Hyperprogressive disease (HPD) is a new pattern of progression in cancer patients treated by anti-PD-1/PD-L1

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Rapid progressions have been anecdotally reported in cancer patients treated with anti-PD-1/PD-L1 monoclonal antibodies. A total of 131 patients treated with anti-PD-1/PD-L1 in phase 1 clinical trials at Gustave Roussy were evaluable for their tumor growth rate (TGR) before treatment (“REFERENCE period”) and upon treatment (“EXPERIMENTAL period”). Patients with hyperprogressive disease (HPD) were defined as patients with disease progression by RECIST criteria with a ≥ two-fold increase in the TGR EXPERIMENTAL vs. REFERENCE. Thus, we identified 12 pts (9%) with an HPD pattern. HPD was not associated with advanced disease and was equally observed with PD-1/PD-L1 blockers, and was observed across tumor types. Importantly, HPD was associated with an older age and with worse overall survival. Overall, this suggests that HPD is a new pattern of progression observed in a fraction of patients, and argues potentially caution when using anti-PD-1/PD-L1 monotherapy in patients older than 65 years old.
ABSTRACT

Purpose

While Immune checkpoint inhibitors are disrupting the management of cancer patients, anecdotal occurrences of rapid progression (i.e. hyperprogressive disease or HPD) under these agents have been described, suggesting potentially deleterious effects of these drugs. The prevalence, the natural history and the predictive factors of HPD in cancer patients treated by anti PD-1/PD-L1 remain unknown.

Experimental design

Medical records from all patients (N =218) prospectively treated in Gustave Roussy by anti PD-1/PD-L1 within phase I clinical trials were analyzed. The tumor growth rate (TGR) prior (“REFERENCE”) and upon (“EXPERIMENTAL”) anti-PD-1/PD-L1 therapy was compared to identify patients with accelerated tumor growth. Associations between TGR, clinico-pathological characteristics and overall survival (OS) were computed.

Results

HPD was defined as a RECIST progression at the first evaluation and as a ≥ two-fold increase of the TGR between the REF and the EXP periods. Out of 131 evaluable patients, 12 patients (9%) were considered as having HPD. HPD was not associated with higher tumor burden at baseline, nor with any specific tumor type. At progression, patients with HPD had a lower rate of new lesions than patients with disease progression without HPD (p<0.05). HPD is associated with a higher age (p<0.05) and a worse outcome (Overall Survival). Interestingly, REFERENCE TGR
(before treatment) was inversely correlated with response to anti-PD-1/PD-L1 (P<0.05) therapy.

Conclusion

A novel aggressive pattern of hyper-progression exists in a fraction of patients treated with anti-PD-1/PD-L1. This observation raises some concerns about treating elderly patients (>65 y.o) with anti-PD-1/PD-L1 monotherapy and suggests further study of this phenomenon.
INTRODUCTION

Immune checkpoint blocking antibodies are profoundly changing the management of cancer patients. At the forefront of this novel anticancer agent class, anti-PD-1/PD-L1 antibodies can exhibit a significant activity by restoring an efficient anti-tumor T-cell response. As a result, these agents are now approved in various tumor types such as melanoma, squamous and non-squamous NSCLC, RCC, HNSCC, bladder cancer and Hodgkin lymphomas (1-7). Interestingly, these new immunotherapies also result in novel tumor response patterns such as delayed tumor responses or pseudoprogressions (8,9). As experience grows with these therapeutics, anecdotal reports are relating rapid disease progressions, which could suggest that immune checkpoint blockade may have a deleterious effect by accelerating the disease in a subset of patients (Figure 1)(10,11).

Briefly, the tumor growth rate (TGR) estimates the increase in tumor volume over time. It incorporates the time between imaging examinations, allowing for a quantitative and dynamic evaluation of the tumor burden along the treatment sequence. Interestingly, this method uses each patient as his/her own control. This simple but powerful method has already been successfully used to evaluate the activity of multiple agents and tumor types and it can be instrumental to identify the specific therapeutic effect of anticancer agents regardless of the disease course of each patient. (12-15).

In order to explore the prevalence, the natural history and the predictive factors of a potential hyperprogressive disease phenomenon (HPD) in cancer patients treated by
anti PD-1/PD-L1, we sought to compare tumor growth rates (TGR) of tumors during REFERENCE (i.e. prior to treatment onset) and EXPERIMENTAL (i.e. between baseline and the first tumor evaluation) treatment periods.
MATERIALS AND METHODS

Patients

The medical records of all consecutive patients (n=218) prospectively enrolled and treated in phase I clinical trials treated with monotherapy by anti-PD-1 or an anti-PD-L1 at Gustave Roussy between December 2011 and January 2014 were analyzed. All the CT-scans were independently reviewed by two senior radiologists.

Definition of the Tumor Growth Rate (TGR)

Tumor size (D) was defined as the sum of the longest diameters of the target lesions as per the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria(16,17). Let t be the time expressed in months at the tumor evaluation. Assuming the tumor growth follows an exponential law, Vt the tumor volume at time t is equal to Vt=V0 exp(TG.t), where V0 is the volume at baseline, and TG is the growth rate. We approximated the tumor volume (V) by V = 4 π R³ / 3, where R, the radius of the sphere is equal to D/2. Consecutively, TG is equal to TG=3 Log(Dt/D0)/t. To report the tumor growth rate (TGR) results in a clinically meaningful way, we expressed TGR as a percent increase in tumor volume during one month using the following transformation: TGR = 100 (exp(TG) -1), where exp(TG) represents the exponential of TG. We calculated the TGR across clinically relevant treatment periods: (i) TGR REFERENCE assessed during the wash-out period (off-therapy) before the introduction of the experimental drug, (ii) TGR EXPERIMENTAL assessed during the first cycle of treatment (i.e.: between the drug introduction and the first evaluation, on-therapy). To compute the TGR REFERENCE, additional imaging
exploring the wash-out period (off-therapy) immediately before the introduction were included when available. As per the RECIST system, patients with non-measurable disease only at baseline could not be assessed by TGR. For patients who had disease progression with new lesions, the TGR was computed on the target lesions only (new lesions were not included in the RECIST sum).

**Statistical analysis**

We performed pairwise comparisons to test the variation of TGR along the treatment sequence using Wilcoxon signed-rank tests. The tumor progression was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) at the first treatment evaluation after the onset of the experimental drug.(16,17) According to RECIST 1.1, patients’ tumor responses were classified into the following classes: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD). Landmark survival rates were calculated using the Kaplan-Meier method(18). As per the different protocols, most patients had to be evaluated after 6 to 8 weeks of drug exposure. Consequently, we set the landmark point at 2 months. Overall survival (OS) was determined as the time between the landmark point and the death from any cause. The comparisons between categorical variables were performed using the log-rank test. Hazard ratios (HR) were estimated from Cox proportional hazard models and were adjusted to the standard clinico-pathological prognostic factors, assessed by the Royal Marsden prognostic score (RMH), as previously described(19). All the tests were two-sided and significance was assumed if P<0.05. All the analyses were carried out using the R statistical software (R version 3.3.0, http://www.R-
project.org/), the ‘survival’ R package (version 2.37.4, published by T. Therneau),
and controlled by a senior statistician.
RESULTS

Description of the cohort

We analyzed a total of 218 pts treated with anti-PD-1 or anti-PD-L1 monotherapy and with a baseline CT-scan. As illustrated in the flowchart (Figure 2) a total of 18 (8%) and 5 (2%) patients stopped because of clinical progression and of toxicity before the first tumor evaluation, respectively. Out of these patients, 27 patients did not have a previous CT-scan available and 2 had no tumor burden measurable by RECIST at the imaging before baseline. Thus, data on 166 patients (76%) could be explored for both the TGR during the REFERENCE periods (i.e. most often, between the imaging exam indicating prior progression and baseline) and the EXPERIMENTAL periods. As tumor kinetics cannot be representative if measured within a too short or too long period, we excluded 35 patients because the reference period lasted less than 2 weeks or was greater than 3 months. Thereby, 131 patients (60%) with a clinically meaningful TGR were evaluable in our analysis (Figure 2). Patient characteristics are described in Table 1 and 2. The distribution of the EXPERIMENTAL and the REFERENCE period are shown in Figure 3A.

By RECIST, a total of 49 (37%) 66 (50%) 15 (12%) and 1 (1%) patients exhibited progressive disease, stable disease, partial response or complete response, respectively. The distribution of TGR across the two periods are as follows: REFERENCE period: median 49.7 (95%CI: 0 - 441.7) and EXPERIMENTAL period: median 3.7 (95%CI: -61.9-147.8).
Exploring the hyperprogressive disease (HPD) phenotype in patients using the variation of TGR between the REFERENCE and the EXPERIMENTAL periods

To investigate whether anecdotal cases of accelerated tumor growth observed by oncologists (Figure 1) were related to actual increase in the tumor kinetics, we computed the variation of TGR between the REFERENCE and the EXPERIMENTAL periods across all patients. An increase in the TGR between the REFERENCE and the EXPERIMENTAL periods was observed in a total of 34 patients (26%) (Figure 3A and 3B), suggesting an absence of therapeutic effect in this subgroup. However, among patients with increase in tumor growth, there were some patients with a marked increase in tumor growth (Figure 3A and 3B). To identify such a population, we computed the number of patients satisfying the condition: TGR EXPERIMENTAL > TGR REFERENCE x t with t being an integer threshold (from 1 to 5) (Figure 3C). We observed a plateau in the number of patients satisfying this condition when t > 2, revealing a specific subset of patients with aggressive disease. Consecutively, we defined as having HPD those patients who were defined as having disease progression by RECIST at the first evaluation and who presented a ≥ two-fold increase in the TGR EXPERIMENTAL compared to the REFERENCE period. Overall, we identified 12 patients with HPD, representing 9% of the evaluable patients and 24% of patients with disease progression by RECIST at the first evaluation (Figure 3D, 3E). As illustrated by Supplementary Figure S1A, the median of the TGR EXPERIMENTAL / TGR REFERENCE ratio in HPD patients is 20.7 fold (range: 2.0 - 141.3). Interestingly, among patients with progressive disease by RECIST at the first evaluation, patients with HPD exhibited a lower rate of new lesions than patients with non-HPD progression (33% vs. 84%, P=0.0019) (Supplementary Figure S1B).
Association between HPD and anatomo-clinical variables (Table 1 and 2)

We first assumed that advanced disease and poor performance status were associated with HPD. However, we found no association between HPD and tumor burden at baseline (estimated by the RECIST sum) \( (P=0.64) \) (Supplementary Figure S1C), the number of metastatic sites \( (P=0.76) \) or the Royal Marsden Hospital (RMH) prognostic score \( (P=0.43) \) (Supplementary Figure S1D).

Further, we examined the potential influence of previous therapies. Again, we did not observe any association between HPD status and the number of previous lines \( (P=0.69) \), the occurrence of corticosteroids at baseline \( (P=0.16) \) or the type of previous treatment line (conventional chemotherapy \( P=0.75 \), targeted therapy \( P=0.55 \), radiotherapy \( P=0.77 \), immunotherapy \( P=0.39 \)).

Although anti-PD-1 or anti-PD-L1 agents might have a different mechanism of action (e.g. PD-L2 and B7-1 partners) and therefore potentially different mechanisms of escape, we did not find any differences in the rate of HPD between these two classes \( (P=1) \). Moreover, we were able to access to the PD-L1 tumor status for 35 patients (27%) and did not find any difference \( (P=0.24) \) between HPD and other patients.

Interestingly, HPD status was observed across many tumor types and was therefore independent of histology \( (P=0.29) \). In addition, there was no difference between HPD and non-HPD patients for the blood characteristics at baseline such as lymphocytes \( (P=0.64) \), neutrophils \( (P=0.69) \), albumin \( (P=0.23) \), fibrinogen \( (P=0.43) \) or LDH \( (P=0.097) \) (Supplementary Figure S1E-S1F).
Importantly, we observed a significant difference between HPD status and age. Patients with HPD were older than patients without HPD (66 vs 55, P=0.007) (Figure 4A). Further, we explored the influence of age on the response by RECIST. We observed a significant correlation (Spearman rho= 0.18, P=0.036) between age as a continuous variable and RECIST response (Figure 4 B-C). Practically, we observed that 19% (7/36) patients older than 65 y.o. presented HPD compared to 5% (5/95) patients younger than 64 years old (Fisher exact test, P= 0.018). It should be noted that the strength of all of these associations is limited by sample size.

**Association between HPD and overall survival**

To investigate the association between HPD status and prognosis, we computed the Kaplan-Meier overall survival estimates (landmark survival analysis) according to the following classes: CR-PR, SD, PD non HPD and HPD. There was a clear trend towards worse outcome for the patients with HPD (median OS: 4.6 months; 95% CI: 2.0-NA) compared to the patients with non-HPD disease progression (median OS: 7.6 months; 95% CI: 5.9-16.0), though this was not significant due to a small number of patients (P=0.19). However, the overall log rank test was highly significant (P<1e-5) among all groups (Figure 4D). The median survival of the CR-PR and the SD groups are described in Supplementary table 1.

We further investigated whether the HPD status remained associated with OS when adjusting to the Royal Marsden prognostic score (RMH). In a multivariate cox model analysis, we observed that both RMH prognostic score and the HPD-RECIST (defined as CR-PR, SD, PD non HPD, HPD) were strongly associated with OS: RMH (HR, 1.61; 95% CI, 0.99–2.62; P=0.06); HPD-adapted RECIST classes (HPD vs. CR-PR: HR, 25.94; 95% CI, 5.57–120.74; P=3.3 e-5). Practically, patients with SD, PD...
and HPD lead to a 4.94, 16.54 and 25.94 fold increase in the death hazard compared to patients with CR-PR, respectively (Supplementary Table 2).

**Response by RECIST is inversely correlated with TGR during the REFERENCE period in patients treated by anti PD-1 / PD-L1 agents**

As observed in Figure 3F, patients with progressive disease by RECIST appeared to have lower REFERENCE TGR. Conversely, patients with partial response by RECIST appeared to have higher REFERENCE TGR. We thus formally computed the correlation between REFERENCE TGR with the RECIST evaluation (%) at the first tumor evaluation (Figure 4E). We found a significant inverse correlation between TGR during the REFERENCE period and the response to anti-PD-1/PD-L1 (P=0.0039).

When fitting a multivariate linear regression model of RECIST (%), both the variables age >65 (estimate: 0.16; P=0.037) and the TGR REFERENCE (estimate: -2.5 e-4, P=8 e-4) remained significant (Supplementary table 3). These latter data suggest that both of these characteristics are crucial for the response to PD-1/PD-L1 blocking agents.
DISCUSSION

Although anti PD-1 and anti PD-L1 monotherapy can lead to profound and durable tumor responses in some cases, our results demonstrate that a subset of patients appears to experience a tumor flare under these agents. To our knowledge, this study is the first to define this hyper-progressive feature in immunotherapy treated patients. The use of TGR was instrumental to shed light on the manifest tumor growth acceleration after treatment onset. A total of 9% of evaluable patients (N=12/131), were identified as experiencing HPD (defined as a ≥ two-fold increase of TGR in patients with disease progression). Interestingly, we also observed that 18 pts (N=18/218, 8% of the total cohort) could not be evaluated because of a clinical progression before the tumor evaluation, thus raising the possibility that HPD frequency might be higher than the here reported 9% frequency. In addition, as the TGR was computed on the target lesions only (i.e. new lesions are not included in the RECIST sum), patients who exhibit a fast growing rate in new lesions only were not considered as HPD. All together, these data may suggest a possible underestimation of the HPD rate.

We observed that age is higher in patients with HPD vs. non HPD. This may be explained by a different immunological background in older patients such as modification of T cell co-stimulatory/co-inhibitory proteins expression or higher concentrations of inflammatory cytokines (20,21). More importantly this is consistent with previous and recurrent publications of three independent phase III trials indicating that older patients appear to benefit less than younger patients (3-5,22). Future prospective studies are warranted to specifically address this issue.
As reported here, we did not observe any difference in the rate of HPD across the different histologies of cancers including melanoma, urothelial, colorectal, ovarian, biliary tract carcinomas and lymphomas. Others have reported similar flare-up phenomenon in NSCLC and in head and neck cancers (10,11). These consistent observations may still be limited by the small number of patients in the series and the multiple tests performed in this study.

Opposing effects of immunotherapy have already been described in melanoma using adjuvant interferon-alpha where patients in the treatment group who died during the study period displayed a significantly reduced time from relapse to death compared to control individuals (23). Interestingly, the phase III study of Nivolumab vs docetaxel in non-squamous NSCLC shows that the OS and PFS curves in patients with PD-L1 negative tumors tend to favor docetaxel until a time point between 3 and 6 months (4). This may indicate that a subset of patients may have had disease progression and/or death earlier than expected. In our analysis, we did not find any difference (P=0.24) between PD-L1 positive vs negative tumors for HPD, although these assertions may be limited by the low number of patients with accessible PD-L1 status (N=35, 27% TGR evaluable patients). This phenomenon of disease progression acceleration is not specific for anti PD-1/PD-L1 agents and was sometimes observed with other therapeutic agents (24,25). Also, rapid progression at treatment discontinuation after long-term response under VEGFR or EGFR TKI has been reported (12,26-28). In this study, the fact that we did not observe any effect related
to the type of previous therapy minimizes the risk that the HPD was related to the previous line of therapy.

The striking acceleration of tumor disease observed in patients with HPD could suggest an oncogenic signaling activation. It has been demonstrated that PD-1/PD-L1 signaling has cell-intrinsic functions in tumor cells (29). Thus, depending of tumor cell genetic alterations, it is possible that PD-1/PD-L1 blockade might affect alternative signaling networks and enhance growth and/or tumorigenesis. Alternatively, immune compensatory mechanisms through the upregulation of alternative immune checkpoints or the modulation of other pro-tumor immune subsets could have occurred (30,31). Activation of tumor lymphocytes could trigger local inflammation, angiogenesis, matrix/tissue remodeling or metabolism modification that could lead to tumor escape (32). Finally, adaptive immune resistance may be a source of tumor heterogeneity and even a cancer-promoting mechanism in several cancers (33-35).

In this study, we observed a significant inverse correlation between TGR during the REFERENCE period and the response to anti-PD-1/PD-L1 (P= 0.0039). This association remained significant even after adjustment for age and RMH score (data not shown). These results showing slower growing tumors are less likely to respond are opposite to what was observed previously for targeted therapy (12,13,15). Indeed for molecular targeted agents, higher TGR during the REFERENCE period was associated with higher risk of disease progression at the first evaluation. These data demonstrate important differences regarding mechanistic and kinetic antitumor effects between anti proliferative agents and immune checkpoint inhibitors.
For the first time ever, oncologists now face drugs with an extraordinary antitumor potential in some patients, but which also may induce a dramatic tumor surge in a fraction of patients. Overall, the HPD phenomenon under immune checkpoint blockade appears to be restricted to a small group of patients (~10%). Our results show that it might represent a concern for the use of PD-1 or PD-L1 blockers in the elderly population. Early tumor assessment with TGR evaluation might help to decipher between HPD and PD from SD or PR patients in this subset of patients. Prospective evaluations of TGR for patients who receive these agents are warranted to better appraise this HPD phenomenon. Pre and early (1 month) post-treatment biopsies would allow to explore the biological mechanisms behind HPD and identify predictive biomarkers to avoid the patients at risk to be treated with an anti-PD-1/PD-L1. Also, this HPD phenomenon might be limited to anti-PD-1/PD-L1 monotherapy and might not be an issue upon combination therapies. This question shall be addressed in the ongoing immunotherapy combination studies.

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NA
REFERENCES


Integrated Analysis of the TARGET and RECORD Phase 3 Trial Data.


20. Goronzy JJ, Weyand CM. Understanding immunosenescence to improve


34. Hölzel M, Tüting T. Inflammation-Induced Plasticity in Melanoma Therapy and

TABLES’ LEGENDS

**TABLE 1**: Patient characteristics and association between HPD and anatomoclinical categorical variables (univariate analysis)

**TABLE 2**: Patient characteristics and association between HPD and anatomoclinical continuous variables (univariate analysis)
FIGURES’ LEGENDS

Figure 1: Case study of patient with hyper progressing disease on PD-L1 inhibitor

(A) Scans before (-8 weeks), at baseline and at first evaluation (+8 weeks) in a 58-year-old woman with metastatic urothelial carcinoma. Evaluation after the 3rd drug injection revealed a massive hepatic progression. (B) Seric LDH evolution is a concomitantly increasing, and appears to accelerate after treatment onset.

FIGURE 2: Flowchart of study selection process.

FIGURE 3: Analysis of the TGR between the REFERENCE and the EXPERIMENTAL periods

(A) Pairwise comparisons of TGR between the reference and the experimental periods in 131 patients treated with PD-1 or PD-L1 inhibitors in phase I clinical trials. Each dot represents a patient. Patients plotted above the black dashed line exhibit an increase in the TGR between the REFERENCE and the EXPERIMENTAL periods.

(B-D) Subset of progressive patients presenting a marked increase in tumor growth

(B) Spider plot depicting the percent change in the sum of the longest diameters of target lesions (RECIST) in the REFERENCE and the EXPERIMENTAL periods in the 131 evaluable patients (green: CR/PR, orange : SD, red : PD).

(C) Variation of the number of patients satisfying the condition: TGR exp. /TGR ref. > t according to a threshold t. When t > 2, the number of patients with TGR exp. /TGR ref. > t stabilizes, revealing a specific subset of hyper progressing patients
(D) Spider plot depicting the percent change in the sum of the longest diameters of target lesions (RECIST) in the REFERENCE and the EXPERIMENTAL periods in the 49 progressing patients. Black triangles represent patients with new lesions at the first evaluation. Red color highlights PD patients presenting the HPD criteria: PD by RECIST at the first evaluation and ≥ two-fold increase in the TGR EXPERIMENTAL compared to REFERENCE period. PD patients as per RECIST criteria that are not HPD are colored in grey.

(E) Pairwise comparisons of TGR between the reference and the experimental periods in the 49 progressing patients by RECIST 1.1. Red dots are set for HPD patients (i.e. PD by RECIST at the first evaluation and a ≥ two-fold increase in the TGR experimental compared to reference period)

(F) Spider plot depicting the percent change in the sum of the longest diameters of target lesions (RECIST) in the REFERENCE and the EXPERIMENTAL periods in the 131 evaluable patients (green: CR/PR, orange: SD, black: PD non-HPD, red: HPD).

FIGURE 4: HPD is associated with older age and a worse outcome

(A-C) Age is associated with HPD: (A) Pairwise comparisons of age between non-HPD and HPD patients in 131 patients (P values are computed from Wilcoxon pairwise tests; n, the number of samples with pairwise age information). (B) Comparisons of the variation of the sum of the longest diameters of target lesions (RECIST %) according to the following age classes: <35, 35-49, 50-64, ≥65 in 131 evaluable patients (P value is computed from the Kruskal-Wallis score), Overall Response Rate (ORR, %) of each group is depicted below. (C) Correlation between the age and the variation of the sum of the longest diameters of target lesions
(RECIST %) (Spearman Rho and its P value are displayed). The red line represents the lowess fit.

(D) Association between HPD and overall survival: Kaplan Meyer estimates of overall survival (landmark method) of patients treated with anti PD-1/PD-L1 according to the following classes: CR-PR, SD, PD non-HPD and HPD.

(E) Response to anti-PD-1/PD-L1 agents appears inversely correlated with TGR during the REFERENCE period: Correlation between the TGR during the REFERENCE period and the variation of the sum of the longest diameters of target lesions (RECIST %) (Spearman Rho and its P value are displayed). The red line and the dashed lines represent the lowess fit with its 95% confidence interval.
Table 1

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<tr>
<td>colorectal</td>
<td>8 (6%)</td>
<td>7 (88%)</td>
<td>1 (12%)</td>
<td></td>
</tr>
<tr>
<td>urothelial</td>
<td>8 (6%)</td>
<td>6 (75%)</td>
<td>2 (25%)</td>
<td></td>
</tr>
<tr>
<td>lymphoma</td>
<td>7 (5%)</td>
<td>6 (86%)</td>
<td>1 (14%)</td>
<td></td>
</tr>
<tr>
<td>HCC</td>
<td>6 (5%)</td>
<td>6 (100%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>head and neck</td>
<td>6 (5%)</td>
<td>6 (100%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>ovarian</td>
<td>5 (4%)</td>
<td>3 (60%)</td>
<td>2 (40%)</td>
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<tr>
<td>breast</td>
<td>4 (3%)</td>
<td>4 (100%)</td>
<td>0</td>
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<tr>
<td>glioblastoma</td>
<td>4 (3%)</td>
<td>4 (100%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>cervix</td>
<td>2 (2%)</td>
<td>2 (100%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>cholangiocarcinoma</td>
<td>2 (2%)</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
<td></td>
</tr>
<tr>
<td>endometrium</td>
<td>2 (2%)</td>
<td>2 (100%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>gastric, oesophagus</td>
<td>2 (2%)</td>
<td>2 (100%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>thyroid</td>
<td>2 (2%)</td>
<td>2 (100%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>uveal melanoma</td>
<td>2 (2%)</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
<td></td>
</tr>
<tr>
<td>mesothelioma</td>
<td>1 (1%)</td>
<td>1 (100%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>pancreas</td>
<td>1 (1%)</td>
<td>1 (100%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>parotid</td>
<td>1 (1%)</td>
<td>1 (100%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>sarcoma</td>
<td>1 (1%)</td>
<td>1 (100%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Type of ICB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD1 inhibitor</td>
<td>78 (60%)</td>
<td>71 (60%)</td>
<td>7 (58%)</td>
<td>1</td>
</tr>
<tr>
<td>PD-L1 inhibitor</td>
<td>53 (40%)</td>
<td>48 (40%)</td>
<td>5 (42%)</td>
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</tr>
<tr>
<td>PDL1 status (IHC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>positive</td>
<td>32 (25%)</td>
<td>30 (94%)</td>
<td>2 (67%)</td>
<td>0.24</td>
</tr>
<tr>
<td>negative</td>
<td>3 (2%)</td>
<td>2 (6%)</td>
<td>1 (33%)</td>
<td></td>
</tr>
<tr>
<td>Number of previous lines: median (range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>123 (94%)</td>
<td>113 (95%)</td>
<td>10 (83%)</td>
<td>0.16</td>
</tr>
<tr>
<td>yes</td>
<td>8 (6%)</td>
<td>6 (5%)</td>
<td>2 (17%)</td>
<td></td>
</tr>
<tr>
<td>Previous radiation therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>72 (55%)</td>
<td>66 (55%)</td>
<td>6 (50%)</td>
<td>0.77</td>
</tr>
<tr>
<td>yes</td>
<td>59 (45%)</td>
<td>53 (45%)</td>
<td>6 (50%)</td>
<td></td>
</tr>
<tr>
<td>Previous chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>43 (33%)</td>
<td>40 (34%)</td>
<td>3 (25%)</td>
<td>0.75</td>
</tr>
<tr>
<td>yes</td>
<td>88 (67%)</td>
<td>79 (66%)</td>
<td>9 (75%)</td>
<td></td>
</tr>
<tr>
<td>Previous targeted therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>58 (44%)</td>
<td>54 (45%)</td>
<td>4 (33%)</td>
<td>0.55</td>
</tr>
<tr>
<td>yes</td>
<td>73 (56%)</td>
<td>65 (55%)</td>
<td>8 (67%)</td>
<td></td>
</tr>
<tr>
<td>Previous immunotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>111 (85%)</td>
<td>102 (86%)</td>
<td>9 (75%)</td>
<td>0.39</td>
</tr>
<tr>
<td>yes</td>
<td>20 (15%)</td>
<td>17 (14%)</td>
<td>3 (25%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All patients (N=131)</td>
<td>Non HPD (N=119)</td>
<td>HPD (N=12)</td>
<td>P value (Wilcoxon test)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------------</td>
<td>-----------------</td>
<td>-----------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Tumor burden (mm)</td>
<td>78 (12-364)</td>
<td>76 (12-364)</td>
<td>91.6 (12-167)</td>
<td>0.64</td>
</tr>
<tr>
<td>(estimated by RECIST 1.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>55 (22-82)</td>
<td>55 (22-82)</td>
<td>65.5 (32-82)</td>
<td>0.007</td>
</tr>
<tr>
<td>Leukocytes (1.e+9/l)</td>
<td>7.1 (2.4-41.7)</td>
<td>7.1 (2.4-41.7)</td>
<td>7.95 (3.5-21.0)</td>
<td>0.45</td>
</tr>
<tr>
<td>Lymphocytes (1e+9/l)</td>
<td>1.2 (0.1-3.5)</td>
<td>1.2 (0.1-3.5)</td>
<td>0.95 (0.6-2.9)</td>
<td>0.64</td>
</tr>
<tr>
<td>Neutrophils (1e+9/l)</td>
<td>5.1 (1.4-37.9)</td>
<td>5.1 (1.4-37.9)</td>
<td>5.0 (2.0-18.7)</td>
<td>0.69</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>21.1 (0.5-317.7)</td>
<td>21.1 (0.5-317.7)</td>
<td>21.7 (5.2-68)</td>
<td>0.97</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>4.8 (2.8-9.6)</td>
<td>4.9 (2.8-9.6)</td>
<td>4.7 (3.2-7.1)</td>
<td>0.43</td>
</tr>
<tr>
<td>LDH (UI/l)</td>
<td>204 (9-1195)</td>
<td>198 (9-1195)</td>
<td>248 (132-547)</td>
<td>0.097</td>
</tr>
<tr>
<td>Albumine (g/l)</td>
<td>36 (20-61)</td>
<td>36 (20-61)</td>
<td>34.5 (30-39)</td>
<td>0.23</td>
</tr>
</tbody>
</table>
Figure 1.

1A

CT evaluations

Before
(-8 weeks)

Baseline

1st Evaluation
(+8 weeks)

1B

REFERENCE PERIOD

EXPERIMENTAL PERIOD

LDH (U)

Weeks from treatment onset (Baseline)
Figure 2.

Patients treated by monotherapy anti PD-1 or anti PD-L1 agents in phase I trials at Gustave Roussy between Dec. 2011 and Jan. 2014
N=218

- Progression before the first evaluation
  N=18
- Toxicity before the first evaluation
  N=5

CT-scan evaluation after baseline available (on treatment)
N=195

- No previous CT-scan
  N=27
- No tumor burden measurable by RECIST on previous CT-scan
  N=2

TGR evaluable patients during the REFERENCE and the EXPERIMENTAL period
N=166

- REFERENCE period shorter than 2 weeks or longer than 3 months
  N=35

Clinically meaningful TGR evaluable patients
N=131
Figure 3.

3A

3B

3C

Number of patients with TGR EXP > TGR REF x 1

3D

3E

3F

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Figure 4.

4A

4B

4C

4D

4E
Hyperprogressive disease (HPD) is a new pattern of progression in cancer patients treated by anti-PD-1/PD-L1

Stephane Champiat, Laurent Dericle, Samy Ammari, et al.

Clin Cancer Res Published OnlineFirst November 8, 2016.

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Access the most recent version of this article at: doi:10.1158/1078-0432.CCR-16-1741

Supplementary Material
Access the most recent supplemental material at: http://clincancerres.aacrjournals.org/content/suppl/2016/11/08/1078-0432.CCR-16-1741.DC1

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