been validated until now. The aims of this prospective monocentric study were:

1. To investigate the accuracy of standard PET criteria, assessed 7 weeks after the initiation of immunotherapy, to identify patients who will clinically benefit from immunotherapy
2. In patients with a first PERCIST progression on PET, to describe the different patterns of tumor metabolic evolution on a mandatory subsequent PET evaluation performed few weeks later, and their association with patients' clinical outcome

## Patients and methods

### Population

From February 2017 to September 2018, 62 patients scheduled to initiate immunotherapy as their first or later systemic treatment for NSCLC were prospectively evaluated in this open, non-randomized, current care study in our institution. The study was approved by the ethics committee (CPP Sud Ouest et Outre Mer III) and regulatory agencies (FDG ECMI, n° ID-RCB: 2018-A02116-49), and a signed informed consent was obtained from all individual participants included in the study.

The inclusion criteria were the following: (1) pathologically proven locally advanced or metastatic NSCLC, irrespectively of the histologic subtype; (2) an indication to start immune checkpoint inhibitors in first or later line; (3) performance status on the Eastern Cooperative Oncology Group corresponding to 0–2. The exclusion criteria were the following: (1) clinical or biological contraindication for immune checkpoints inhibitors, (2) evidence of concurrent cancer, (3) vulnerable patients as defined in Article L1121-5 to -8 of the French Public Health Code, (4) refusal of written consent, and (5) high glycaemia ( $> 9$  mmol/l) before FDG PET scans.

Patients received one of two possible treatment regimens, either pembrolizumab administered intravenously at a standard dose of 2 mg/kg every 3 weeks or nivolumab at a standard dose of 240 mg every 2 weeks. If available, the pre-treatment PD-L1 tumor expression was recorded.

### PET protocol

$^{18}\text{F}$ FDG PET scans were performed before the start of immune checkpoints inhibitor ( $\text{PET}_{\text{baseline}}$ ), after 7 weeks of treatment ( $\text{PET}_{\text{interim1}}$ ) and after 3 months of treatment ( $\text{PET}_{\text{interim2}}$ ).

All PET scans were performed using the same PET/CT system (Biograph mCT, Siemens Healthcare). Patients were instructed to fast for at least 6 h before the intravenous injection of 3 MBq/kg of  $^{18}\text{F}$ -FDG. Sixty minutes later, a low-dose attenuation CT acquisition was performed (50 kV, 50 mA, 5 mm slice thickness) followed by a static 3D PET acquisition with image duration of 150 s per bed position, an axial field of view of 13 cm, and a matrix of  $256 \times 256$ . Lastly, a diagnostic CT acquisition was done (auto-kV, auto-mA, 1 mm slice

thickness) after a venous injection of iodinated contrast agent in the absence of allergy or renal impairment. PET images were reconstructed using the ordered subsets expectation maximization (OSEM 3D) iterative algorithm (2 iterations, 21 subsets), with point spread function and time-of-flight correction (ultra-HD PET). Peak-standardized uptake values, normalized either by body weight ( $SUV_{peak}$ ) or by lean body mass ( $SUL_{peak}$ ), were calculated on the highest uptake site of the tumors at baseline and interim exams. Pathological hypermetabolic foci obviously deemed to be due to the therapy-related inflammation or immune activation (for example, symmetrical uptake in enlarged hilar/mediastinal lymph nodes, diffuse splenic uptake, colitis) were excluded of the lesion analyses.

### PET<sub>interim1</sub> (after 7 weeks of treatment)

Different metabolic parameters were assessed:

- PERCIST criteria were used to define complete metabolic response (CR), partial metabolic response (PR), stable metabolic disease (SD), or progressive metabolic disease (PD), considering the lesion with the highest FDG uptake ( $SUL_{peak}$ ) on each of these scans and the appearance of new hypermetabolic lesions [5].
- $\Delta SUV_{peak}$  corresponding to the SUV percentage change of the most intense lesion (not necessarily the same) between baseline and interim PET, regardless of the appearance of new lesions.

$$\Delta SUV_{peak} (\%) = 100 \times (SUV_{peak1} - SUV_{peak2}) / SUV_{peak1}$$

- The appearance of new hypermetabolic lymph node or visceral/bone lesion(s), regardless of  $SUV_{peak}$  changes.

Because of the investigational nature of PET<sub>interim1</sub> and the knowledge of the specific immune-related response pattern with CT, the result from this scan was not directly used to guide patient management. The treatment was continued even in the case of PD. Nonetheless, for patient security, the patient's clinical status was assessed at each course of treatment and it could be stopped at any time in case of clinical worsening or toxicity.

### PET<sub>interim2</sub> (after 3 months of treatment)

These scans were performed for patients with PD as assessed by PERCIST on PET<sub>interim1</sub>. The PERCIST criteria were used for the interpretation of these scans but adding new evolutive patterns adapted to the issue of immunotherapy:

- Pseudo-progression (PsPD): in the case of CR, PR, or SD according to PERCIST criteria, the nuclear physician concluded to PsPD, defined as a delayed tumor response or stability for tumor lesions that had initially been assessed as progressive. In this case, the oncologist could continue immunotherapy if no clinical worsening was observed.
- In the case of FDG PET imaging showing a second and consecutive tumor progression according to PERCIST, two different progressive patterns were distinguished:
  - Immune homogeneous progressive disease (iPD<sub>homogeneous</sub>)
  - Immune dissociated response (iDR) defined as concomitant decrease in certain hypermetabolic lesions associated with an increase in others lesions.

The decision to stop or continue the immunotherapy was then decided during a multi-disciplinary tumor board, confronting the patient's clinical status and the PET results. Thus, the treatment could be continued in all of the 3 evolutive patterns on PET<sub>interim2</sub>.

### Follow-up and clinical endpoints

Patients were followed during a 6-month period with regular clinical evaluations and standard of care imaging (including follow-up brain MRI, <sup>18</sup>F-FDG PET, and CT exams). The delay between the initiation of the treatment and the decision to stop it, as well as the reason of it, was recorded. If treatment was maintained at this 6-month follow-up endpoint, patients were considered having a durable clinical benefit (DCB) of immunotherapy, as done in previous studies [11, 12]. DCB was thus the primary endpoint. Overall survival (OS) was recorded and defined as the time from initial immunotherapy to death from any cause.

### Statistical analyses

The required number of patient to be evaluated was calculated by considering the 95% confidence interval (CI) of sensitivity analysis between response and a durable clinical benefit. The hypotheses were the following: an expected sensitivity of 85% [12–14], alpha (bilateral) = 0.025. The estimated sample size of responding patients was calculated at 20 subjects. Taking into account that we expected a response rate of 40% [12, 14] and a 15% of patient's loss to follow up, the inclusion of 60 patients satisfied the initial hypotheses.

Data entry and management were performed on the capture system (Ennov Clinical®). Qualitative data were presented as absolute frequencies and percentages. The quantitative data were presented in mean value and standard deviation, or median and extreme values. The sensibility, specificity, positive predictive value (PPV), negative predictive value (NPV), and Youden's index (summarizing the performance of the diagnosis) of metabolic variables on PET<sub>interim1</sub> in their capacity to

predict no-DCB of immunotherapy. The McNemar test was used for comparison of sensitivity and specificity of the different sets of criteria, and the Bonferroni adjustment was applied to counteract the problem of multiple comparisons ( $N = 6$ ;  $P$  cutoff = 0.008). Exact McNemar test calculations were performed using R package exact2x2® version 3.2.2.

## Results

### Patients' characteristics (Table 1)

Sixty-two patients were prospectively included. Seven patients were excluded because the treatment was stopped in the very first weeks of treatment, with the PET<sub>interim1</sub> being waived: 4/7 patients due to an early hyperprogressive disease (HPD) with severe clinical worsening and 3/7 due to severe treatment toxicity. Five patients were excluded for: lost to follow-up ( $N = 1$ ), no PET target lesion due to concomitant radiotherapy on the only hypermetabolic lesion ( $N = 1$ ), PET<sub>interim1</sub> cancellation or wrong timing ( $N = 3$ ). Fifty remaining patients were therefore evaluated in this study. Mean patient age was  $63.4 \pm 10.2$  years (range 42–83 years). All patients had a metastatic NSCLC: 20% (10/50) of squamous cell carcinoma and 80% (40/50) of adenocarcinoma. Forty-eight percent (24/50) of patients were treated with pembrolizumab, mostly in first line of the metastatic setting, and 52% (26/50) of patients were treated with nivolumab, mostly in second line of the metastatic setting.

Mean delay between introduction of immunotherapy and PET<sub>interim1</sub> to evaluate response was  $49 \pm 5$  days. Mean delay

between introduction of immunotherapy and PET<sub>interim2</sub> was  $92 \pm 15$  days.

Patients' median follow-up was 11.5 months (95% CI = 11.1–13.8) for the whole cohort, 11.5 months (95% CI = 8.8–NA) for patients in the first-line setting, and 11.6 months (95% CI = 11.1–17.3) for patients in second or further line setting.

### Results of PET<sub>interim1</sub> (Fig. 1)

#### PERCIST criteria

- 32% of patients achieved a CR or PR ( $N = 16/50$ )  
Among them, 87.5% (14/16) reached a DCB, whereas treatment was stopped before the 6-month endpoint in the remaining 12.5% (2/16) patients due to tumor progression. None of these patients died during the 6-month follow-up.
- 10% of patients presented a SD ( $N = 5/50$ )  
Eighty percent (4/5) of them reached a DCB. The treatment was stopped before 6 months in the only remaining patient due to severe toxicity. None of these patients died during the 6-month follow-up
- 58% of patients presented with a PD ( $N = 29/50$ )  
37.9% (11/29) of them reached a DCB, whereas the treatment was stopped before 6 months in the remaining 62.1% (18/29) of these patients due to tumor progression with clinical worsening. The sensitivity, specificity, PPV, NPV, and Youden's index of a first PERCIST PD to predict no-DCB were calculated at 85.7%, 62.1%, 62.1%, 85.7%, and 0.48, respectively. Among these patients with no-DCB, 50% (9/18) died during the 6-month follow-up.

#### $\Delta$ SUV<sub>peak</sub> criteria

The mean  $\Delta$ SUV<sub>peak</sub> on PET<sub>interim1</sub> was  $-3.3 \pm 50\%$  with:

- 32% of patients (16/50) having a SUV<sub>peak</sub> decrease ( $\Delta$ SUV<sub>peak</sub>  $\leq -30\%$ )
- 46% of patients (23/50) having a SUV<sub>peak</sub> stability ( $-30\% \leq \Delta$ SUV<sub>peak</sub>  $\leq +30\%$ )
- 22% of patients (11/50) having a SUV<sub>peak</sub> increase ( $\Delta$ SUV<sub>peak</sub>  $\geq +30\%$ )

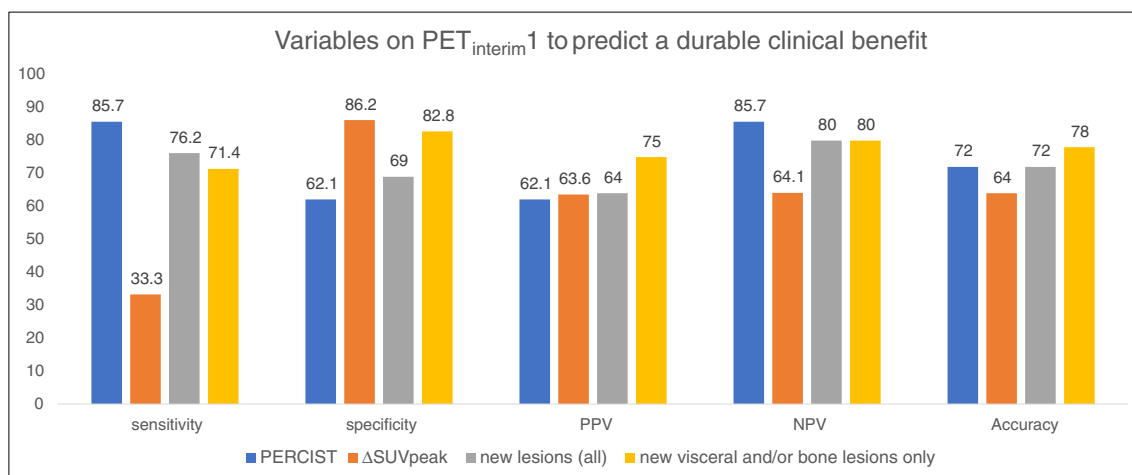
A DCB was obtained in 93.7% (15/16) of patients with a SUV<sub>peak</sub> decrease, 43.5% (10/23) with a SUV<sub>peak</sub> stability, and 36.4% (4/11) with a SUV<sub>peak</sub> increase.

The sensitivity, specificity, PPV, NPV, and Youden's index of a  $\Delta$ SUV<sub>peak</sub>  $\geq +30\%$  to predict no-DCB were 33.3%, 86.2%, 63.6%, 64.1%, and 0.2, respectively.

After multiple comparison correction, the  $\Delta$ SUV<sub>peak</sub> had a significantly lower sensitivity but significantly higher specificity than the PERCIST criteria ( $P = 0.0001$  and  $0.007$ , McNemar test).

**Table 1** Patient's clinical characteristics at baseline

	N	Percent (%)
Total patients	50	100
Age in years, mean $\pm$ SD	$63.4 \pm 10.2$	
Sex		
Male	32	64
Female	18	36
Histology		
Squamous cell carcinoma	10	20
Adenocarcinoma	40	80
Previous lines of chemotherapy		
None	13	26
1	21	42
2	9	18
3	7	14
Treatment		
Nivolumab	26	52
Pembrolizumab	24	48



**Fig. 1** Performances of different PET<sub>interim1</sub> metabolic variables/criteria for predicting durable clinical benefit of treatment. PPV, positive predictive value; NPV, negative predictive value

### New hypermetabolic lesion(s)

Half of the patients (25/50) showed at least one new hypermetabolic lesion on PET<sub>interim1</sub>; 10% ( $N = 5$ ) had only new lymph node(s) whereas 40% ( $N = 20$ ) had also new visceral/bone lesion(s).

- All types of new lesions (including lymph nodes)
  - 80.0% (20/25) of patients without new lesions had a DCB, compared with only 36.0% (9/25) of patients with at least one new lesion.
  - The sensitivity, specificity, PPV, NPV, and Youden's index of the apparition of new lesion(s) on PET<sub>interim1</sub> to predict no-DCB were 76.2%, 69%, 64%, 80%, and 0.45, respectively.

After multiple comparison correction, the sensitivity and specificity were not significantly different from PERCIST criteria ( $P = 0.5$  and  $0.1$ , respectively).

- Exclusively visceral/bone new lesion(s)
  - 80.0% (24/30) of patients without new visceral/bone lesions had a DCB, compared with only 25.0% (5/20) of patients with at least one new visceral/bone lesion.
  - The sensitivity, specificity, PPV, NPV, and Youden's index to predict no-DCB were 71.4%, 82.8%, 75%, 80%, and 0.54, respectively.

After multiple comparison correction, the sensitivity and specificity were not significantly different from PERCIST criteria ( $P = 0.06$  and  $0.25$ , respectively).

### Results of PET<sub>interim2</sub>

Among the patients presenting with a first PERCIST progression on PET<sub>interim1</sub>, PET<sub>interim2</sub> was waved in 34% (10/29) due to a major clinical worsening and treatment stop. Therefore, 19/29 patients underwent PET<sub>interim2</sub>:

- 31.6% (6/19) of patients had a PsPD. They corresponded to patients with a metabolic CR (1/19), PR (2/19), or SD (3/19) on PET<sub>interim2</sub> after an initial PD on PET<sub>interim1</sub>. All of these patients had a DCB.
- 68.4% (13/19) of patients had a second and consecutive PERCIST PD on PET<sub>interim2</sub>. Among them:
  - 26.3% (5/19) had iDR (Figs. 2 and 3). In all these patients, the treatment was continued (due to an improved, or at least stable, clinical status according to the tumor board) and they all achieved a durable clinical benefit of immunotherapy.
  - 42.1% (8/19) had iPD<sub>homogeneous</sub>. All of them stopped the treatment and did not have a durable clinical benefit of immunotherapy. Three of them died during this 6-month follow-up.

### Correlation between the number of previous treatment line(s), PD-L1 tumor expression, and patients' response to treatment

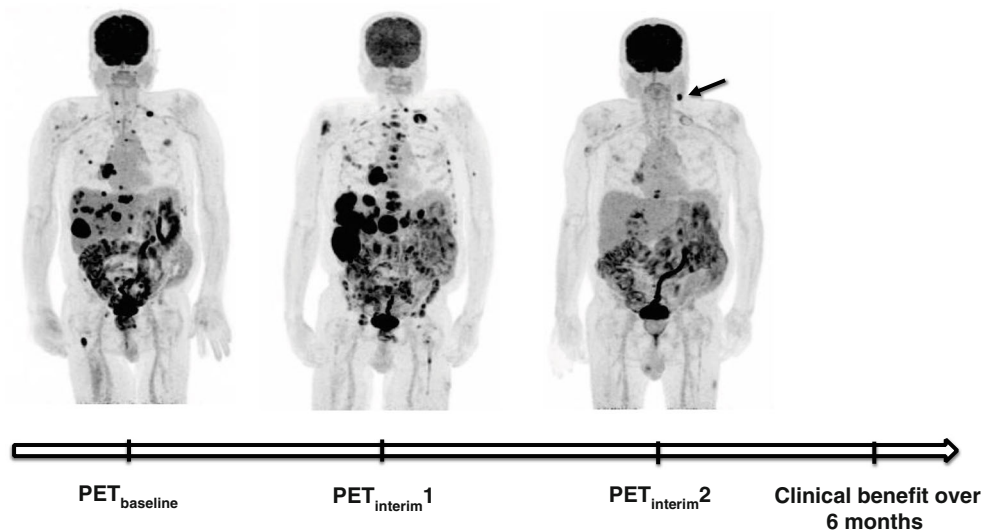
No significant differences of PET response patterns or DCB rates were assessed between patients in first or further treatment lines (Table 2).

No significant differences of PET response patterns or DCB rates were assessed according to the tumor PD-L1 expression (under or over 50%) (Table 3).

### Discussion

Because tumor metabolic changes due to chemotherapy occur earlier than morphologic changes, <sup>18</sup>F PET is widely used





**Fig. 2** A 76-year-old man with metastatic squamous cell carcinoma treated with a second line of nivolumab. On PET<sub>interim 1</sub> at 7 weeks of treatment (4 cycles), the maximum intensity projection image (MIP) showed a major metabolic progression of bone and liver metastases. PET<sub>interim 2</sub>, at 3 months of treatment (8 cycles), showed an immune-dissociated

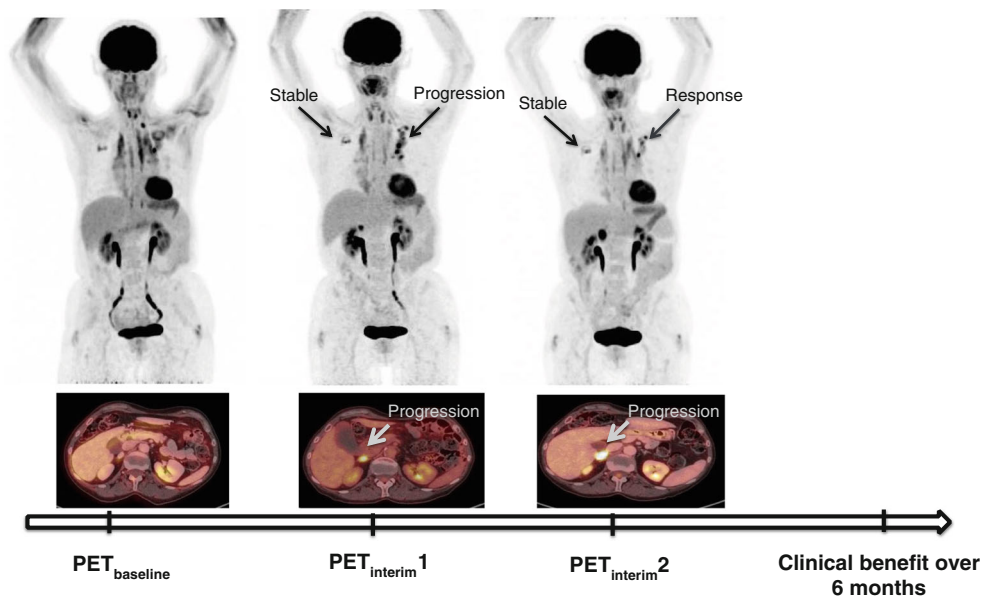
response (iDR) with disappearance of most liver and bone lesions but appearance of a new hypermetabolic cervical lymph node (black arrow). The patient had a durable clinical benefit and, at the last follow-up (12 months of treatment), was still treated with nivolumab

in oncology for monitoring response to conventional chemotherapy [15]. Nonetheless, few data are available concerning tumor response monitoring with <sup>18</sup>F-FDG PET in metastatic lung cancer treated with anti-PD-1 or anti-PDL-1-based immunotherapies [14, 16, 17]. Based on limited patients’ cohort, new immune-related PET criteria have been proposed, mainly focusing on melanoma or lymphoma [13, 14, 18, 19]. Before robust and validated criteria can be defined by expert consensus, there is a strong need to firstly describe the imaging PET patterns of tumor metabolic changes to immunotherapy, and their association with patients’ clinical outcome. Because the issue of pseudo-progression has deeply changed the paradigm

for tumor response evaluation; the prospective design of the present study is crucial. It guarantees a homogenized imaging protocol, image interpretation, and clinical decision in the case of a tumor progression on <sup>18</sup>F-FDG PET.

In the setting of immunotherapy monitoring, the recent iRECIST recommendations have introduced a new metabolic response category in the case of a first tumor progression, termed “indeterminate progression” [9, 10]. This new classification provides the flexibility to have patients continue with treatment despite a first tumor progression if clinically stable. A subsequent evaluation is then required a few weeks later to confirm or deny true PD. When using <sup>18</sup>F-FDG PET, the risk of

**Fig. 3** A 68-year-old women with metastatic adenocarcinoma treated with pembrolizumab. On PET<sub>interim 1</sub> at 7 weeks of treatment (3 cycles), the maximum intensity projection image (MIP) showed a metabolic progression of adrenal and mediastinal lymph nodes and showed a stability of pulmonary lesion. PET<sub>interim 2</sub>, performed at 3 months of treatment (5 cycles), showed an immune-dissociated response with disappearance of most mediastinal lymph nodes, stability of pulmonary lesion, and progression of adrenal lesion. Because, the clinical status of the patient remained stable, the treatment was continued and the patient finally obtained a durable clinical benefit of immunotherapy



**Table 2** Patient's response characteristics according to the number of previous treatment lines

	First line, <i>N</i> (%)	2nd or further lines, <i>N</i> (%)	<i>P</i> *
Total patients ( <i>N</i> )	13 (26)	37 (74)	-
PET <sub>interim1</sub>			1
PERCIST progression	8 (61.5)	21 (56.8)	
No-PERCIST progression	5 (38.5)	16 (43.2)	
PET <sub>interim2</sub> **			1
iPD <sub>homogeneous</sub>	2 (15.4)	6 (16.2)	
iDR	1 (7.7)	4 (10.8)	
PsPD	1 (7.7)	5 (15.5)	
Durable clinical benefit			0.12
Yes	5 (38.5)	24 (64.9)	
No	8 (61.5)	13 (35.1)	

\*Fisher exact test

\*\*In patient with a first progressive disease on PET<sub>interim1</sub> and treatment continuation

iPD<sub>homogeneous</sub>, immune homogeneous progressive disease; iDR, immune dissociated response; PsPD, pseudo-progression

falsely concluding to treatment failure after a first tumor progression is even higher than with CT because of its high sensitivity in detecting metabolic lesion activation, linked with the immune infiltrate. In the present study, new visceral/bone lesion(s) was the best surrogate criteria of treatment failure on PET<sub>interim1</sub> but still misclassified a high number of responding patients (PPV = 75%). As previously suggested in melanoma and lymphoma, it supports the need to introduce the “indeterminate response” PET category in the case of a first PERCIST progression that should be termed iUPD (immune unconfirmed progressive disease), as for iRECIST [19].

### Pseudo-progression (PsPD) and progression

PsPD to immunotherapy is defined as a transient increase followed by a decrease in total tumor burden [7, 9, 20]. In the literature, pseudo-progression is assessed with CT in up to 10% of patients with melanoma but is very rare in NSCLC (0–5%) [9, 12, 20–23]. In our cohort, using <sup>18</sup>F<sup>18</sup>FDG PET, pseudo-progression was observed in 12% (6/50) of patients, which is close from the only other PET retrospective study in lung cancer [14]. We found that PsPD is a common finding with PET and a surrogate of good tumor response to immunotherapy as all these patients obtained a DCB.

But the present study found a more unexpected finding: the immunotherapy was finally maintained in many patients with two consecutive PD according to PERCIST, and all these patients exhibited a durable clinical benefit of immunotherapy. The reasons that led clinicians to continue the immunotherapy were based both on the good clinical status and on a

dissociated tumor evolution on PET, with concomitant progressive and responding lesions. Contrary to iRECIST, two consecutive PD on PET is not a robust criterion to confirm treatment failure to immunotherapy. The pattern of a dissociated progressive disease on PET<sub>interim2</sub> is strongly associated with a clinical benefit of immunotherapy and we propose to reterm it “immune dissociated response” (iDR). Using CT, Tazdait et al. have also described a dissociated pattern of tumor response (7.5% of patients vs 10% in our cohort) which was associated with significantly longer median OS than patients with confirmed progression [12]. Using PET, the retrospective study of Goldfarb et al. did not describe this dissociated evolutive pattern [14]. It may mainly be explained by our prospective design, leading to a higher proportion of patients treated beyond a first PERCIST progression and benefiting of a subsequent PET<sub>interim2</sub> (around 66% vs 30%).

Thus, our study demonstrates a new paradigm; pseudo-progression and dissociated-response are both very common findings when using <sup>18</sup>F<sup>18</sup>FDG PET to monitor NSCLC response to immunotherapy and are surrogates of good tumor response. If the clinical condition of the patient is not worsening, these two atypical evolutive patterns should systematically be considered when assessing a first tumor progression with PET. Indeed, not to stop an effective treatment is a main issue in this critical setting. Based on these findings, an algorithm could be proposed for the use of <sup>18</sup>F<sup>18</sup>FDG PET to monitor response of NSCLC to immunotherapy (Fig. 4).

### Response and stability on PET<sub>interim1</sub>

Seven weeks after the initiation of immunotherapy, a PERCIST response (CR or PR) was observed in nearly a third of patients and appears as a reliable surrogate of a durable clinical benefit of the treatment. Indeed, immunotherapy was continued over the 6-month follow-up period in 87.5% (14/16) of these patients.

Around 10% of patients demonstrated a stable PERCIST disease, equivalent to the rate of SD observed with CT [12]. Most of these patients achieved a durable clinical benefit of immunotherapy.

### Endpoints of the study

Due to the issue of pseudo-progression, traditional endpoints such as progression-free survival may not be a good surrogate of treatment efficacy of anticancer immunotherapies. Consequently, early metabolic changes observed at PET<sub>interim1</sub> and PET<sub>interim2</sub> were analyzed for their capacity to predict a durable clinical benefit, which we defined as continuation of treatment and maintained patients' clinical status over 6 months after the initiation of immunotherapy. A durable clinical benefit was also the main endpoint in other recent studies researching predictive biomarkers for immunotherapy

**Table 3** Patient’s characteristics according to the tumor expression of PD-L1

	PD-L1 = 0–50%, N (%)	PD-L1 > 50%, N (%)	Missing PD-L1 values	P*
Total patients	14 (28)	18 (36)	18 (36%)	
Number of treatment lines				< 0.001
1st line	1 (7.1)	12 (66.7)	0	
2nd line or further	13 (92.9)	6 (33.3)	18	
PET <sub>interim</sub> 1				1
PERCIST progression	8 (57.1)	11 (61.1)	10	
No-PERCIST progression	6 (42.9)	7 (38.9)	8	
PET <sub>interim</sub> 2**				1
iPD <sub>homogeneous</sub>	1 (7.1)	2 (11.1)	5	
iDR	0 (0)	3 (16.7)	2	
PsPD	1 (7.1)	2 (11.1)	3	
Durable clinical benefit				0.72
Yes	6 (42.9)	10 (55.6)	13	
No	8 (57.1)	8 (44.4)	5	

\*Fisher exact test

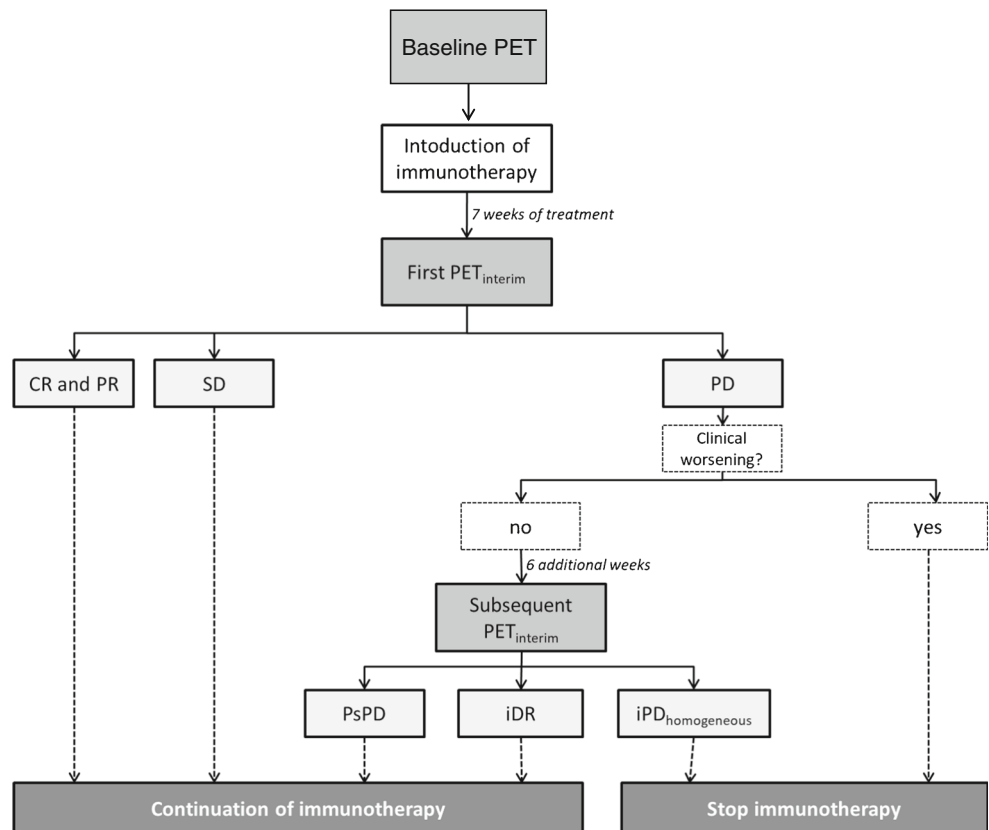
\*\*In patient with a first progressive disease on PET<sub>interim</sub>1 and treatment continuation

iPD<sub>homogeneous</sub>, immune homogeneous progressive disease; iDR, immune dissociated response; PsPD, pseudo-progression

[11–13, 18]. Nonetheless, overall survival remains the major endpoint and a longer patient follow-up will be necessary in future studies.

The early identification of patients that will achieve a durable clinical benefit from immunotherapy may provide major information to the clinician for patient follow-up. In

**Fig. 4** Proposed algorithm for the use of <sup>18</sup>F<sup>18</sup>FDG PET to monitor response of NSCLC to immunotherapy. Response categories according to PERCIST criteria: CR, complete metabolic response, PR, partial metabolic response; SD, stable metabolic disease; PD, progressive metabolic disease. New immune-adapted response categories adapted to immunotherapy: PsPD, pseudo-progression; iDR, immune-dissociated response (heterogeneous evolution of lesions on the subsequent PET<sub>interim</sub>); iPD<sub>homogeneous</sub>, immune-confirmed progressive disease (homogeneous progression of lesions on the subsequent PET<sub>interim</sub>)





responding patients, it will allow not to stop an effective treatment mistakenly in cases with atypical PET evolutive patterns actually linked to treatment efficiency. In non-responding patients, it will allow an earlier treatment discontinuation. The benefits will then be the early stop of an inefficient treatment with possible adverse effects, the earlier start of a more efficient therapeutic modality for the patient, and the cost reduction of immunotherapy for society.

### Limits of the study

In NSCLC, Ferrara et al. classified 13.8% of patients as having hyperprogressive disease and a poor prognosis [24]. In our study, 4/62 patients were excluded due to a severe clinical degradation and treatment stop before PET<sub>interim1</sub>. Determining the molecular mechanisms involved, as well as seeking for baseline biomarkers of HPD, remain an important challenge.

In the present study, 20% (10/50) of patients had a PD on PET<sub>interim1</sub>, concomitant with a significant clinical worsening. These patients were considered having an early treatment failure and the immunotherapy was stopped before PET<sub>interim2</sub>. Among these patients, 6/10 died during the 6-month follow-up. Nonetheless, we cannot be sure that the remaining 4/10 patients would not have showed a delayed tumor response. Indeed, previous case reports described pseudo-progressions accompanied with worsening of clinical symptoms, followed by delayed and drastic treatment response to immunotherapy [25].

Compared with CT, the limit of <sup>18</sup>F-DG PET/CT to monitor tumor response to immunotherapy is the lack of specific guidelines/criteria for response assessment, such as iRECIST [10]. Robust studies comparing the concordance between RECIST, iRECIST, and PERCIST in this setting are also needed. Moreover, brain is a common site of metastatic spread in patients with NSCLC. The gold standard for the diagnosis of brain metastases is MRI. <sup>18</sup>F-DG PET/CT has indeed a lower sensitivity in detecting brain metastases [26]. Thus, when using PET/CT for the initial staging of NSCLC, brain MRI cannot be withdrawn. During the course of their disease, some patients with NSCLC will develop brain metastases. Because some of them may be detected by <sup>18</sup>F-DG PET/CT [27], the brain should be included in the PET acquisition field, and iodinated contrast agent should be injected if there are no contraindications. Nonetheless, new brain metastases will still be missed if no brain MRI is performed in the follow-up.

In conclusion, a PERCIST response assessed on FDG PET performed 7 weeks after beginning immunotherapy may accurately identify NSCLC patients with a durable clinical benefit of immunotherapy. To identify treatment failure, new visceral/bone hypermetabolic lesion is not a good criterion as it does not avoid misclassification of many responding patients. In patients with a first PD on PERCIST and treatment

continuation, a subsequent PET identifies more than half of patients with an atypical response pattern, either pseudo-progression or immune dissociated response (iDR), both being strongly associated with a favorable clinical outcome.

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### Compliance with ethical standards

**Conflict of interest** O. Humbert, N. Cadour, M. Paquet, R. Schiappa, M. Poudenx, D. Chardin, D. Borchiellini, D. Benisvy, M.J. Ouvrier, C. Zwarthoed, A. Schiazza, H. Ghalloussi, P.M. Koulibaly, J. Darcourt, and J. Otto declare that they have no conflict of interest. M. Ilie reports personal fees from AstraZeneca, Bristol-Myers Squibb, Roche, Boehringer-Ingelheim, and Merck & Co outside the submitted work.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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