

Hyperprogressive Disease Is a New Pattern of Progression in Cancer Patients Treated by Anti-PD-1/PD-L1

Stéphane Champiat^{1,2}, Laurent Dercle³, Samy Ammari⁴, Christophe Massard¹, Antoine Hollebecque¹, Sophie Postel-Vinay^{1,2}, Nathalie Chaput^{5,6,7,8}, Alexander Eggermont⁹, Aurélien Marabelle^{1,10}, Jean-Charles Soria^{1,2}, and Charles Ferte^{1,11,12}

Abstract

Purpose: While immune checkpoint inhibitors are disrupting the management of patients with cancer, 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 patients with cancer 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"; REF) and upon ("EXPERIMENTAL"; EXP) anti-PD-1/PD-L1 therapy was compared to identify patients with accelerated tumor growth. Associations between TGR, clinicopathologic characteristics, and overall survival (OS) were computed.

Results: HPD was defined as a RECIST progression at the first evaluation and as a ≥ 2 -fold increase of the TGR between the REF and the EXP periods. 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, REF TGR (before treatment) was inversely correlated with response to anti-PD-1/PD-L1 ($P < 0.05$) therapy.

Conclusions: A novel aggressive pattern of hyperprogression exists in a fraction of patients treated with anti-PD-1/PD-L1. This observation raises some concerns about treating elderly patients (>65 years old) with anti-PD-1/PD-L1 monotherapy and suggests further study of this phenomenon. *Clin Cancer Res*; 1–9. ©2016 AACR.

Introduction

Immune checkpoint blocking antibodies are profoundly changing the management of patients with cancer. At the

forefront of this novel anticancer agent class, anti-PD-1/PD-L1 antibodies can exhibit a significant activity by restoring an efficient antitumor T-cell response. As a result, these agents are now approved in various tumor types such as melanoma, squamous, and nonsquamous non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), head and neck squamous cell carcinoma (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 pseudoprogessions (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 (Fig. 1; refs. 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).

To explore the prevalence, the natural history, and the predictive factors of a potential hyperprogressive disease (HPD) phenomenon in patients with cancer treated by anti-PD-1/PD-L1, we

¹Département d'Innovation Thérapeutique et des Essais Précoces (DITEP), Gustave Roussy, Université Paris Saclay, Villejuif, France. ²INSERM, U981, Villejuif, France. ³Département de l'Imagerie Médicale, Service de Médecine Nucléaire et d'Endocrinologie, Gustave Roussy, Université Paris Saclay, Villejuif, France. ⁴Département de l'Imagerie Médicale, Service d'Imagerie Diagnostique, Gustave Roussy, Université Paris Saclay, Villejuif, France. ⁵Gustave Roussy, Université Paris Saclay, Laboratoire d'Immunomonitoring en Oncologie, Villejuif, France. ⁶CNRS, UMS 3655, Villejuif, France. ⁷INSERM, US23, Villejuif, France. ⁸INSERM, Centre d'Investigation Clinique Biothérapie 1428, Villejuif, France. ⁹Gustave Roussy, Université Paris Saclay, Villejuif, France. ¹⁰INSERM, U1015, Villejuif, France. ¹¹Département de Cancérologie Cervico Faciale, Gustave Roussy, Université Paris Saclay, Villejuif, France. ¹²INSERM, U1030, Villejuif, France.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (<http://clincancerres.aacrjournals.org/>).

J.-C. Soria and C. Ferte share senior authorship of this article.

Corresponding Authors: Charles Ferte, Département de Cancérologie Cervico Faciale, Gustave Roussy, 114 rue Edouard Vaillant, Villejuif 94800, France. Phone: 3301-4211-4617; Fax: +33 (0)1 42 11 64 44; E-mail: charles.ferte@gustaveroussy.fr; and Jean-Charles Soria, jean-charles.soria@gustaveroussy.fr

doi: 10.1158/1078-0432.CCR-16-1741

©2016 American Association for Cancer Research.

Translational Relevance

Rapid progressions have been anecdotally reported in patients with cancer treated with anti-PD-1/PD-L1 mAbs. A total of 131 patients treated with anti-PD-1/PD-L1 in phase I clinical trials at Gustave Roussy were evaluable for their tumor growth rate (TGR) before treatment ("REFERENCE period"; REF) and upon treatment ("EXPERIMENTAL period"; EXP). Patients with hyperprogressive disease (HPD) were defined as patients with disease progression by RECIST criteria with a ≥ 2 -fold increase in the TGR EXP versus REF. Thus, we identified 12 patients (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.

sought to compare TGRs of tumors during REFERENCE (i.e., prior to treatment onset; REF) and EXPERIMENTAL (i.e., between baseline and the first tumor evaluation; EXP) 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 2 senior radiologists.

Definition of 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, V_t , the tumor volume at time t , is equal to $V_t = V_0 \exp(\text{TG} \cdot t)$, where V_0 is the volume at baseline and TG is the growth rate. We approximated the tumor volume (V) by $V = 4 \pi R^3/3$, where R , the radius of the sphere is equal to $D/2$. Consecutively, TG is equal to $\text{TG} = 3 \text{Log}(D_t/D_0)/t$. To report the TGR results in a clinically meaningful way, we expressed TGR as a percentage increase in tumor volume during 1 month using the following transformation: $\text{TGR} = 100 [\exp(\text{TG}) - 1]$, where $\exp(\text{TG})$ represents the exponential of TG.

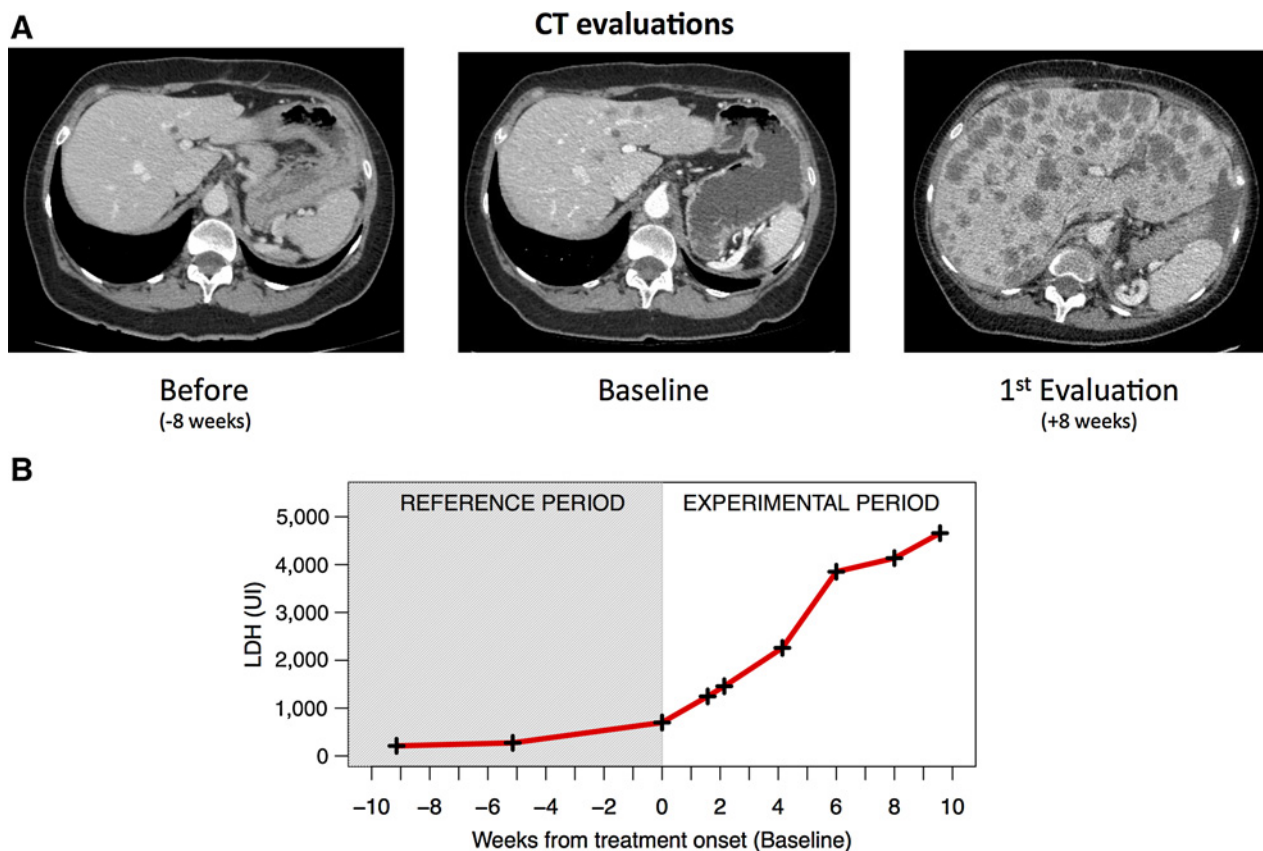


Figure 1.

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 third drug injection revealed a massive hepatic progression. **B**, Seric lactate dehydrogenase evolution is concomitantly increasing and appears to accelerate after treatment onset.

We calculated the TGR across clinically relevant treatment periods: (i) TGR REF assessed during the wash-out period (off-therapy) before the introduction of the experimental drug and (ii) TGR EXP assessed during the first cycle of treatment (i.e., between the drug introduction and the first evaluation, on-therapy). To compute the TGR REF, additional imaging exploring the wash-out period (off-therapy) immediately before the introduction were included when available. As per the RECIST system, patients with nonmeasurable 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 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), and 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. HRs were estimated from Cox proportional hazard models and were adjusted to the standard clinicopathologic prognostic factors, assessed by the Royal Marsden prognostic score (RMH), as previously described (19). All the tests were 2-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 patients treated with anti-PD-1 or anti-PD-L1 monotherapy and with a baseline CT scan. As illustrated in the flowchart (Fig. 2), a total of 18 (8%) and 5 (2%) patients stopped because of clinical progression and of toxicity before the first tumor evaluation, respectively. 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 TGR during both the REF periods (i.e., most often, between the imaging exam indicating prior progression and baseline) and the EXP 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 (Fig. 2). Patient characteristics are described in Tables 1 and 2. The distribution of the EXP and the REF period are shown in Fig. 3A.

By RECIST, a total of 49 (37%) 66 (50%) 15 (12%), and 1 (1%) patients exhibited PD, SD, PR, or CR, respectively. The distribution of TGR across the 2 periods is as follows: REF period: median

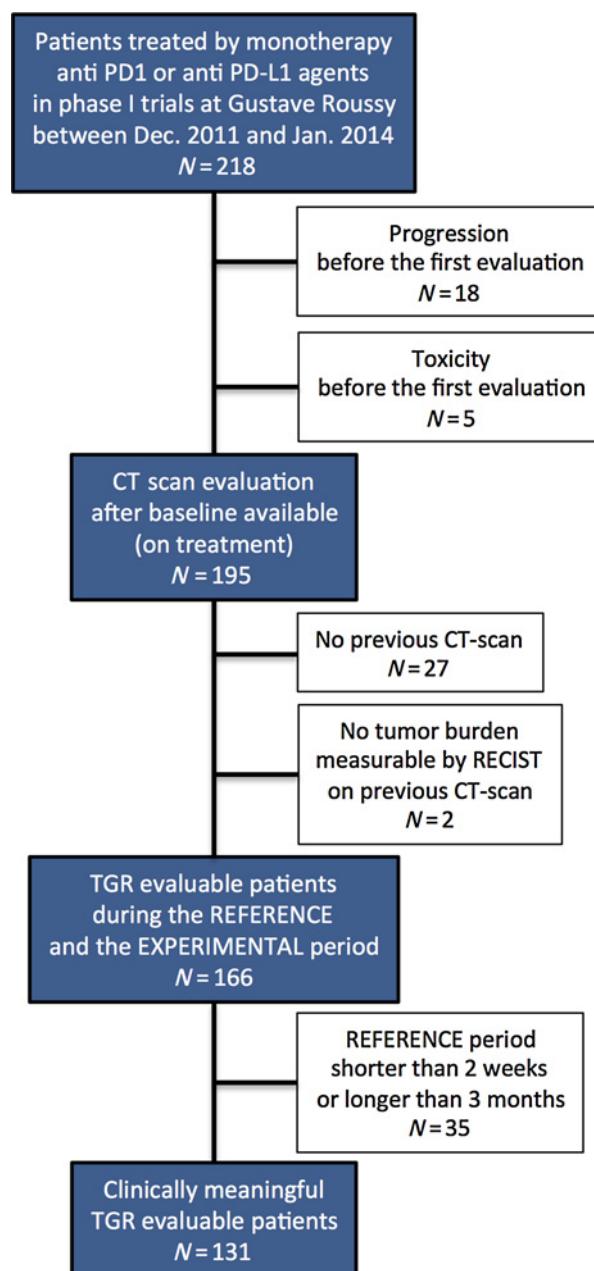


Figure 2. Flowchart of study selection process.

49.7 [95% confidence interval (CI), 0–441.7] and EXP period: median 3.7 (95% CI, –61.9–147.8).

Exploring the HPD phenotype in patients using the variation of TGR between the REF and the EXP periods

To investigate whether anecdotal cases of accelerated tumor growth observed by oncologists (Fig. 1) were related to actual increase in the tumor kinetics, we computed the variation of TGR between the REF and the EXP periods across all patients. An increase in the TGR between the REF and the EXP periods was observed in a total of 34 patients (26%; Fig. 3A and B),

Table 1. Patient characteristics and association between HPD and anatomoclinical categorical variables (univariate analysis)

	All patients (n = 131)	Non-HPD (n = 119)	HPD (n = 12)	P (Fisher exact test)
Gender				0.14
Male	71 (54%)	67 (56%)	4 (33%)	
Female	60 (46%)	52 (44%)	8 (67%)	
RMH score				0.43
0	35 (27%)	33 (28%)	2 (17%)	
1	47 (36%)	44 (37%)	3 (25%)	
2	42 (32%)	36 (30%)	6 (50%)	
3	7 (5%)	6 (5%)	1 (8%)	
Metastatic site				0.76
≤2	58 (44%)	52 (44%)	6 (50%)	
>2	73 (56%)	67 (56%)	6 (50%)	
Histology				0.29
Melanoma	45 (34%)	41 (91%)	4 (9%)	
Lung	13 (10%)	13 (100%)	0	
Renal	9 (7%)	9 (100%)	0	
Colorectal	8 (6%)	7 (88%)	1 (12%)	
Urothelial	8 (6%)	6 (75%)	2 (25%)	
Lymphoma	7 (5%)	6 (86%)	1 (14%)	
HCC	6 (5%)	6 (100%)	0	
Head and neck	6 (5%)	6 (100%)	0	
Ovarian	5 (4%)	3 (60%)	2 (40%)	
Breast	4 (3%)	4 (100%)	0	
Glioblastoma	4 (3%)	4 (100%)	0	
Cervix	2 (2%)	2 (100%)	0	
Cholangiocarcinoma	2 (2%)	1 (50%)	1 (50%)	
Endometrium	2 (2%)	2 (100%)	0	
Gastric, esophagus	2 (2%)	2 (100%)	0	
Thyroid	2 (2%)	2 (100%)	0	
Uveal melanoma	2 (2%)	1 (50%)	1 (50%)	
Mesothelioma	1 (1%)	1 (100%)	0	
Pancreas	1 (1%)	1 (100%)	0	
Parotid	1 (1%)	1 (100%)	0	
Sarcoma	1 (1%)	1 (100%)	0	
Type of ICB				1
PD-1 inhibitor	78 (60%)	71 (60%)	7 (58%)	
PD-L1 inhibitor	53 (40%)	48 (40%)	5 (42%)	
PD-L1 status (IHC)				0.24
Positive	32 (25%)	30 (94%)	2 (67%)	
Negative	3 (2%)	2 (6%)	1 (33%)	
Number of previous lines: median (range)	2.0 (0-9)	2.0 (0-9)	2.5 (0-6)	0.69
Corticosteroids at baseline				0.16
No	123 (94%)	113 (95%)	10 (83%)	
Yes	8 (6%)	6 (5%)	2 (17%)	
Previous radiation therapy				0.77
No	72 (55%)	66 (55%)	6 (50%)	
Yes	59 (45%)	53 (45%)	6 (50%)	
Previous chemotherapy				0.75
No	43 (33%)	40 (34%)	3 (25%)	
Yes	88 (67%)	79 (66%)	9 (75%)	
Previous targeted therapy				0.55
No	58 (44%)	54 (45%)	4 (33%)	
Yes	73 (56%)	65 (55%)	8 (67%)	
Previous immunotherapy				0.39
No	111 (85%)	102 (86%)	9 (75%)	
Yes	20 (15%)	17 (14%)	3 (25%)	

Abbreviations: HCC, hepatocellular carcinoma; ICB, immune checkpoint blockade; IHC, immunohistochemistry.

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

(Fig. 3A and B). To identify such a population, we computed the number of patients satisfying the condition: $TGR_{EXP} > TGR_{REF} \times t$ with t being an integer threshold (from 1 to 5; Fig. 3C).

Table 2. Patient characteristics and association between HPD and anatomoclinical continuous variables (univariate analysis)

	All patients (n = 131)	Non-HPD (n = 119)	HPD (n = 12)	P value (Wilcoxon test)
Tumor burden (estimated by RECIST 1.1), mm	78 (12–364)	76 (12–364)	91.6 (12–167)	0.64
Age, y	55 (22–82)	55 (22–82)	65.5 (32–82)	0.007
Leukocytes (1e+9/L)	7.1 (2.4–41.7)	7.1 (2.4–41.7)	7.95 (3.5–21.0)	0.45
Lymphocytes (1e+9/L)	1.2 (0.1–3.5)	1.2 (0.1–3.5)	0.95 (0.6–2.9)	0.64
Neutrophils (1e+9/L)	5.1 (1.4–37.9)	5.1 (1.4–37.9)	5.0 (2.0–18.7)	0.69
CRP (mg/L)	21.1 (0.5–317.7)	21.1 (0.5–317.7)	21.7 (5.2–68)	0.97
Fibrinogen (g/L)	4.8 (2.8–9.6)	4.9 (2.8–9.6)	4.7 (3.2–7.1)	0.43
LDH (U/L)	204 (9–1195)	198 (9–1195)	248 (132–547)	0.097
Albumin (g/L)	36 (20–61)	36 (20–61)	34.5 (30–39)	0.23

Abbreviations: CRP, C-reactive protein; LDH, lactate dehydrogenase.

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 ≥ 2 -fold increase in the TGR EXP compared with the REF 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 (Fig. 3D and E). As illustrated by Supplementary Fig. S1A, the median of the TGR EXP/TGR REF ratio in patients with HPD is 20.7-fold (range, 2.0–141.3). Interestingly, among patients with PD 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 Fig. S1B).

Association between HPD and anatomoclinical variables

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 Fig. S1C), the number of metastatic sites ($P = 0.76$), or the Royal Marsden Hospital (RMH) prognostic score ($P = 0.43$; Supplementary Fig. S1D; Tables 1 and 2).

Furthermore, 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 2 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 lactate dehydrogenase ($P = 0.097$; Supplementary Fig. S1E and S1F).

Importantly, we observed a significant difference between HPD status and age. Patients with HPD were older than patients without HPD (66 vs. 55, $P = 0.007$; Fig. 4A). Furthermore, 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 (Fig. 4B and C). Practically, we observed that 19% (7 of 36) patients older than 65 years presented HPD compared with 5% (5 of 95) patients younger than 64 years (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 OS

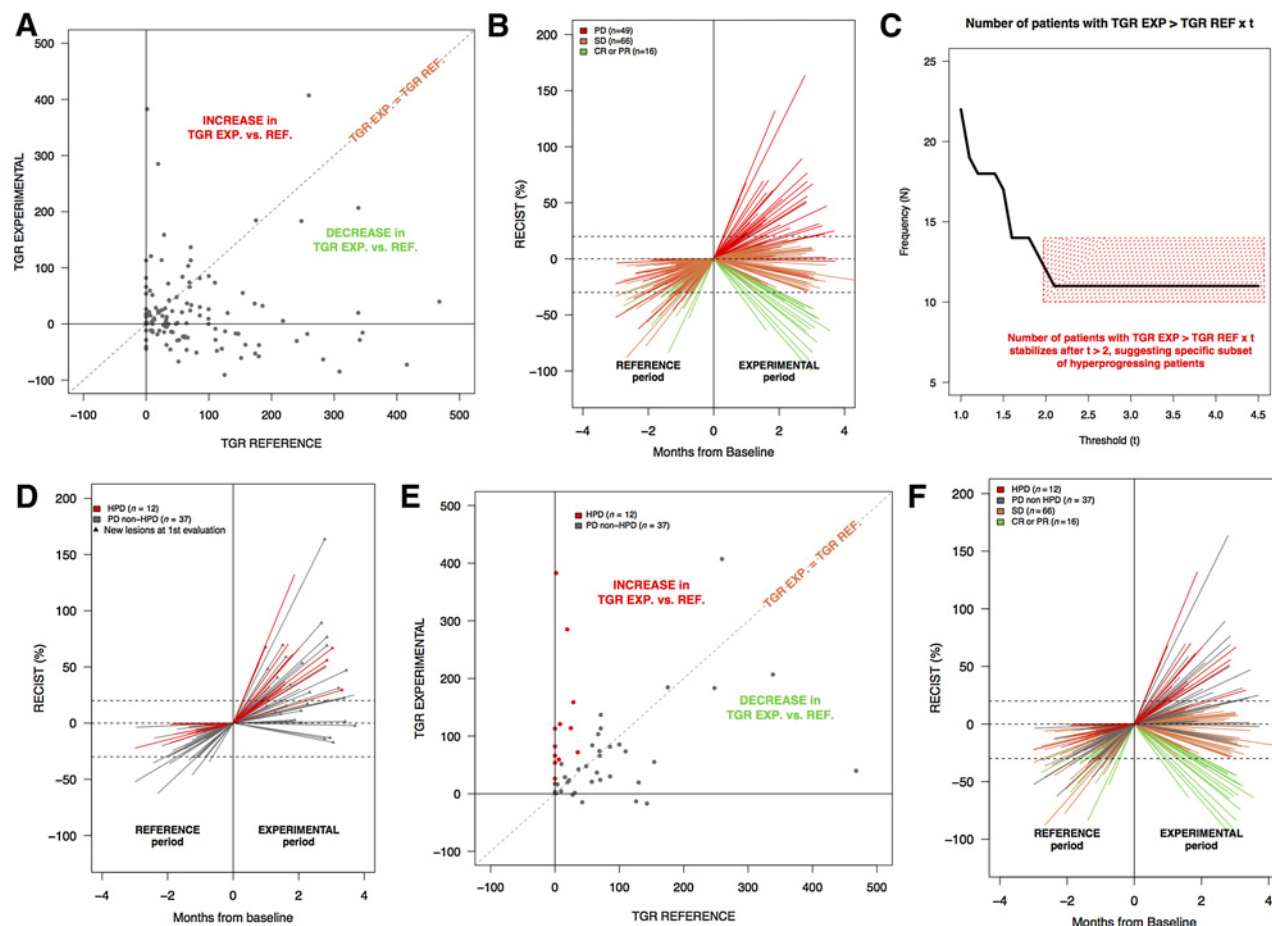
To investigate the association between HPD status and prognosis, we computed the Kaplan–Meier OS estimates (landmark survival analysis) according to the following classes: CR-PR, SD, PD, non-HPD, and HPD. There was a clear trend toward worse outcome for the patients with HPD (median OS, 4.6 months; 95% CI, 2.0–NA) compared with the patients with non-HPD disease progression (median OS, 7.6 months; 95% CI, 5.9–16.0), although 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 (Fig. 4D). The median survival of the CR-PR and the SD groups is described in Supplementary Table S1.

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 with patients with CR-PR, respectively (Supplementary Table S2).

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

As observed in Fig. 3F, patients with PD by RECIST appeared to have lower REF TGR. Conversely, patients with partial response by RECIST appeared to have higher REF TGR. We thus formally computed the correlation between REF TGR with the RECIST evaluation (%) at the first tumor evaluation (Fig. 4E). We found a significant inverse correlation between TGR during the REF 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 REF (estimate: $-2.5e-4$, $P = 8e-4$) remained significant (Supplementary Table S3). These latter data suggest that both of these characteristics are crucial for the response to PD-1/PD-L1 blocking agents.

**Figure 3.**

Analysis of the TGR between the REF and the EXP 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 REF and the EXP 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 REF and the EXP 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 hyperprogressing patients. **D**, Spider plot depicting the percent change in the sum of the longest diameters of target lesions (RECIST) in the REF and the EXP periods in the 49 progressing patients. Black triangles represent patients with new lesions at the first evaluation. Red color highlights patients with PD presenting the HPD criteria: PD by RECIST at the first evaluation and ≥ 2 -fold increase in the TGR EXP compared with REF period. Patients with PD as per RECIST criteria who are non-HPD are colored in gray. **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 ≥ 2 -fold increase in the TGR experimental compared to reference period). **F**, Spider plot depicting the percentage change in the sum of the longest diameters of target lesions (RECIST) in the REF and the EXP periods in the 131 evaluable patients (green: CR/PR, orange: SD, black: PD non-HPD, red: HPD).

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 hyperprogressive 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 ($n = 12$ of 131) were identified as experiencing HPD (defined as a ≥ 2 -fold increase of TGR in patients with disease progression). Interestingly, we also observed that 18 patients ($N = 18$ of 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 versus 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 3 independent phase III trials, indicating that older

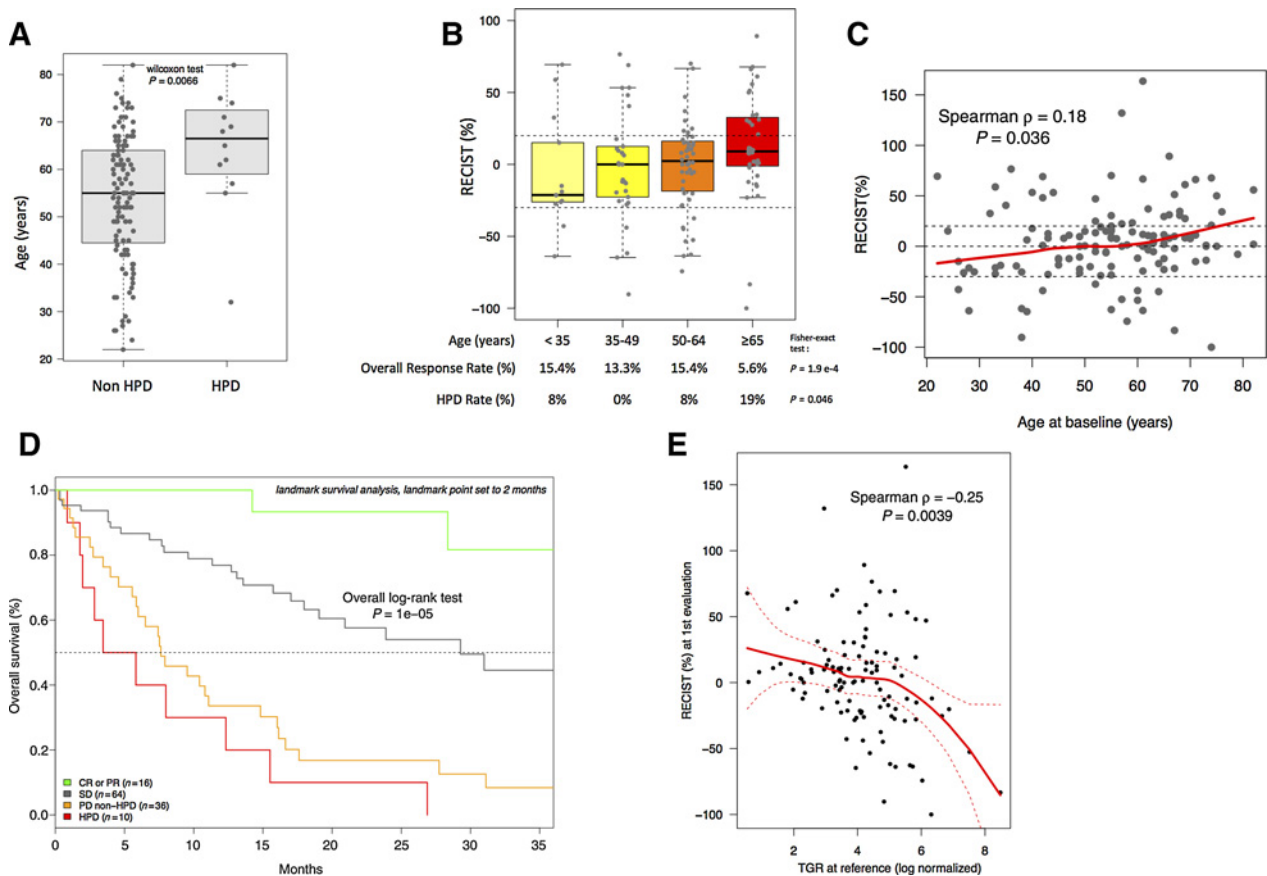


Figure 4.

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 years 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 ρ and its P value are displayed). The red line represents the Lowess fit. **D**, Association between HPD and OS: Kaplan–Meier estimates of OS (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 REF period: Correlation between the TGR during the REF period and the variation of the sum of the longest diameters of target lesions (RECIST %; Spearman ρ and its P value are displayed). The red line and the dashed lines represent the Lowess fit with its 95% CI.

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 IFN α where patients in the treatment group who died during the study period displayed a significantly reduced time from relapse to death compared with control individuals (23). Interestingly, the phase III study of nivolumab versus docetaxel in nonsquamous NSCLC shows that the OS and progression-free survival 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 versus -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 tyrosine kinase inhibitor (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 on 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 protumor 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 REF 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 REF 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 antiproliferative 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 decipher between HPD and PD from SD or PR patients in this subsets 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) posttreatment biopsies would allow to explore the biologic 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.

Disclosure of Potential Conflicts of Interest

C. Massard is a consultant/advisory board member for Amgen, Astra Zeneca, Bayer, Celgene, Genentech, Ipsen, Jansen, Lilly, Novartis, Orion, Pfizer, Roche, and Sanofi. A. Eggermont is a consultant/advisory board member for Actelion, Bristol-Myers Squibb, Incyte, MSD, and Novartis. J.-C. Soria is a consultant/advisory board member for Astra Zeneca, Pfizer, and Roche. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: S. Champiat, L. Derclé, S. Ammari, C. Massard, J.-C. Soria, C. Féré

Development of methodology: S. Champiat, L. Derclé, C. Féré

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Champiat, L. Derclé, S. Ammari, C. Massard, A. Hollebecque, C. Féré

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S. Champiat, L. Derclé, S. Ammari, C. Massard, A. Hollebecque, J.-C. Soria, C. Féré

Writing, review, and/or revision of the manuscript: S. Champiat, L. Derclé, S. Ammari, C. Massard, A. Hollebecque, S. Postel-Vinay, N. Chaput, A. Eggermont, A. Marabelle, J.-C. Soria, C. Féré

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S. Champiat, L. Derclé, C. Massard, C. Féré

Study supervision: S. Champiat, S. Ammari, C. Féré

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received July 12, 2016; revised September 26, 2016; accepted October 28, 2016; published OnlineFirst November 8, 2016.

References

- Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015;372:320–30.
- Robert C, Schachter J, Long GV, Arance A, Grob J-J, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med* 2015;372:2521–32.
- Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubska E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015;373:123–35.
- Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015;373:1627–39.
- Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 2015;373:1803–13.
- Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet* 2016;387:1909–20.
- Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med* 2015;372:311–9.
- Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res* 2009;15:7412–20.
- Hodi FS, Hwu WJ, Kefford R, Weber JS, Daud A, Hamid O, et al. Evaluation of immune-related response criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab. *J Clin Oncol* 2016;34:1510–7.
- Lahmar J, Facchinetti F, Koscielny S, Ferte C, Mezquita L, Bluthgen MV, et al. Effect of tumor growth rate (TGR) on response patterns of checkpoint inhibitors in non-small cell lung cancer (NSCLC). *J Clin Oncol* 34, 2016 (suppl; abstr 9034).
- Saada-Bouazid E, Defaucheux C, Karabadjian A, Palomar Coloma V, Servois V, Paoletti X, et al. Tumor's flare-up and patterns of recurrence in patients (pts) with recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) treated with anti-PD-1/PD-L1 inhibitors. *J Clin Oncol* 34, 2016(suppl; abstr 6072).
- Ferte C, Fernandez M, Hollebecque A, Koscielny S, Levy A, Massard C, et al. Tumor growth rate is an early indicator of antitumor drug activity in phase I clinical trials. *Clin Cancer Res* 2014;20:246–52.
- Féré C, Koscielny S, Albiges L, Rocher L, Soria J-C, Iacovelli R, et al. Tumor growth rate provides useful information to evaluate sorafenib and everolimus treatment in metastatic renal cell carcinoma patients: an integrated

- analysis of the TARGET and RECORD phase 3 trial data. *Eur Urol* 2014; 65:713–20.
14. Nishino M, Dahlberg SE, Fulton LE, Digumarthy SR, Hatabu H, Johnson BE, et al. Volumetric tumor response and progression in EGFR-mutant NSCLC patients treated with erlotinib or gefitinib. *Acad Radiol* 2016;23: 329–36.
 15. Gomez-Roca C, Koscielny S, Ribrag V, Dromain C, Marzouk I, Bidault F, et al. Tumour growth rates and RECIST criteria in early drug development. *Eur J Cancer* 2011;47:2512–6.
 16. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–16.
 17. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.
 18. Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response. *J Clin Oncol* 1983;1:710–9.
 19. Arkenau HT, Barriuso J, Olmos D, Ang JE, de Bono J, Judson I, et al. Prospective validation of a prognostic score to improve patient selection for oncology phase I trials. *J Clin Oncol* 2009;27:2692–6.
 20. Goronzy JJ, Weyand CM. Understanding immunosenescence to improve responses to vaccines. *Nat Immunol* 2013;14:428–36.
 21. Solana R, Tarazona R, Gayoso I, Lesur O, Dupuis G, Fulop T. Innate immunosenescence: Effect of aging on cells and receptors of the innate immune system in humans. *Semin Immunol* 2012;24:331–41.
 22. Landre T, Taleb C, Nicolas P, Des Guetz G. Is there a clinical benefit of anti-PD-1 in patients older than 75 years with previously treated solid tumour? *J Clin Oncol* 34, 2016(suppl; abstr 3070).
 23. Strannegård Ö, Thorén FB. Opposing effects of immunotherapy in melanoma using multisubtype interferon-alpha - can tumor immune escape after immunotherapy accelerate disease progression? *Oncoimmunology* 2016;5:e1091147.
 24. Mellema WW, Burgers SA, Smit EF. Tumor flare after start of RAF inhibition in KRAS mutated NSCLC: A case report. *Lung Cancer* 2015;87:201–3.
 25. Kuriyama Y, Kim YH, Nagai H, Ozasa H, Sakamori Y, Mishima M. Disease flare after discontinuation of crizotinib in anaplastic lymphoma kinase-positive lung cancer. *Case Rep Oncol* 2013;6:430–3.
 26. Chaft JE, Oxnard GR, Sima CS, Kris MG, Miller VA, Riely GJ. Disease flare after tyrosine kinase inhibitor discontinuation in patients with EGFR-mutant lung cancer and acquired resistance to erlotinib or gefitinib: implications for clinical trial design. *Clin Cancer Res* 2011;17:6298–303.
 27. Iacovelli R, Massari F, Albiges L, Lorient Y, Massard C, Fizazi K, et al. Evidence and clinical relevance of tumor flare in patients who discontinue tyrosine kinase inhibitors for treatment of metastatic renal cell carcinoma. *Eur Urol* 2015;68:154–60.
 28. Riely GJ, Kris MG, Zhao B, Akhurst T, Milton DT, Moore E, et al. Prospective assessment of discontinuation and reinitiation of erlotinib or gefitinib in patients with acquired resistance to erlotinib or gefitinib followed by the addition of everolimus. *Clin Cancer Res* 2007;13:5150–5.
 29. Kleffel S, Posch C, Barthel SR, Mueller H, Schlapbach C, Guenova E, et al. Melanoma cell-intrinsic PD-1 receptor functions promote tumor growth. *Cell* 2015;162:1242–56.
 30. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. *Immunol Rev* 2010;236:219–42.
 31. Koyama S, Akbay EA, Li YY, Herter-Sprie GS, Buczkowski KA, Richards WG, et al. Adaptive resistance to therapeutic PD-1 blockade is associated with upregulation of alternative immune checkpoints. *Nat Commun* 2016;7:1–9.
 32. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis* 2009;30:1073–81.
 33. Coussens LM, Werb Z. Inflammation and cancer. *Nature* 2002;420:860–7.
 34. Hölzel M, Tüting T. Inflammation-induced plasticity in melanoma therapy and metastasis. *Trends Immunol* 2016;37:364–74.
 35. Hölzel M, Bovier A, Tüting T. Plasticity of tumour and immune cells: a source of heterogeneity and a cause for therapy resistance? *Nat Rev Cancer* 2013;13:365–76.

Clinical Cancer Research

Hyperprogressive Disease Is a New Pattern of Progression in Cancer Patients Treated by Anti-PD-1/PD-L1

Stéphane Champiat, Laurent Derle, Samy Ammari, et al.

Clin Cancer Res Published OnlineFirst November 8, 2016.

Updated version Access the most recent version of this article at:
doi:[10.1158/1078-0432.CCR-16-1741](https://doi.org/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>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link
<http://clincancerres.aacrjournals.org/content/early/2017/02/06/1078-0432.CCR-16-1741>.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.