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^{18}F-FDG PET and CT-scan Detect New Imaging Patterns of Response and Progression in Patients with Hodgkin Lymphoma Treated by Anti-PD1 Immune Checkpoint Inhibitor

SHORT RUNNING TITLE
Immune Patterns of Response in HL

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ABSTRACT

The response evaluation criteria in patients with Hodgkin Lymphoma (HL) were designed for the assessment of chemotherapy and targeted molecular agents. We investigated the accuracy of 3-month-18F-FDG-PET/CT for the identification of HL patients (pts) responding to immune-checkpoint blockade by Anti-Programmed Death 1 antibodies (anti-PD1). We also reported the frequency of new immune patterns of response and progression.

Methods. Retrospectively, we recruited consecutive HL patients treated by anti-PD1 (Pembrolizumab or Nivolumab) at Gustave Roussy, Villejuif, France, from 2013-2015. FDG-PET/CTs and contrast-enhanced CT-scans were acquired every three months. We recorded the best overall response according to the International Harmonization Project Cheson 2014 criteria and LYRIC 2016 revised criteria. Patients achieving an objective response at any time during the anti-PD1 treatment were classified as responders.

Results. Sixteen relapsed or refractory classical HL pts were included. Median age was 39 (19-69) years. Median previous lines of therapy was 6 (3-13).

The mean follow-up was 22.6 months. Nine out of sixteen pts (56%) achieved an objective response. Two deaths occurred due to progressive disease at 7 months.

18F-FDG-PET/CT detected all responders at 3 months and reclassified best overall response in 5 pts compared to CT-scan alone. Decrease in tumor metabolism and volume (SUVmean, MTV) and increase in healthy splenic metabolism at 3-month were observed in responders (AUC>0.85, P<0.04).

Five out of sixteen pts (31%) displayed new imaging patterns related to anti-PD1; we observed two transient progressions consistent with indeterminate response according to the LYRIC 2016 criteria (IR2b at 14 months and IR3 at 18 months), and three patients with new lesions associated with immune-related adverse events.

Conclusions. 3-month-18F-FDG-PET/CTs detect HL pts responding to anti-PD1. New patterns were encountered in 31% of pts, emphasizing the need for further evaluation in larger series and close collaboration between imaging and oncology specialists on per patient basis.

KEY WORDS.

Hodgkin lymphoma, FDG-PET/CT, immunomodulatory, Cheson, Lugano

INTRODUCTION

Hodgkin Reed-Sternberg cells escape immune surveillance through a genetic alteration in chromosome 9p24.1, that leads to an overexpression of the programmed death-1 ligands (*1*). Pembrolizumab and nivolumab are programmed death-1 blockade antibodies (anti-PD1) that restore immunity against Hodgkin Reed-Sternberg cells. Anti-PD1 have recently demonstrated high (64%-87%) response rates in relapsed or refractory HL (*2,3*).

Hodgkin lesions constitute a unique microenvironment, with a minority of Hodgkin Reed-Sternberg cells (often less than 1%) that interact with numerous microenvironment cells (*4-6*). The high avidity of Hodgkin lesions for glucose analog translates into a high 18F-Fludeoxyglucose (18F-FDG) uptake visible on Positron Emission Tomography (PET) (*7*). The Warburg effect (*8*) leads to an important increase in glucose consumption in proliferative tissue or tumor (as compared to differentiated tissue) due to an increase in anaerobic glycolysis. Theoretically, anti-PD1 could lead to an activation of antitumor microenvironment immune cells translating into increased glucose metabolic consumption by an up-regulation of Glut mRNA (to provide cellular energy), up-regulation of Glut proteins (to compete for hexoses uptake) (*9,10*) leading to increased FDG uptake (*11*). This could mask anti-PD1 treatment efficacy on 18F-FDG PET in HL.

Anti-PD1 induce new patterns of progression and possibly new response paradigms that can alter decision-making in patients' management and ultimately patient outcomes. Indeed, 5-10% of patients with solid tumors (*12*) experience "pseudo-progression", usually early during treatment, with imaging findings suggestive of progressive disease but followed by later imaging response (*12-17*). The LYmphoma Response to Immunomodulatory therapy Criteria (LYRIC) introduced in 2016 the term "Indeterminate Response" (IR) - instead of progression - in the time interval until a biopsy or subsequent imaging confirm either a pseudo progression or a true progression (*18*) restraining clinicians to a wait and see strategy. Additionally, new immune patterns were described such as abscopal effect (i.e. a tumor antigens released by radiotherapy lead to the regression of metastatic cancer size and metabolism at distance from the irradiated site due to the enhancement of the diversity of the T-cell receptor) (*19*) and hyperprogression (i.e. anti-PD1 initiation leads to a paradoxal increase in tumor growth rate) (*20*).

The reference standards for the monitoring of HL are Computed Tomography scan (CT-scan) and 18F-FDG PET (*18,21,22*). Interim 18F-FDG PET is indeed crucial for assessing the response to Adriamycin, Bleomycin, Vinblastine, Dacarbazine (*23*) as well as Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Oncovin, Procarbazine and Prednisone regimen (*24*). The

current response criteria were however designed for chemotherapies and drugs targeting the cancer cells. Therefore, a treatment response is defined by a tumor shrinkage (IWG-Cheson) (*22*) and/or a decrease of tumor glycolytic metabolism (Lugano classification) (*21*) within Hodgkin lesions. Imaging-based response evaluation criteria should now integrate the paradigm shift introduced by anti-PD1, which aims the activation of the antitumor immune system. We investigated, in a pilot patient-based and lesion-based imaging study, the metabolic pattern of response in HL treated with anti-PD1.

MATERIALS AND METHODS

Patient selection.

Patient selection and treatment [see TABLE 1]. In a single center study, 16 adult HL pts treated with anti-PD1 were retrospectively selected, 15 treated by pembrolizumab IV in clinical trials (NCT01953692, NCT02453594) and another treated by nivolumab IV in a compassionate program. Pts were treated for HL relapsing or refractory to salvage chemotherapy including brentuximab vedotin and auto-stem cell transplantation at Gustave Roussy, Villejuif, France from December 2013 to December 2015. All pts had a 18F-FDG PET and contrast enhanced CTs evaluations at baseline and every 3 mo until progression or cessation of treatment for up to 2y. The protocols (NCT01953692 and NCT02453594) were approved by ethics committee and all subjects signed a written informed consent.

18F-FDG PET and CT-scan acquisitions.

18F-FDG PET/CTs acquisitions and reconstructions were performed according to guidelines (*25*) using a Discovery 690 (General Electric Medical

Systems, Waukesha, WI, USA) with an activity of 3-4 MBq/Kg of 18F-FDG, a 2-minute per bed acquisition time and a 90-minute delay after 18F-FDG injection. Whole-body CT-scan acquisitions were performed using a 64 HiSpeed spiral scanner (GE Medical Systems, Milwaukee, WI) after administration of intravenous contrast agent.

Response evaluation criteria.

A central consensus review of all imaging data was performed. The change in the sum of the product of the perpendicular diameters of target lesions (Delta SPD-Cheson) on contrast-enhanced CT-scan was measured using Cheson 2014 criteria (*18,21,22*). The evolution of non-target lesions and new lesions was recorded. The 18F-FDG PET was scored according to the 5-point scale scoring system (PET-5PS) (*18,21,22*): (1) No uptake; (2) Uptake < mediastinum; (3) Uptake > mediastinum but < liver; (4) Uptake moderately more than liver uptake, at any site; (5) Markedly increased uptake at any site and/or new sites of disease.

Monitoring of imaging studies

The change in CT and PET biomarkers across anti-PD1 treatment sequence was measured [see TABLE 2] to compute their predictive value [see TABLE 3]: (i) skeletal muscle index (SMI) on CT-scans (marker of sarcopenia, predictor of outcome (*26*)); (ii) metabolic tumor volume (MTV) and total lesion glycolysis

(TLG) measured inside the whole tumor volume defined by Lugano criteria (*18,21,22*) using the Nestle approach for the segmentation (*27*); (iii) maximum Standardized Uptake value (SUVmax) and mean SUV (SUVmean) measured inside the whole tumor volume previously segmented ; (iv) glucose consumption of healthy lymphoid tissue (spleen, thymus, ileocaecal valve and healthy osteomedullary bone) (our driving hypothesis was that the activation of antitumor immunity by anti-PD1 could translate into increased glucose consumption outside the Hodgkin tumor lesions).

Monitoring of non-imaging biomarkers

The variation in full blood count parameters across the treatment sequence was measured (see TABLE 4).

Pattern of response and progression

Best overall response (BOR) was defined per Cheson 2014 criteria (*2*) and took into consideration the 2016 LYRIC classification concept of “Indeterminate Response” (IR) (*18*) (see TABLE 6). Pts having achieved an objective partial or complete response at any time during the treatment were defined as responders. Pts having achieved stability or progression as BOR at any time were classified as refractory. The reference-standard was the multidisciplinary experts’ consensus based on clinical and imaging results and if feasible on biopsy and histology when 18F-FDG positive lesion was persistent (*18,21,22*).

Identification of responders to anti-PD1 at three months

For all pts, we measured the change in response evaluation criteria, imaging biomarkers and full blood count parameters between baseline and 3mo [see TABLES 2, 3]. We evaluated if 3mo changes in biomarkers allowed for the identification of patients responding to anti-PD1 (TABLES 2, 3).

Lesion-based analysis

In a subset of 290 Hodgkin lesions identified at baseline, we monitored the glucose consumption at 3mo, 6mo and 9mo and calculated the positive and negative predictive value (PPV and NPV) of the PET-5PS Lugano (TABLE 5).

Statistical methods

Descriptive statistics were performed using conventional metrics (mean, median, range). Non-parametric tests were used for comparison or correlation. Wilcoxon tests compared the mean value of the two populations. Area Under the Receiver Operating Characteristic curve (AUC) evaluated the accuracy of imaginings features for the detection of refractory patients. Statistical analyses were performed using SPSS software version 23.0.

RESULTS

Patients' characteristics

Patients Characteristics. See TABLE 1. Anti-PD1 median period between lymphoma diagnosis and initiating anti-PD1 treatment was 4.4 years (0.6:14.8). Patients had a median of 6 (3:13) previous therapeutic lines. Sixteen patients received previous chemotherapy, and eight patients received autologous stem-cell transplant.

Treatment. 9 out of 16 pts achieved an objective response. 13 patients stopped treatment after a mean duration of 15.3 months at the cut-off date of analysis. The mean follow-up was 22.6 months. The estimated (95% CI) overall survival in the overall population was 34.7 (29.6-39.7) months according to Kaplan-Meier analysis. None of negative 18F-FDG-PET pts died. Two pts died due to progressive disease at 7 months (pts 7 and 9).

Change in Anthropomorphic Characteristics. At three months, there was no significant difference between responders and refractory pts. At 6 months and beyond, stability or improvement of the SMI was observed in 10/16 patients, mostly in the responders (FIGURES 1-3).

Patterns of response and progression in patients

Best Overall Response. The BOR with Cheson 2014 criteria combining 18F-FDG PET/CT and contrast enhanced CT-scan was: Complete Response: 4 pts, Partial Response: 6 pts, Stable Disease: 3 pts, Progressive Disease: 3 pts. Compared to CT-scan alone, 18F-FDG PET reclassified 5 pts: one SD as PD, one CR as PR and 3 PR as CR. The range of BOR within 6 months after treatment initiation was widely different among pts (FIGURES 1-3).

Depth of the Response Over Time. All pts who achieved objective response did it at the first 3mo assessment. FIGURE 1 shows that the depth of the response in most pts slightly increased between 3 and 6 mo and even for pts 1, 4, 5, 6 lasted for more than 1 year.

Indeterminate Responses (IR) by LYRIC Criteria. 7 pts were indeterminate, 5 proved to be true progressions and 2 transient progressions. Pt 16 had IR1 and IR2 profile: new lesion and increase in tumor burden at 3 mo without clinical deterioration that were subsequently confirmed as tumor lesions. 6/16 pts analyzed during the first 6 months were qualified as IR2a (a new lesion at any time). In these 6 pts, 46 new tumors sites were detected (lesion sites: 30 lymph nodes, 7 lung, 6 spleen, 2 bones and 1 multifocal bone involvement). All these new lesions persisted and considered as progressive lesions. Pt 4 experienced an IR2b between 14mo and 16mo (FIGURE 4): transient progression in tumor

size and 18F-FDG uptake. In Pt 1 (FIGURE 5), a transient progression of SUVmax is detailed; the lesion qualified as IR3 but ultimately progressed morphologically and metabolically at 36-month after the discontinuation of anti-PD1.

New Non-tumor Lesions. 6 pts had new 18F-FDG positive lesions during anti-PD1 treatment (FIGURE 6) that were not tumor lesions. 18F-FDG PET detected concurrent pulmonary infection and zona activation in Pts 5 and 14. 18F-FDG PET detected IRAEs in Pts 3, 6, 9 and 16: one confirmed colitis, two interstitial pneumonitis (one confirmed as IRAE) and one confirmed pancreatitis.

Hyperprogression. There was no case of hyperprogression. The tumor growth rate decreased in all pts after anti-PD1 initiation (e.g. FIGURE 7).

Three months prediction of BOR

We evaluated if early changes in CTs, PETs and blood biological biomarkers measured at baseline and 3 mo predicted BOR and thus identified responders to anti-PD1. The most accurate biomarker was ΔMTV according to ROC analysis (TABLES 2 and 3).

Change in Tumor Burden. The mean shrinkage of target tumor lesions at 3 mo was significantly greater in responders (TABLE 2) as demonstrated by

ΔSPD-Cheson, ΔMTV, ΔTLG (P<0.03). The AUC of those biomarkers was above 0.95 (P<0.008) (TABLE 3). No refractory pts achieved MTV shrinkage greater than 50% at 3 months (Se: 71%, Spe: 100%).

PET-5PS. PET-5PS was not significantly different between refractory and responding patients as demonstrated by the comparison of the mean value (P=0.13, TABLE 2) and the AUC (P=0.13, TABLE 3).

Change in Tumor Glucose Consumption. Responders had significantly greater decrease in SUVmean and SUVmax, which AUC was above 0.87 (P<0.03) (TABLES 2 and 3). A 3 mo decrease in SUVmax (Δ<-50%) was observed exclusively in responders.

Change in Healthy Lymphoid Tissues SUVmax. The variation of glucose consumption within healthy lymphoid tissues was not measurable in some patients due to splenectomy (Pt 12), thymus infiltration (Pt 13), osteomedullary infiltration (Pt 11). A significant increase in spleen glucose consumption – delta SUVmax – was observed in responders (TABLES 2 and 3). Variation in glucose consumption within spleen, thymus and bone medulla were not statistically significant (P>0.21) predictor of outcome.

Change in Full Blood Count Parameters. None was significantly associated with immune-response (TABLE 4).

Lesion-based analysis

Positive and Negative Predictive Value of Lesions. TABLE 5 shows the excellent accuracy of the PET-5PS classification for the prediction of the outcome of a Hodgkin lesion at 3, 6 and 9 months. The PPV and the NPV were respectively above 88% and 97% with no pseudo-progression phenomenon observed.

Correlation Between 18F-FDG Uptake and Biopsies. Good correlation between persistent 18F-FDG uptake and persistent tumor Hodgkin Reed-Sternberg cells in 3 biopsies performed in 3 different patients at 24.7 months (Pt 2), 23.1 months (Pt 4) and 9.6 months (Pt 12).

DISCUSSION

To the best of our knowledge, this is the first study of new metabolic patterns of response in HL pts treated with anti-PD1 at a patient-level and lesion-level. 18F-FDG PET allowed refining the BOR classification in one third of patients as compared to CT-scan only, demonstrating the potential added value of 18F-FDG PET for response assessment.

The evaluation of anti-PD1 treatment effect by 18F-FDG PET at three months is clinically relevant, as it clearly identify responders. Indeed, all responders have reached the response by three months. Future studies might evaluate the predictive value of earlier evaluation.

On a 18F-FDG PET interpretation perspective, we showed that the PET-5PS has an excellent positive and predictive value at a lesion level although it might be outperformed by quantitative PET metrics on a patient-based analysis (*2*). Indeed, the persistence of 18F-FDG PET positive lesions at 3-month does not preclude a prolonged clinical benefit. Our pilot study described the significant shrinkage in tumor volume (ΔSPD-Cheson, ΔMTV, ΔTLG), decrease in tumor glucose metabolism (ΔSUVmean, ΔSUVmax), and increase in spleen metabolism observed in responders (n=9) that may be useful for the calibration of decision support classification threshold. Additionally, we showed that the interpretation of SUVmax needs to be careful because transient-progression of SUVmax can be observed in lesions (Figure 4 and 5) and association between SUVmax variation and treatment response is not obvious. Interestingly, healthy spleen tissue 18F-FDG uptake appears significantly increase in responders suggesting a favorable immunological reconstitution. Further prospective and largest studies are required to validate these biomarkers.

Most patients have achieved a very good partial and prolonged response, while only few patients were in a complete response. We have confirmed, through histological restaging, that residual 18F-FDG positive lesions remained of lymphomatous origin. As described by Armand P. in the redefined LYRIC 2016 classification (TABLE 6), we observed in the present series 13% of “indeterminate responses”. Importantly, we did not find any early "pseudo-progression" as defined at three months, as all the new lesions observed at that time had proved to be real progressions. The “indeterminate responses” observed in our series were delayed. These IR occurred beyond the first year of treatment, with transient fluctuations in tumor size or glucose uptake of residual Hodgkin lesions. In a daily management point of view, the “indeterminate responses” is important to be considered if the patient is clinically doing well, encouraging to not prematurely withdrew the anti-PD1 treatment. Otherwise, 18F-FDG PET had detected non-tumor lesions in 37% of patients, mainly related to immune side effects. In contrast to solid tumors studies, we have not encountered "hyper progressions" profiles (*20*) in this pilot series.

CONCLUSION

These data demonstrate that the 18-FDG PET evaluation of anti-PD1 treatment is different from classical chemotherapy. Patients may remain in prolonged partial responses, while continuing to likely benefit from anti-PD1 treatment. New imaging patterns related to anti-PD1 were encountered in 31%

of patients. 18-FDG-PET may also reveal “indeterminate responses” mainly during the second year of treatment, as well as non-tumor lesions mainly due to immune-related adverse events.

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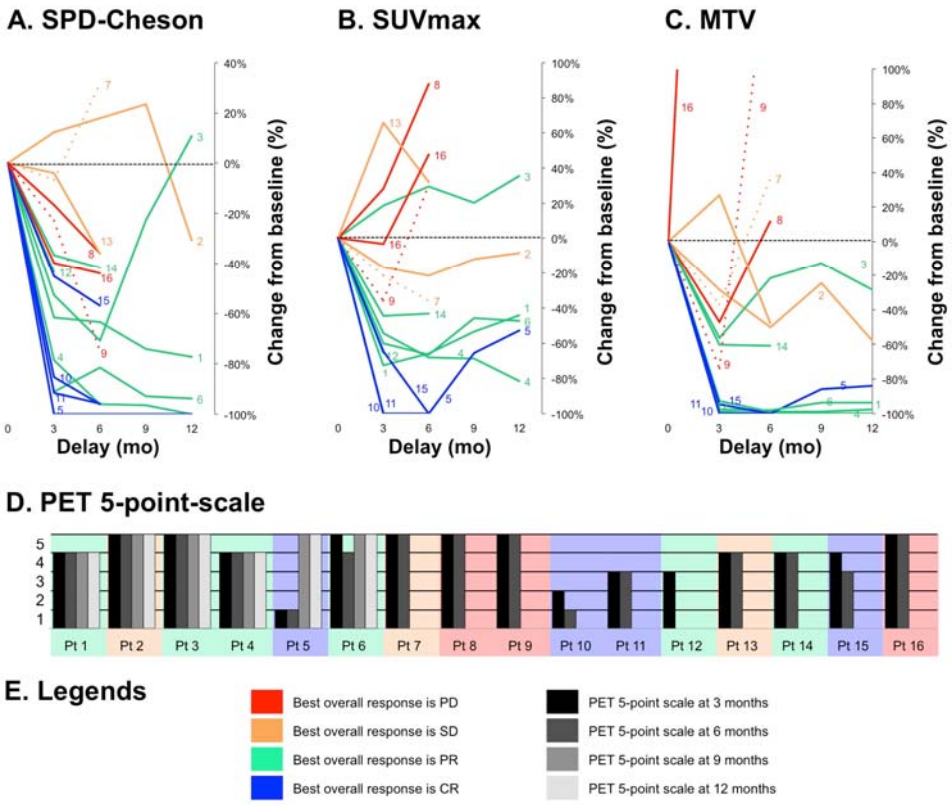

Figure 1. Patterns of response on CT-scan and FDG-PET

Figure 1 legend. Evolution of patients after the initiation of Anti-PD1. A number identifies each patient. The dotted lines distinguish two patients that died from progression. The color indicates the BOR according to Cheson 2014 criteria (blue=CR, green=PR, orange=SD, red=PD).

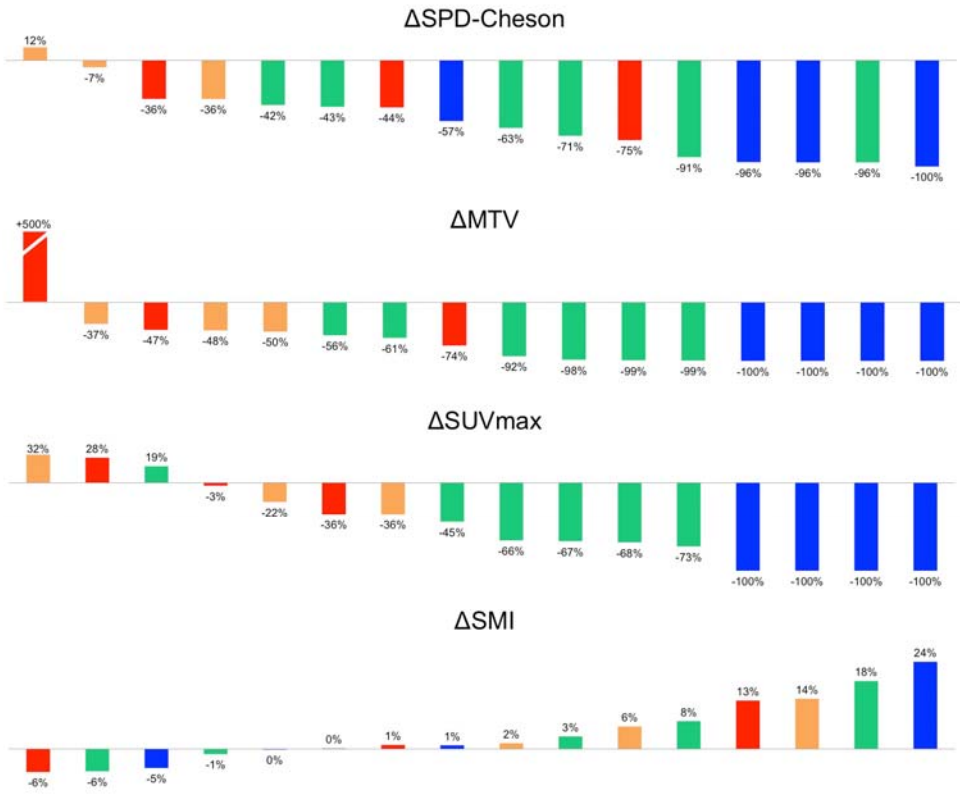

Figure 2. Best 6-month variation in imaging biomarkers

Figure 2 legend. The color code refers to the BOR according to Cheson 2014 criteria (blue=CR, green=PR, orange=SD, red=PD).

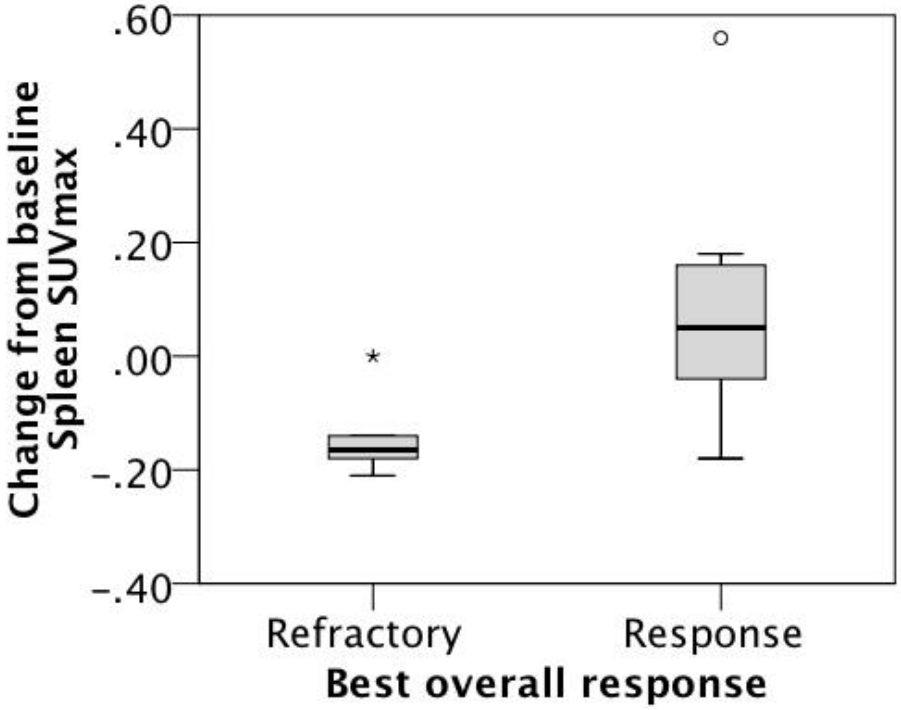

Figure 3. Responders have an increase in spleen metabolism (delta-SUVspleen) at 3 months

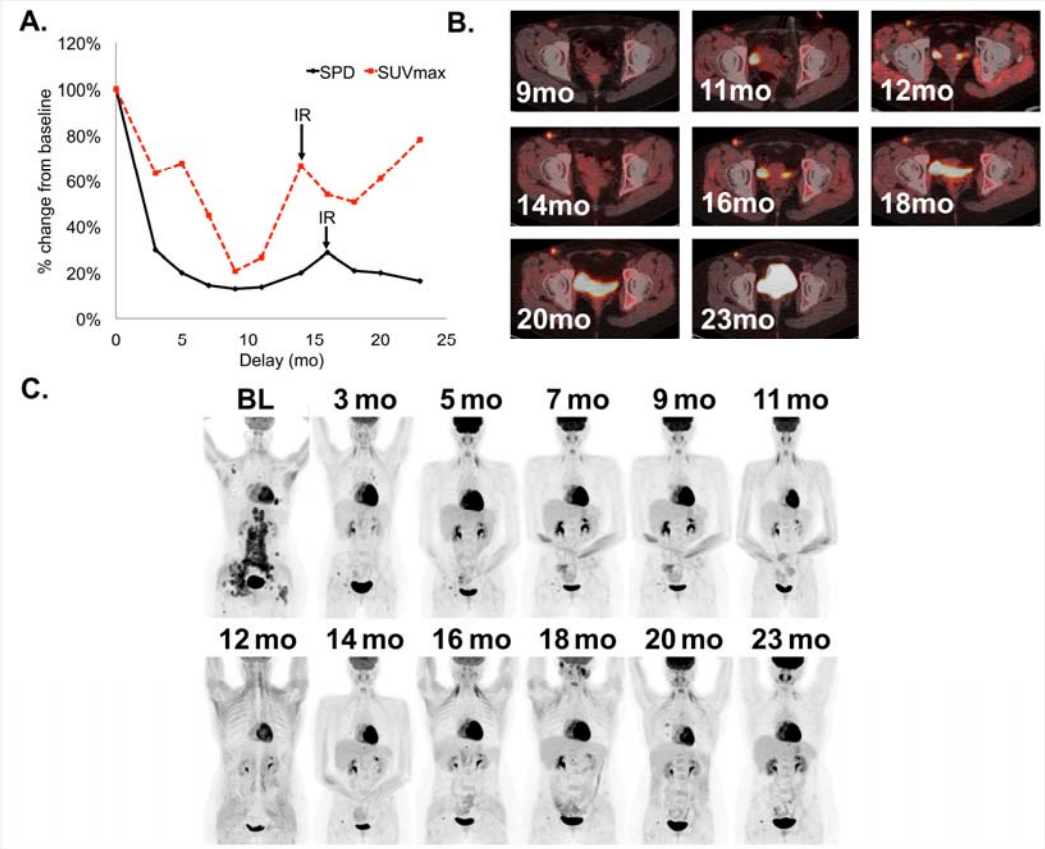

Figure 4. Indeterminate response type 2: transient size progression

Figure 4 legend. Evolution of SPD and SUVmax after treatment initiation expressed as a percentage (A). Evolution of the right inguinal lesion (B). Evolution of the patient (C).

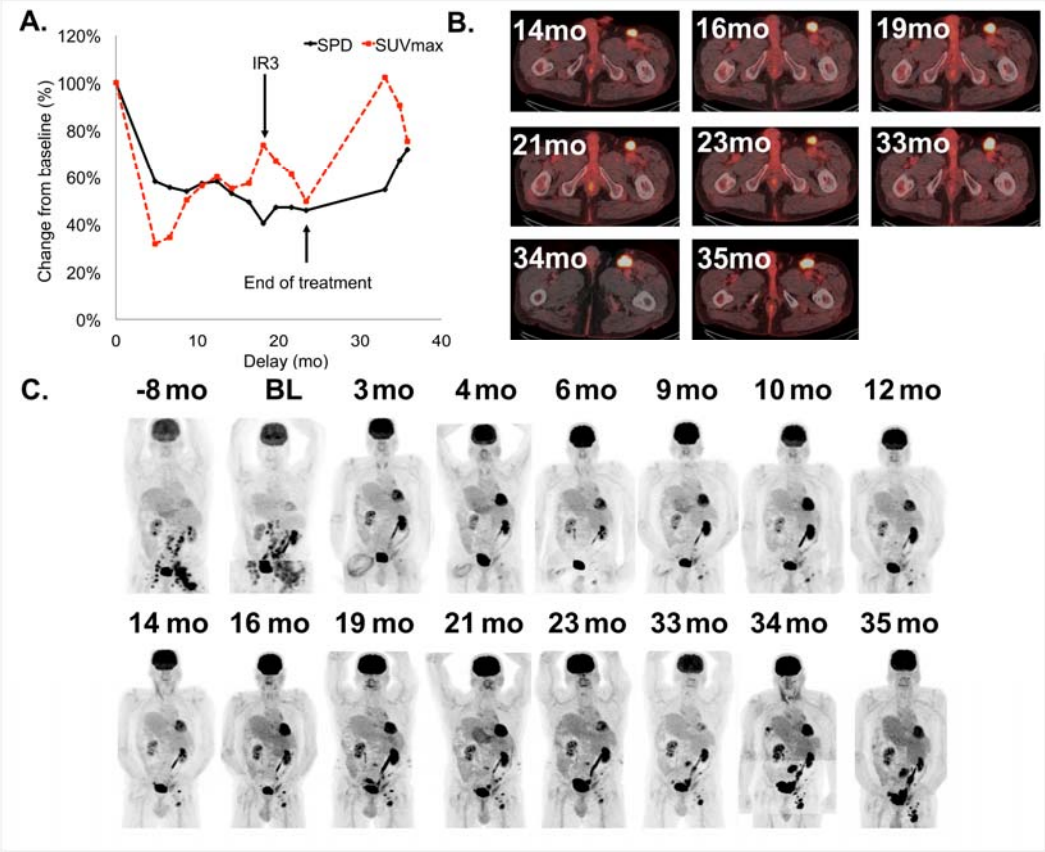

Figure 5. Indeterminate response type 3: transient SUVmax progression

Figure 5 legend. Evolution of SPD and SUVmax after treatment initiation expressed as a percentage (A). Evolution of the left inguinal lesion (B) and of the patient (C).

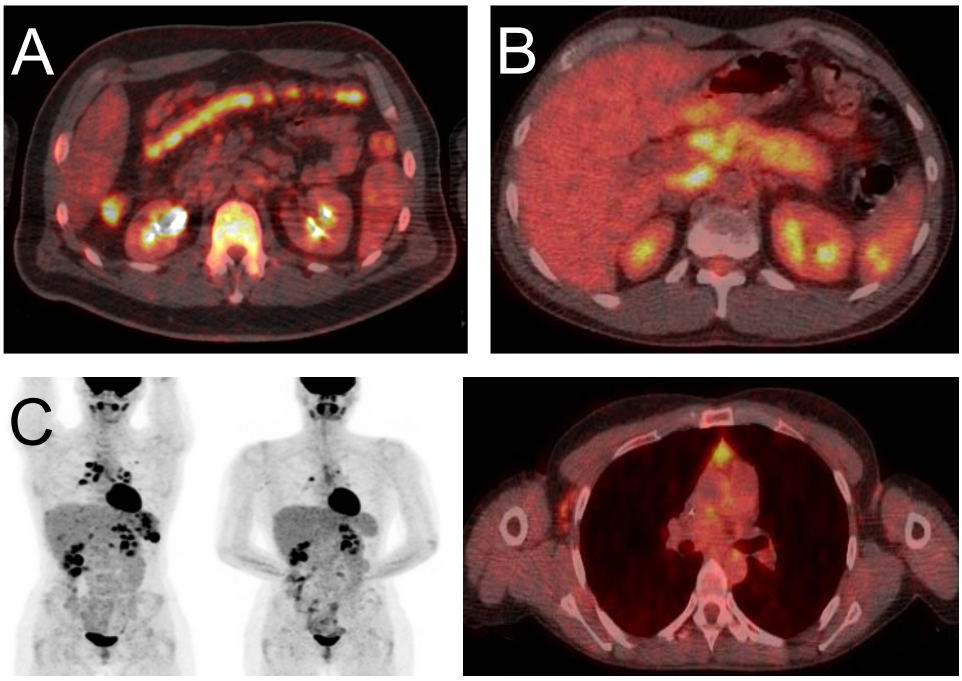

Figure 6. New non-Hodgkin lesions appeared during Anti-PD1 treatment

Figure 6 legend. FDG-PET/CT detected a grade 2 colitis (A), a pancreatitis (B) and a zona activation in the right axilla (C, from left to right: MIP baseline, MIP and Fused PET/CT image during follow-up).

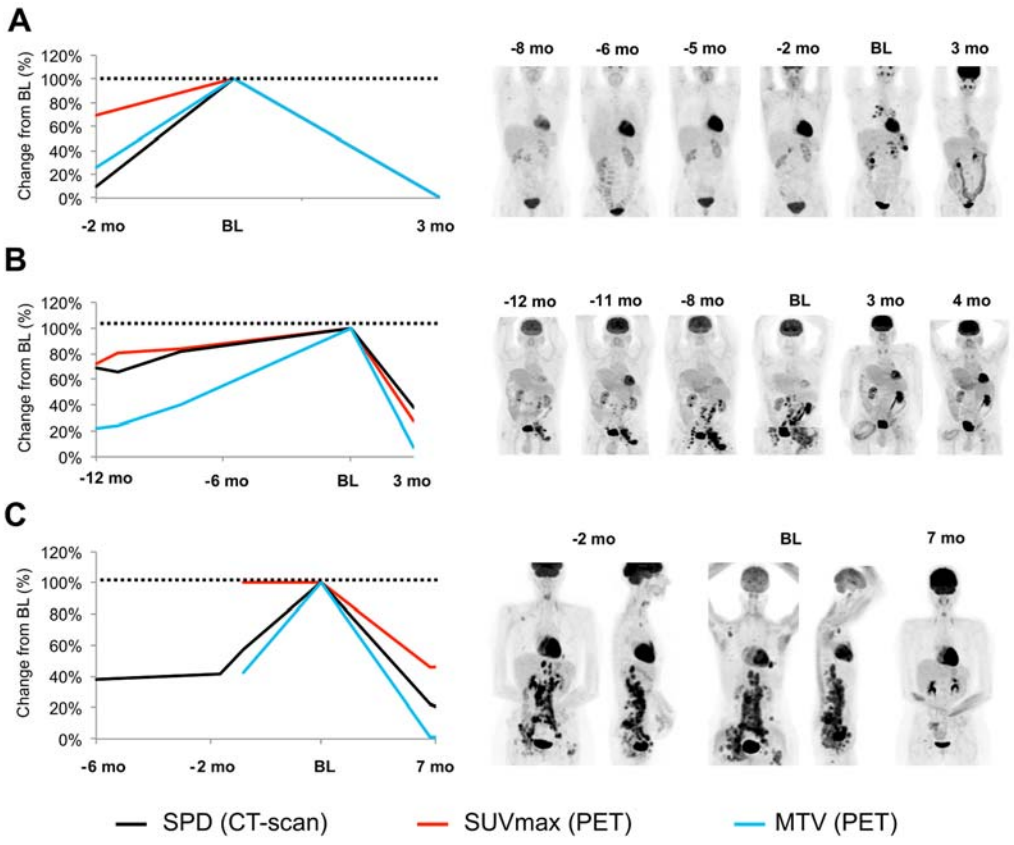

Figure 7. No hyperprogression was observed after Anti-PD1 initiation

Figure 7 legend. The tumor growth rate decreased in all patients (e.g. A, B, C). The value of SPD, SUVmax and MTV is set up at 100% at baseline in order to evaluate their variation before and after treatment initiation.

Table 1. Patients' characteristics

	Characteristics	Total patients population (N=16) No. (%) Median (range)
Gender	Male	9 (56%)
	Female	7 (44%)
Treatment	Pembrolizumab (clinical trial)	15 (94%)
	200 mg / 2 weeks (NCT01953692)	8 (50%)
	200 mg / 3 weeks (NCT02453594)	7 (44%)
	Nivolumab (compassionate)	1 (6%)
	3 mg / kg / 2 weeks	1 (6%)
	Age	39 (19-69)
	Delay since first diagnosis	4.4 years (0.6-14.8)
Ann Arbor stage	Localized	5 (31%)
	I	0 (0%)
	IIA	2 (13%)
	IIB	3 (19%)
	Advanced	11 (69%)
	III	1 (6%)
	IV	10 (63%)
Prior treatments	Previous lines of therapy[a]	6 (3-13)
	Chemotherapies	16 (100%)
	Targeted molecular agents	5 (31%)
	Autologous stem cell transplantation	8 (50%)
	Radiation therapy	5 (31%)

[a] excluding high-dose preparative regimen prior autologous stem cell transplantation.

Table 2. 18F-FDG PET and CT response at 3 months predict BOR

Table 2 legend. Distribution of imaging biomarkers in refractory and responding patients at baseline (BL) and changes 3 months after Anti-PD1 initiation (Δ3, expressed as a percentage). The Wilcoxon test shows significant differences between the two groups. Each missing data in the refractory and response groups are respectively mentioned by * and †.

		Refractory (n=7)		**Responding (n=9)**		
		Mean	Median	Mean	Median	P-value
Guidelines						
SPD-Cheson	BL (cm2)	23.7	20.1	40.3	16.5	0.31
	Δ3	-19%	-17%	-70%	-79%	**0.03**
PET-5PS	3 months	4.43	5	3.56	4	0.13
Tumor 18F-FDG uptake						
SUVmean	BL	4.42	4.7	5.52	5.3	0.11
	Δ3	-11%	-13%	-54%	-44%	**0.03**
SUVmax	BL	12.33	14.3	16.18	14.4	0.31
	Δ3	-8%	-17%	-63%	-65%	0.09
MTV	BL (cm3)	85	54	339	41	0.06
	Δ3	49%	-37%	-90%	-98%	**0.02**
TLG	BL (SUV.cm3)	85	54	339	41	0.06
	Δ3	49%	-37%	-90%	-98%	**0.02**
Lymphoid 18F-FDG uptake						
Spleen	BL*	3	2.9	2.67	2.5	0.46
	Δ3*	-14%	-16%	8%	5%	**0.03**
Thymus	BL*	1.62	1.5	1.76	1.9	0.6
	Δ3*	-5%	0%	11%	8%	0.6
Ileocaecal	BL	3.71	2.9	2.78	2.6	0.74
	Δ3	-11%	-7%	9%	17%	0.74
Osteomedullary	BL†	2.79	2.6	3.71	3.05	0.21
	Δ3†	-6%	-13%	-4%	-4%	0.74
Sarcopenia						
SMI	BL (cm2.m-2)	68	65	74	71	0.87
	Δ3	3%	3%	3%	0%	1

Table 4. 18F-FDG PET and CT response at 3 months predict BOR

Variables	AUC [CI95]	P-value
Guidelines		
ΔSPD-Cheson	.95 [.83-1.0]	.008
PET 5-point scale	.80 [.55-1.0]	.079
Intensity of glucose consumption - tumor volume		
ΔSUVmean	.89 [.72-1.0]	.01
ΔSUVmax	.87 [.67-1.0]	.028
Tumor Burden		
ΔMTV	.98 [.90-1.0]	.005
ΔTLG	.95 [.86-1.0]	.003
Intensity of glucose consumption - healthy lymphoid tissue		
ΔSUVmax spleen	.85 [.63-1.0]	.04

Table 4 legends. Responders have a significant decrease in tumor volume and metabolism and increase in spleen metabolism at 3 months.

Table 3. Biological response at 3 months does not predict BOR

Table 3 legend. This table shows the distribution of biological biomarkers in refractory and responding patients at baseline (BL) and their change 3 months after Anti-PD1 initiation (Δ3, expressed as a percentage). The Wilcoxon test does not show significant mean differences between those two groups.

		Refractory (n=7)		**Responding (n=9)**		**P-value**
		Mean	Median	Mean	Median	
Albumin	BL (g/l)	38	38	34	39	0.31
	Δ3	9%	5%	8%	2%	0.87
LDH	BL (UI/l)	211	208	239	225	0.74
	Δ3	-4%	0%	-12%	-21%	0.50
Leucocyte	BL (G/l)	10.5	9.6	11.07	7.7	1.00
	Δ3	-20%	-14%	-19%	-18%	0.50
PNN	BL (G/l)	6.6	6.6	8.71	6.7	0.61
	Δ3	-19%	-32%	-30%	-28%	1.00
PNEo	BL (G/l)	1.19	0.5	0.22	0.1	0.15
	Δ3†	39%	0%	499%	75%	0.75
PNBaso	BL (G/l)	0.17	0	0.01	0	0.20
	Δ3**********††††††††††	-67%	-100%	-100%		
Lymphocytes	BL (G/l)	1.83	1.4	1	1.1	0.17
	Δ3*	13%	-2%	62%	33%	0.35
Monocytes	BL (G/l)	0.81	0.7	1.1	0.6	0.92
	Δ3	-2%	0%	1%	0%	0.50
CRP	BL (mg/dl)	79	40	132	113	0.40
	Δ3**††	57%	-85%	-55%	-91%	0.29
Fibrinogen	BL (G/l)*	6.32	6.8	5.64	5.7	0.60
	Δ3**††	-16%	-29%	-32%	-29%	0.14

Table 5. PET 5-point scale classification has a good predictive value for lesions outcome

Table 5 legend. We evaluated the glucose metabolism within 290 Hodgkin lesions at baseline, and every 3 months after Anti-PD1 initiation. PET-5PS has an excellent negative and positive predictive value.

		FDG-avid at 3 months			FDG-avid at 6 months		
		+	-	Total	+	-	Total
FDG-avid 3 months later	**+**	119	13	132	63	4	67
	-	16	142	158	2	138	140
	Total	135 PPV: 88%	155 NPV: 92%	290	65 PPV: 97%	142 NPV: 97%	207

Table 6. Comparison of Lugano and LYRIC criteria

Table 6 legend. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy as proposed by Cheson et al (*18*).

Criteria	CR	PR	PD
Lugano	PET-CT score 1, 2, or 3 with or without a residual mass on 5PS OR on CT, target nodes/nodal masses must regress to ≤1.5 cm in LDi	PET-CT score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size. OR On CT ≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites	PET-CT score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment. OR On CT, an individual node/lesion must be abnormal with: longest diameter >1.5 cm and increase by ≥50% from product of the perpendicular diameters nadir and an increase in longest diameter or short diameter from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm
			In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by ≥2 cm from baseline. New or recurrent splenomegaly
			New or clear progression of preexisiting nonmeasured lesions
			Regrowth of previously resolved lesions
			A new node >1.5 cm in any axis or a new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma
			Assessable disease of any size unequivocally attributable to lymphoma
			AND/OR new or recurrent involvement of the bone marrow
LYRIC	Same as Lugano	Same as Lugano	As with Lugano with the following exceptions
			IR1: ≥50% increase in SPD in first 12 weeks
			IR2a: <50% increase in SPD with new lesion(s)
			IR2b: <50% increase in SPD with ≥50% increase in PPD of a lesion or set of lesions at any time during treatment
			IR3: Increase in FDG uptake without a concomitant increase in lesion size meeting criteria for PD