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Hyperprogressive Disease in Patients With Advanced Non–Small Cell Lung Cancer Treated With PD-1/PD-L1 Inhibitors or With Single-Agent Chemotherapy

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IMPORTANCE Hyperprogressive disease (HPD) is a new pattern of progression recently described in patients with cancer treated with programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors. The rate and outcome of HPD in advanced non–small cell lung cancer (NSCLC) are unknown.

OBJECTIVES To investigate whether HPD is observed in patients with advanced NSCLC treated with PD-1/PD-L1 inhibitors compared with single-agent chemotherapy and whether there is an association between treatment and HPD.

DESIGN, SETTING, AND PARTICIPANTS In this multicenter retrospective study that included patients treated between August 4, 2011, and April 5, 2017, the setting was pretreated patients with advanced NSCLC who received PD-1/PD-L1 inhibitors (8 institutions) or single-agent chemotherapy (4 institutions) in France. Measurable disease defined by Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) on at least 2 computed tomographic scans before treatment and 1 computed tomographic scan during treatment was required.

INTERVENTIONS The tumor growth rate (TGR) before and during treatment and variation per month (ΔTGR) were calculated. Hyperprogressive disease was defined as disease progression at the first evaluation with ΔTGR exceeding 50%.

MAIN OUTCOMES AND MEASURES The primary end point was assessment of the HPD rate in patients treated with IO or chemotherapy.

RESULTS Among 406 eligible patients treated with PD-1/PD-L1 inhibitors (63.8% male), 46.3% (n = 188) were 65 years or older, 72.4% (n = 294) had nonsquamous histology, and 92.9% (n = 377) received a PD-1 inhibitor as monotherapy in second-line therapy or later. The median follow-up was 12.1 months (95% CI, 10.1-13.8 months), and the median overall survival (OS) was 13.4 months (95% CI, 10.2-17.0 months). Fifty-six patients (13.8%) were classified as having HPD. Pseudoprogression was observed in 4.7% (n = 19) of the population. Hyperprogressive disease was significantly associated with more than 2 metastatic sites before PD-1/PD-L1 inhibitors compared with non-HPD (62.5% [35 of 56] vs 42.6% [149 of 350]; *P* = .006). Patients experiencing HPD within the first 6 weeks of PD-1/PD-L1 inhibitor treatment had significantly lower OS compared with patients with progressive disease (median OS, 3.4 months [95% CI, 2.8-7.5 months] vs 6.2 months [95% CI, 5.3-7.9 months]; hazard ratio, 2.18 [95% CI, 1.29-3.69]; *P* = .003). Among 59 eligible patients treated with chemotherapy, 3 (5.1%) were classified as having HPD.

CONCLUSIONS AND RELEVANCE Our study suggests that HPD is more common with PD-1/PD-L1 inhibitors compared with chemotherapy in pretreated patients with NSCLC and is also associated with high metastatic burden and poor prognosis in patients treated with PD-1/PD-L1 inhibitors. Additional studies are needed to determine the molecular mechanisms involved in HPD.

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Author Audio Interview

Supplemental content

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In the era of immuno-oncology, programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors have demonstrated a clear survival benefit as a single agent or in combination compared with standard chemotherapy in both treatment-naive patients[1-4] and patients previously treated[5-8] for advanced non–small cell lung cancer (NSCLC). However, progression rates reported with single-agent PD-1/PD-L1 inhibitors are in some cases equal to or higher than with conventional treatment, ranging from 33% to 44% in pretreated patients with NSCLC.[5-7] Recently, an acceleration of tumor growth during immunotherapy, defined as hyperprogressive disease (HPD), was reported in 9% of advanced cancers[9] and in 29% of patients with head and neck cancer[10] treated with PD-1/PD-L1 inhibitors.

The tumor growth rate (TGR) is a tool for estimating the increase in tumor volume over time based on 2 computed tomography (CT) scan measurements.[11] The TGR takes into account the sum of the target lesions defined by Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) and the interval between 2 CT scans. It can be used to quantitatively assess tumor dynamics and kinetics during treatment; specifically, it can be applied to identify the subset of patients experiencing HPD.

To explore if HPD is an unforeseen pattern of progression during IO therapy in NSCLC, we compared the TGR before and during IO therapy in a cohort of pretreated patients with advanced NSCLC. To investigate if HPD is a specific PD-1/PD-L1 inhibitor pattern, we assessed the TGR and HPD prevalence among a control cohort receiving single-agent chemotherapy.

Key Points

Question Do programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors accelerate tumor growth, a phenomenon defined as hyperprogressive disease?

Findings In this multicenter cohort study including 406 patients with advanced non–small cell lung cancer (NSCLC) treated with PD-1/PD-L1 inhibitors, hyperprogressive disease was observed in 13.8% (n = 56) of the population. Patients experiencing hyperprogression had significantly worse overall survival (3.4 months) compared with patients with progression not classified as hyperprogressive disease (6.2 months).

Meaning Hyperprogressive disease is a novel pattern of progression in patients receiving treatment with PD-1/PD-L1 inhibitors for NSCLC, of which patients and clinicians should be aware to properly select the best treatment and carefully monitor disease evolution.

Methods

Patients and Treatment

In this multicenter study, data were retrospectively collected from all consecutive eligible patients with advanced NSCLC treated with IO (nivolumab, pembrolizumab, atezolizumab, or durvalumab) from November 10, 2012, to April 5, 2017, in 8 French institutions. For the control cohort, equivalent data were collected in patients with advanced NSCLC failing a platinum-based regimen and treated with single-agent chemotherapy (taxanes, pemetrexed, vinorelbine tartrate, or gemcitabine chlorohydrate) from August 4, 2011, to June 13, 2016, in 4 French institutions.

To be eligible, patients had to be 18 years or older, with histologically or cytologically confirmed stage III or IV NSCLC and available CT scans for radiological evaluation. In the single-agent chemotherapy control cohort, patients who received previous treatment with IO were excluded. The PD-L1 expression was analyzed by immunohistochemistry on tumor cells in archived biopsy specimens, when available, and the cutoff for positivity was 1%. This study was approved by the institutional review board of Gustave Roussy, and informed consent from participants was not required because of the retrospective nature.

Radiological Evaluation

At least 2 CT scans before PD-1/PD-L1 inhibitor therapy or chemotherapy (baseline and the most recent scan before baseline) and 1 CT scan during treatment were mandatory for radiological evaluation. The baseline CT had to be performed within 6 weeks before initiating treatment, and a minimum of 2 weeks between CT scans was required. All CT scans were centrally reviewed by 2 senior radiologists (L.T. and C.C.). The target lesions were defined according to RECIST version 1.1. An extensive assessment of noneligibility for radiological evaluation was performed in 1 center (Gustave Roussy) to refine inclusion of patients in subsequent centers. Therefore, patients from other centers were included only if eligible for radiological evaluation (ie, availability of the required CT scans, adequate intervals between them, and the presence of the target lesions). In cases of progression, if the patient was clinically stable, PD-1/PD-L1 inhibitors could be continued, with a subsequent evaluation at least 4 weeks later, according to immunotherapy response criteria recommendations.[12] Pseudoprogression was defined as initial progression, followed by complete response or partial response or stable disease lasting more than 6 months.[13]

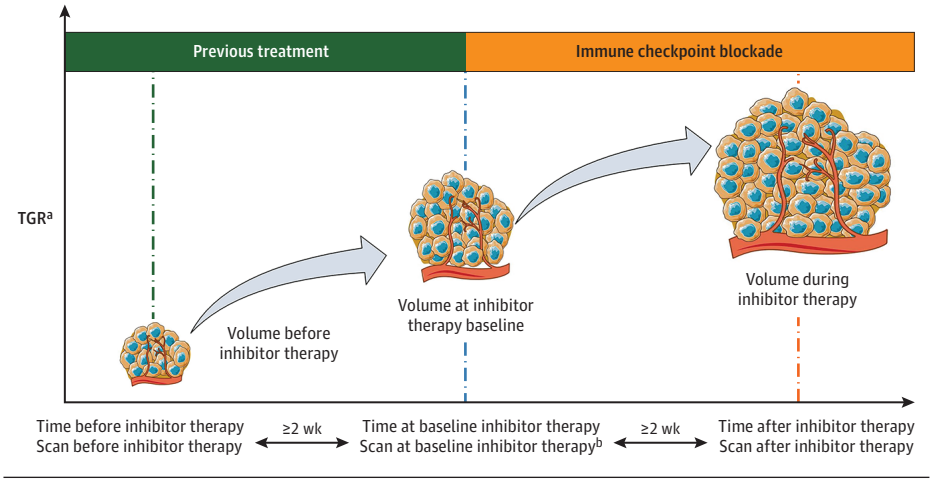
Tumor Growth Rate

The TGR was calculated according to the definition by Ferté et al[14] and was computed from the sum of the largest diameters of the target lesions as per RECIST version 1.1 (eMethods in the Supplement). The TGR results were reported as a percentage increase in tumor volume per month. New lesions and nonmeasurable disease were excluded from the RECIST version 1.1 sum, and the TGR was only quantified for the target lesions.[14]

The TGR was measured before and after PD-1/PD-L1 inhibitors (or chemotherapy in the control cohort). The difference (ΔTGR is the TGR on treatment minus the TGR before treatment) was used to assess the association of treatment with tumor growth. Delta TGR exceeding 0% means that treatment may accelerate tumor growth.

Hyperprogressive disease was defined as RECIST version 1.1 progressive disease on the first CT scan during treatment

Figure 1. Hypothetical Tumor Volume Variation and Definition of Hyperprogressive Disease (HPD) in the Immunotherapy Cohort



Variation of tumor growth rate (TGR) volume per month was calculated both before the start of programmed cell death (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitor therapy and during PD-1/PD-L1 inhibitor therapy. Hyperprogressive disease was defined as Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 progressive disease at the first computed tomography (CT) scan during PD-1/PD-L1 inhibitor therapy and an absolute increase in the TGR exceeding 50% per month.
[a]New lesions and nonmeasurable disease not included in the TGR.
[b]The baseline CT scan performed within 6 weeks before PD-1/PD-L1 inhibitor therapy initiation.

and ΔTGR exceeding 50%, corresponding to an absolute increase in the TGR exceeding 50% per month. A graphical representation of the hypothetical tumor volume variation and the HPD definition for the immunotherapy cohort is shown in **Figure 1**.

Statistical Analysis

Associations between HPD and categorical or continuous variables were evaluated using the Fisher exact test and the *t* test, respectively. Because the diagnosis of HPD depends on the timing of the radiological assessment and could induce a lead-time bias,[15] a landmark analysis was performed to assess the association of HPD with overall survival (OS) using a time point at 6 weeks after PD-1/PD-L1 inhibitor or chemotherapy initiation. Patients alive at this time point and with progression on their first CT scan during PD-1/PD-L1 inhibitor therapy or chemotherapy were considered hyperprogressors or not hyperprogressors according to the diagnosis of HPD within the first 6 weeks of treatment. Overall survival curves were estimated with the Kaplan-Meier method and compared by the log-rank test. The hazard ratio (HR) was estimated using the univariate Cox proportional hazards regression model. All *P* values were 2 sided, and values less than .05 were considered statistically significant. Statistical analyses were performed using a software program (SAS for Windows, version 9.4; SAS Institute Inc).

Results

Immunotherapy Cohort

Overall, 406 patients (63.8% male) were included in the TGR analysis. The reasons for exclusion were evaluated in a single-center cohort (at Gustave Roussy, Villejuif, France) (n = 249) and included the following: unavailability of CT scans before baseline, at baseline, or during PD-1/PD-L1 inhibitor therapy; inadequate intervals between CT scans; or the absence of measurable disease. Of 249 patients, 76 (30.5%) were not evaluable for the TGR analysis, among whom 13.3% (33 of 249) experienced clinical progression and/or death before the first tumor evaluation during PD-1/PD-L1 inhibitor therapy (eFigure 1 in the Supplement).

The main characteristics of the 406 patients in the immunotherapy multicenter cohort are listed in the **Table**. The median follow-up was 12.1 months (95% CI, 10.1-13.8 months), the objective response rate was 18.9% (77 of 406), and 41.9% (170 of 406) of patients had progressive disease as the best response to immunotherapy (eTable 1 in the Supplement). The median progression-free survival (PFS) and OS were 2.1 months (95% CI, 1.8-3.1 months) and 13.4 months (95% CI, 10.2-17.0 months), respectively.

Before immunotherapy, 75 of 406 patients (18.5%) had a TGR of 0 or less (eTable 2 in the Supplement), but all were classified as having progressive disease because of the appearance of new lesions or progression in the nontarget lesions. During immunotherapy, the TGR was stable or decreased (ΔTGR ≤0) in 266 patients (65.5%) and increased (ΔTGR >0) in 140 patients (34.5%). Among them, 62 patients (15.3% of the overall population) were initially classified as having HPD (**Figure 2**A and **Figure 3**).

Overall, 19 patients (4.7%) had progressive disease, followed by complete response and/or partial response or stable disease longer than 6 months, and were thus classified as pseudoprogressors (eTable 1 in the Supplement). Six pseudoprogressors were initially classified as having HPD on the first CT scan. Excluding these 6 patients from the 62 patients with HPD, the definitive rate of HPD was 13.8% (56 patients). Hyperprogressive disease was significantly associated with more than 2 metastatic sites before PD-1/PD-L1 inhibitors compared with non-HPD (62.5% [35 of 56] vs 42.6% [149 of 350]; *P* = .006) (Table). No significant differences were observed according to the baseline tumor burden, the number of previous lines of therapy (eFigure 2 in the Supplement), or age (Table).

In the landmark survival analysis, patients experiencing HPD within the first 6 weeks of beginning PD-1/PD-L1 inhibitor therapy (n = 23) had significantly lower OS compared with

Table. Patient Characteristics and Association Between HPD Status and Clinical Categorical Variables for Immunotherapy-Treated Patients With NSCLC

Variable	No./Total No. (%)			Fisher Exact Test *P* Value
	Total (N = 406)	Non-HPD (n = 350)	HPD (n = 56)	
Age, y				
≥65	188 (46.3)	166 (47.4)	22 (39.3)	.31
<65	218 (53.7)	184 (52.6)	34 (60.7)	
Smoking history				
Current/former	371 (91.4)	319 (91.1)	52 (92.9)	>.99
None	35 (8.6)	31 (8.9)	4 (7.1)	
Smoking exposure, pack-years				
≤30	136 (33.5)	115/312 (36.9)	21/50 (42.0)	.53
>30	226 (55.7)	197/312 (63.1)	29/50 (58.0)	
Missing	44 (10.8)	38	6	
Histology				
Nonsquamous	294 (72.4)	252 (72.0)	42 (75.0)	.75
Squamous	112 (27.6)	98 (28.0)	14 (25.0)	
Stage[a]				
III	70 (17.2)	61 (17.4)	9 (16.1)	>.99
IV	336 (82.8)	289 (82.6)	47 (83.9)	
PD-L1 status[b]				
Negative	39 (9.6)	32/105 (30.5)	7/12 (58.3)	.10
Positive	78 (19.2)	73/105 (69.5)	5/12 (41.7)	
Missing	289 (71.2)	245	44	
Molecular status				
ALK rearrangement	4 (1.0)	3/233 (1.3)	1/36 (2.8)	.34
EGFR mutation	16 (3.9)	16/233 (6.9)	0	
KRAS mutation	87 (21.4)	74/233 (31.8)	13/36 (36.1)	
Wild type[c]	104 (25.6)	88/233 (37.8)	16/36 (44.4)	
Other alterations	58 (14.3)	52/233 (22.3)	6/36 (16.7)	
Missing	137 (33.7)	117	20	
No. of molecular alterations				
0-1	218 (53.7)	185/227 (81.5)	33/36 (91.7)	.16
≥2	45 (11.1)	42/227 (18.5)	3/36 (8.3)	
Missing	143 (35.2)	123	20	
Type of treatment before PD-1/PD-L1 inhibitor therapy				
Platinum-based chemotherapy	229 (56.4)	192 (54.9)	37 (66.1)	.61
Chemoradiotherapy	17 (4.2)	17 (4.9)	0	
Pemetrexed	17 (4.2)	15 (4.3)	2 (3.6)	
Taxanes	44 (10.8)	39 (11.1)	5 (8.9)	
Other chemotherapy	43 (10.6)	37 (10.6)	6 (10.7)	
Targeted therapy[d]	12 (3.0)	11 (3.1)	1 (1.8)	
Tyrosine kinase inhibitors[e]	37 (9.1)	33 (9.4)	4 (7.1)	
Immunotherapy	3 (0.7)	2 (0.6)	1 (1.8)	
No prior therapy	4 (1.0)	4 (1.1)	0	
Response to line before PD-1/PD-L1 inhibitor therapy				
Complete response/partial response	90 (22.2)	75/344 (21.8)	15/55 (27.3)	.08
Stable disease	185 (45.6)	167/344 (48.5)	18/55 (32.7)	
Progressive disease	124 (30.5)	102/344 (29.7)	22/55 (40.0)	
Missing	7 (1.7)	6	1	

(continued)

Table. Patient Characteristics and Association Between HPD Status and Clinical Categorical Variables for Immunotherapy-Treated Patients With NSCLC (continued)

Variable	No./Total No. (%)			Fisher Exact Test *P* Value
	Total (N = 406)	Non-HPD (n = 350)	HPD (n = 56)	
PD-1/PD-L1 inhibitor therapy line, range 1-9				
≤2[f]	218 (53.7)	186 (53.1)	32 (57.1)	.67
>2	188 (46.3)	164 (46.9)	24 (42.9)	
No. of metastatic sites before PD-1/PD-L1 inhibitor therapy				
≤2	222 (54.7)	201 (57.4)	21 (37.5)	.006
>2	184 (45.3)	149 (42.6)	35 (62.5)	
Type of inhibitor				
PD-1	377 (92.9)	325 (92.9)	52 (92.9)	>.99
PD-L1	29 (7.1)	25 (7.1)	4 (7.1)	
Monotherapy or combination				
Monotherapy	380 (93.6)	326 (92.9)	54 (96.4)	.56
Combination[g]	26 (6.4)	24 (6.9)	2 (3.6)	
ECOG performance status				
0-1	360 (88.7)	311 (88.9)	49 (87.5)	.82
≥2	46 (11.3)	39 (11.1)	7 (12.5)	
Subsequent therapy				
No	111 (27.3)	86/215 (40.0)	25/54 (46.3)	.44
Yes	158 (38.9)	129/215 (60.0)	29/54 (53.7)	
PD-1/PD-L1 inhibitor therapy ongoing or missing	137 (33.7)	135	2	
Neutrophil count, /μL				
≤7500	209 (51.5)	188/254 (74.0)	21/31 (67.7)	.52
>7500	76 (18.7)	66/254 (26.0)	10/31 (32.3)	
Missing	121 (29.8)	96	25	
Derived neutrophil-to-lymphocyte ratio				
≤3	195 (48.0)	174/254 (68.5)	21/31 (67.7)	>.99
>3	90 (22.2)	80/254 (31.5)	10/31 (32.3)	
Missing	121 (29.8)	96	25	
Lactate dehydrogenase level				
≤Upper limit of normal[h]	150 (36.9)	133/192 (69.3)	17/27 (63.0)	.51
>Upper limit of normal	69 (17.0)	59/192 (30.7)	10/27 (37.0)	
Missing	187 (46.1)	158	29	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HPD, hyperprogressive disease; NSCLC, non–small cell lung cancer; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1.

SI conversion factor: To convert neutrophil count to 10^9/L, multiply by 0.001.

[a] TNM stage (seventh edition) at advanced disease detection.

[b] Immunohistochemistry cutoff for positivity on tumor cells of 1% or higher.

[c] Wild type for *ALK* rearrangement, *EGFR* mutation, and *KRAS* mutation.

[d] In oncogene-addicted NSCLC.

[e] In non–oncogene-addicted NSCLC.

[f] Four patients treated in first line for metastatic disease.

[g] Combination of PD-1/PD-L1 inhibitor therapy and anti-EGFR monoclonal antibodies, PD-1/PD-L1 inhibitor therapy and chemotherapy, or PD-1/PD-L1 inhibitor therapy and immunotherapy (patients enrolled in clinical trials).

[h] Upper limit of normal defined according to the cutoff of each center.

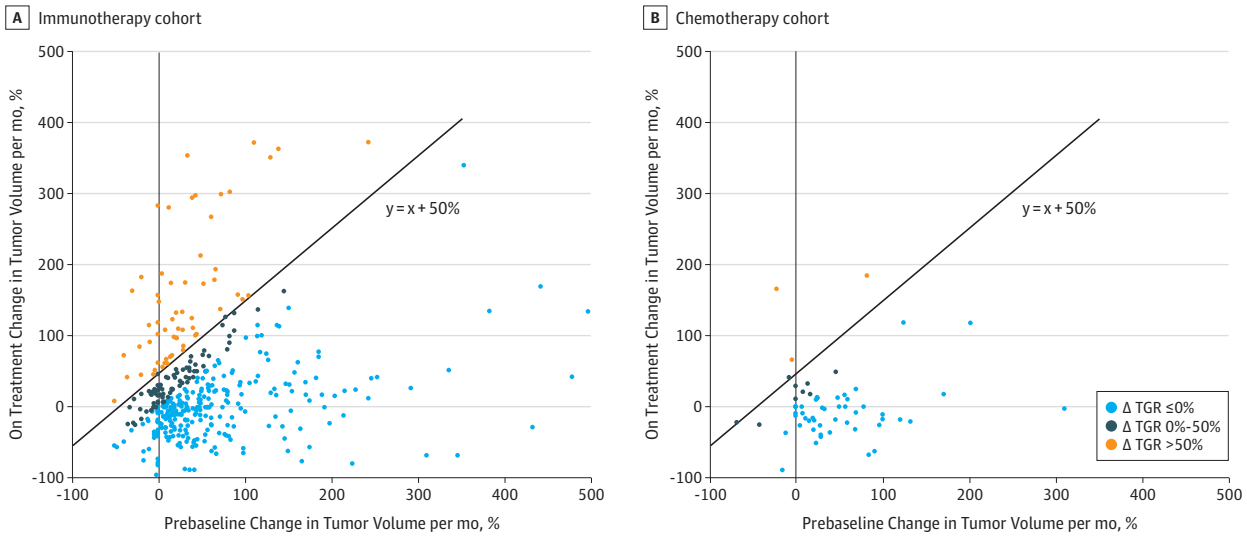
other patients with progressive disease (ie, non-HPD patients with progressive disease at the first evaluation [n = 138]) (median OS, 3.4 months [95% CI, 2.8-7.5 months] vs 6.2 months [95% CI, 5.3-7.9 months]; HR, 2.18 [95% CI, 1.29-3.69]; *P* = .003) (**Figure 4**A). As a sensitivity analysis, 2 other landmark time points were tested. With a time point at 4 weeks, the difference in OS remained significant. However, when choosing a time point of 8 weeks, the difference in OS did not reach statistical significance.

Chemotherapy Cohort

Overall, 59 patients were included in the TGR analysis. The reasons for exclusion were evaluated in a single-center cohort (at Gustave Roussy) (n = 77) (eFigure 3 in the Supplement). The main characteristics of the 59 patients are listed in eTable 3 in the Supplement. The median follow-up was 26.3 months (95% CI, 22.6-35.5 months), the objective response rate was 10.2% (6 of 59), and 30.5% (18 of 59) of patients had progressive disease as the best response (eTable 1 in the Supplement). The median PFS and OS were 3.9 months (95% CI, 3.1-4.8 months) and 8.6 months (95% CI, 6.2-13.4 months), respectively. No pseudoprogression was observed.

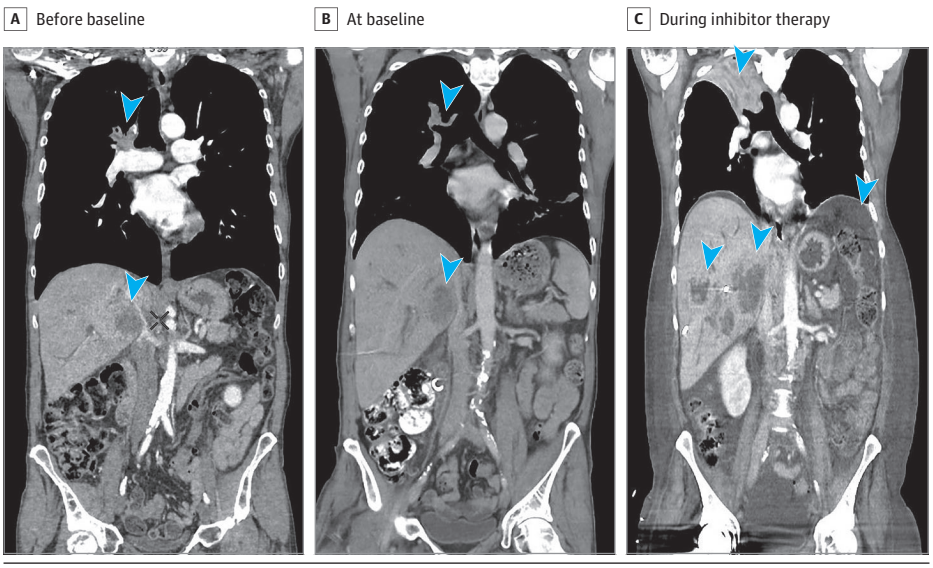
The TGR analysis is summarized in eTable 2 in the Supplement. Delta TGR was greater than 0 in 12 patients; among them, 3 patients were classified as having HPD (Figure 2B). A landmark analysis at 6 weeks showed a median OS of 4.5 months (95% CI, 2.5-6.5 months) in patients diagnosed as having HPD (n = 3) and 3.9 months (95% CI, 2.7-6.9 months) in other patients with progressive disease (ie, non-HPD patients with progressive disease at the first evaluation [n = 18]) (*P* = .60) (Figure 4B).

Figure 2. Scatterplots With Response According to Delta Tumor Growth Rate (TGR) in the Immunotherapy and Chemotherapy Cohorts



A, Light blue spots show 266 patients with regressing or stable tumors, dark blue spots show 78 patients with progressing tumors, and orange spots show 62 patients with accelerated tumor growth during programmed cell death (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitor therapy. B, Light blue spots show 47 patients with regressing or stable tumors, dark blue spots show 9 patients with progressing tumors, and orange spots show 3 patients with accelerated tumor growth during chemotherapy. Diagonal lines separate patients with delta TGR exceeding 50% from patients with delta TGR of 50% or less.

Figure 3. Case Study of a Patient With Non–Small Cell Lung Cancer With Hyperprogressive Disease During Treatment With a PD-1 Inhibitor



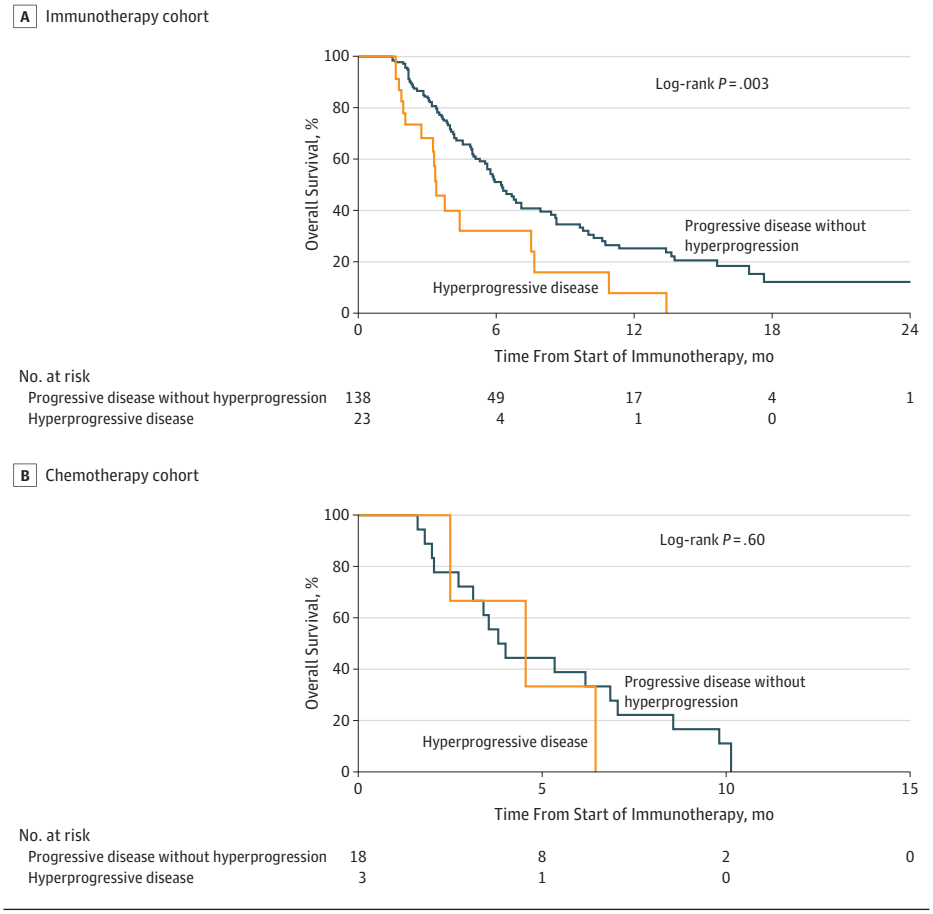
Shown are computed tomographic scans before baseline (A), at baseline about 3 weeks later (B), and during programmed cell death (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitor therapy 1 month later (C) in a man in his mid-50s with stage IV (lung, liver, and bone metastases) *HER2*-amplified lung adenocarcinoma treated with anti–PD-1 therapy in the third line. After 2 administrations, there was evidence of extensive lung, liver, and peritoneal progression. Arrowheads show lung and liver metastases before and during anti–PD-1 treatment.

Discussion

In this study of pretreated patients with advanced NSCLC, HPD was observed in 13.8% (56 of 406) of patients treated with PD-1/PD-L1 inhibitors compared with 5.1% (3 of 59) of patients treated with single-agent chemotherapy. Our rate of HPD is concordant with the few relevant previously reported studies. Champiat et al[9] identified HPD in 9% of 131 patients with advanced cancer treated with PD-1/PD-L1 inhibitors in phase 1 trials; only 13 patients had lung cancer, and none were classified as having HPD. Hyperprogressive disease was identified more frequently (29%) by Saâda-Bouzid et al[10] among 34 patients with recurrent or metastatic head and neck cancer. This higher rate could have occurred because of the tumor type and/or their different definition of HPD.

In our study, HPD was associated with poor survival in patients with NSCLC treated with PD-1/PD-L1 inhibitors. Hyperprogressive disease could potentially explain the initial excess of death in some phase 3 trials. For example, in the CheckMate

Figure 4. Overall Survival for Hyperprogressive Disease (HPD) Compared With Progressive Disease Without Hyperprogression in the Immunotherapy and Chemotherapy Cohorts (6-Weeks Landmark Analysis)



A, Fourteen patients and 2 patients with pseudoprogression were excluded from the progressive disease without hyperprogression and HPD cohorts, respectively. The median overall survival is shown for 138 patients with progressive disease without hyperprogression at the first evaluation vs for 23 patients with diagnosed HPD within the first 6 weeks of treatment. B, The median overall survival is shown for 18 patients with progressive disease without hyperprogression at the first evaluation vs for 3 patients with diagnosed HPD within the first 6 weeks of treatment.

057 study,[5] the progression rate was 44% with nivolumab and 29% with docetaxel, with an excess of 14 deaths during the first 3 months in the nivolumab arm.[16] As a result, OS curves crossed at 6 months, with an initial survival benefit in favor of docetaxel. In addition, a recent retrospective study[17] reported that approximately 15% of early deaths were due to disease progression during the first 3 months of nivolumab treatment in patients with advanced NSCLC. The European Medicines Agency recently included an alert in the summary of product information for nivolumab regarding treatment of patients with NSCLC with poor prognostic features or aggressive disease.[18] In our study, the absence of a significant survival difference using a landmark analysis at 8 weeks is likely because of the small number of patients with HPD alive at that time point and eligible for the landmark analysis. This finding further suggests that HPD is a rapid phenomenon, which leads to early death mostly in the first 2 months of treatment.

There is no consensus on the optimal definition of HPD. Champiat et al[9] defined HPD as progressive disease at the first evaluation in addition to an increase of at least 2-fold in the TGR during PD-1/PD-L1 inhibitor therapy compared with the TGR before PD-1/PD-L1 inhibitors. Saâda-Bouzid et al[10] described HPD as an increase of at least 2-fold in tumor growth kinetics after PD-1/PD-L1 inhibitor initiation, which measured the variation of the sum of the largest diameters of the target lesions per unit of time during immunotherapy compared with tumor growth kinetic before PD-1/PD-L1 inhibitors. We used a stringent definition of HPD that requires a high-volume increase per month to classify a patient as a hyperprogressor. For example, a tumor with a 20% volume increase per month before immunotherapy had to have a 70% increase per month during immunotherapy to be labeled as HPD. Despite the differences in methods, the present analysis and the 2 previous studies[9,10] highlight the importance of quantifying tumor growth speed to discriminate between progression due to natural history of the disease (the tumor growth speed is already high before the start of the new treatment) and progression due to the potential intrinsic association of the experimental treatment (the tumor growth speed is lower before the start of the new treatment). Unfortunately, the TGR assessment cannot be validated in published randomized studies because the radiological evaluations before the baseline CT scan data were not captured.

In our immunotherapy cohort, HPD was significantly associated with a high number of metastatic sites before PD-1/PD-L1 inhibitors, whereas no association with the baseline tumor burden was found. However, the target lesions defined by RECIST version 1.1 do not always perfectly reflect the whole tumor burden, especially in patients with nonmeasurable dis-

ease (lung lymphangitis, bone metastases, and pleural or peritoneal effusions). Furthermore, high lactate dehydrogenase levels and a derived neutrophil to lymphocyte ratio exceeding 3 were recently shown to negatively influence the survival outcome of patients with NSCLC treated with PD-1/PD-L1 inhibitors.[19] In our analysis, no significant association was found between these biomarkers and HPD status; however, lactate dehydrogenase levels and neutrophil counts were not available for 46.1% (187 of 406) and 29.8% (121 of 406) of patients, respectively. Contrary to what was observed by Champiat et al,[9] no significant association between HPD and age was found in our study, probably because of the different methods used to assess HPD. Recently, Kato et al[20] identified *EGFR* mutations and *MDM2* amplification as possible molecular predictors of HPD. In our cohort, none of 16 patients with *EGFR*-mutated lung adenocarcinoma experienced HPD. Despite the association between *EGFR* mutations and decreased benefit from immunotherapy in patients with NSCLC,[21] the potential role of *EGFR* mutations in driving HPD remains unknown. The phenomenon of disease progression acceleration was previously described in oncogene-addicted NSCLC after interruption of targeted agents, such as RAF,[22] ALK,[23] and EGFR[24] inhibitors. In the present analysis, no significant association between HPD and the type of previous therapy was found, minimizing the risk of such an association.

In 6 of the 62 patients with HPD (9.7%), initial HPD was further reclassified as pseudoprogression, a feature described in 4.7% (19 of 406) of our total population, in line with a recently published study in the same setting.[25] Variable rates of pseudoprogression have been reported in patients with NSCLC (2%-19%),[26,27] melanoma (4%-7%),[28,29] and renal cell carcinoma (1%-15%)[30-32] on PD-1/PD-L1 blockade. However, a comparison of these numbers should be interpreted with caution in the absence of a common definition of pseudoprogression across the studies.[33] We identified HPD in only 3 of 59 patients (5.1%) treated with single-agent chemotherapy, and no pseudoprogression was described, suggesting that these patterns are new and specific to PD-1/PD-L1 inhibitors.

To our knowledge, the present study is the largest analysis exploring HPD to date and is the first conducted in a dedicated NSCLC population. In addition, we believe that this is the only study to include a control cohort of chemotherapy-treated patients with NSCLC and is thus able to assess the negative association with survivial of HPD compared with conventional disease progression during PD-1/PD-L1 inhibitor therapy. Although in some immunotherapy trials[5,6,8] the first CT scan was performed at week 9, the fact that HPD drives toward early death (mainly in the first 6 weeks of treatment) prompts discussion over an anticipated first radiological evaluation during PD-1/PD-L1 inhibitor therapy to properly identify hyperprogressors. Ultimately, because of the poor OS associated with HPD, an early switch to salvage chemotherapy in these patients should be considered.

Limitations

Our study has some limitations, mainly related to its retrospective nature. First, a potential underestimation of HPD may have occurred because 30.5% (76 of 249) of the patients treated in 1 center (Gustave Roussy) were excluded from the TGR analysis, mostly because of rapid progression and/or death that prevented any further evaluation or because of the absence of the target lesions. In addition, in our study, PD-L1 expression was not available for 71.2% (289 of 406) of patients because this information was not mandatory for PD-1/PD-L1 inhibitor prescription in pretreated patients with NSCLC and because the percentage of positive expression was often not provided and tested with heterogeneous methods; therefore, we were unable to precisely characterize the interplay between PD-L1 status and HPD. Similarly, tumor mutational burden (TMB) was not available because it was not routinely assessed outside of clinical trials. In our study, only 26 patients (2 classified as having HPD) were treated with immunotherapy in combination with other drugs. Recently, a significant survival benefit for first-line PD-1/PD-L1 inhibitors–chemotherapy (KEYNOTE-021 study,[34] IMpower150 study,[35] KEYNOTE-189 study[3], KEYNOTE 407 study,[36] and IMpower131 study[37]) and PD-1/PD-L1 inhibitor–PD-1/PD-L1 inhibitor (CheckMate 227 study[4]) combinations compared with platinum doublets has been reported. In high-TMB patients with NSCLC, the PFS curves of nivolumab plus ipilimumab and platinum-based chemotherapy treatments cross between 3 and 6 months; in patients receiving platinum-based chemotherapy in combination with pembrolizumab or placebo, an early separation of both PFS and OS curves has been observed.[3,36] These findings suggest a considerable rate of fast progressions or early deaths, potentially due to HPD, in patients treated with double immune checkpoint blockade; in contrast, the addition of chemotherapy to PD-1/PD-L1 inhibitors may hamper PD-1/PD-L1 inhibitor resistance and HPD. Overall, whether HPD is an issue in PD-L1 or TMB selected patients with NSCLC or develops on PD-1/PD-L1 inhibitor combinatorial strategies remains an open question that should be addressed in future studies.

Finally, despite the large sample population herein, it was impossible to define a particular clinical or pathological phenotype for HPD because of the limited number of hyperprogressors. Likewise, the characterization of the molecular basis of HPD remains an unmet need. Some immune checkpoint molecules, such as PD-1 expression[38] and Tim-3 expression,[39] might temper T-regulatory (Treg) cell proliferation and immune suppressive functions, a phenomenon defined as "contra-suppression."[40] Furthermore, a high level of interferon γ (IFN-γ), usually released by PD-1 blockade,[41] may have detrimental effects on immunity as observed in murine mycobacterial infections[42] or in cancer models where increased IFN-γ was associated with activation of tumor immunosuppressive myeloid cells[43] and upregulation of inhibitory metabolites[44] (eg, indoleamine 2,3-dioxygenase) involved in Treg differentiation.[45] Alternatively, PD-1/PD-L1 blockade may upregulate the interleukin 6, interleukin 17, and neutrophil axis, generating a potent aberrant inflammation responsible for immune escape and accelerated growth, as shown in tuberculosis[46] and lung cancer[47] in vivo models. Future studies with prospective assessment of tumor and blood samples from patients with HPD both before treatment and on treatment help clarify the mechanisms behind this phenomenon and its causal relation to treatment.

Conclusions

We identified HPD in 13.8% (56 of 406) of patients with advanced NSCLC treated with PD-1/PD-L1 inhibitors and in only 5.1% (3 of 59) of patients with advanced NSCLC treated with single-agent chemotherapy. In this study, HPD was associated with a high number of metastatic sites at baseline and poor survival (3.4 months), suggesting a detrimental association of immunotherapy in a subset of patients with NSCLC. Additional studies are needed to characterize the molecular basis of HPD.

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Dr Audigier-Valette reported serving in a consulting/advisory role for Bristol-Myers Squibb and Merck Sharp & Dohme. Dr Mazieres reported serving in a consulting/advisory role for Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, AstraZeneca, and Eli Lilly and reported receiving research funding from Roche, Bristol-Myers Squibb, and AstraZeneca. Dr Duchemann reported serving in a consulting/advisory role for Roche and Bristol-Myers Squibb and reported receiving travel/accommodation funding from Roche. Dr Westeel reported serving in a consulting/advisory role for Bristol-Myers Squibb, Merck Sharp & Dohme, and AstraZeneca; reported receiving honoraria from Bristol-Myers Squibb and AstraZeneca; reported serving on speakers bureaus for Bristol-Myers Squibb and Merck Sharp & Dohme; and reported receiving travel/accommodation funding from Bristol-Myers Squibb, Roche, and AstraZeneca. Dr Remon reported receiving travel/accommodation funding from Merck Sharp & Dohme and OSE Pharma. Dr Adam reported serving in a consulting/advisory role for Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, and AstraZeneca. Dr Bria reported receiving speakers fees from Bristol-Myers Squibb, Novartis, AstraZeneca, Merck Sharp & Dohme, Celgene, Pfizer, Helsinn, Eli Lilly, and Roche and reported receiving research funding from AstraZeneca, Roche, Open Innovation, Italian Association for Cancer Research (AIRC), and Cariverona Foundation. Dr Soria reported serving in a consulting/advisory role for Roche, AstraZeneca, and Pfizer. Dr Besse reported receiving research funding from GlaxoSmithKline, Roche/Genentech, Clovis Oncology, Pfizer, Boehringer, Eli Lilly, Servier, Onxeo, Bristol-Myers Squibb, Merck Sharp & Dohme, OSE Pharma, Inivata, and AstraZeneca. No other disclosures were reported.

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