

# Comparison of Different Methods for Defining Hyperprogressive Disease in NSCLC



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Received 7 July 2020; revised 6 October 2020; accepted 20 October 2020

Available online - 28 October 2020

## ABSTRACT

**Introduction:** Hyperprogressive disease (HPD) as a consequence of immune checkpoint inhibitors in NSCLC has been reported in multiple studies. However, inconsistent results in incidence and survival outcomes within studies, together with different assessment methods, have led to increasing controversy regarding the concept of HPD.

**Methods:** Consecutive patients treated with nivolumab (N = 42) or docetaxel (N = 37) were evaluated. HPD was quantified by applying three different methods (tumor growth rate [TGR], tumor growth kinetics [TGK], and Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST 1.1]). HPD rates were compared between and within both cohorts using the different methods.

**Results:** Using TGR, TGK, and RECIST 1.1, we identified seven (16.7%), seven (16.7%), and six (14.3%) patients with HPD in the nivolumab cohort and three (8.1%), four (10.8%), and five (13.6%) in the docetaxel cohort, respectively. We observed a higher concordance between TGR and TGK (90.1%) compared with RECIST 1.1 (31.3% and 37.5% with TGR and TGK, respectively). We found no significant differences in the overall survival between patients with progressive disease and HPD in either cohort.

**Conclusions:** TGR and TGK revealed high concordance rates for identifying patients with HPD in NSCLC. The incidence of HPD was numerically higher in patients treated with immune checkpoint inhibitors. Standardization of methods for measuring HPD and its exploration in larger studies are needed to establish its clinical meaning in NSCLC.

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**Keywords:** Hyperprogressive disease; NSCLC; Immune checkpoint inhibitors; Chemotherapy

## Introduction

After the introduction of immune checkpoint inhibitors (ICIs) in cancer treatment, new radiologic tumor

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Drs. Ramal and Ripoll contributed equally to this work.

**Disclosure:** Dr. Arriola reports receiving grants, personal fees, and nonfinancial support from Roche; personal fees from AstraZeneca; grants and personal fees from Pfizer; and personal fees and nonfinancial support from Bristol-Myers Squibb, Merck Sharp & Dohme, Boehringer Ingelheim, and Eli Lilly outside of the submitted work. Dr. Taus reports receiving nonfinancial support from Eli Lilly; personal fees and nonfinancial support from Boehringer Ingelheim and Roche; and personal fees from Bristol-Myers Squibb, Merck Sharp & Dohme, and Pfizer outside of the submitted work. The remaining authors declare no conflict of interest.

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Cite this article as: Rocha P, et al. Comparison of Different Methods for Defining Hyperprogressive Disease in NSCLC. *JTO Clin Res Rep* 2:100115

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ISSN: 2666-3643

<https://doi.org/10.1016/j.jtocrr.2020.100115>

dynamics have been reported, leading to the definition of new entities such as pseudoprogression and hyperprogression.<sup>1,2</sup> Specifically, hyperprogressive disease (HPD) has been defined as an exponential increase in tumor growth, promoted by ICI.<sup>3,4</sup> In NSCLC, initial phase 3 clinical trials that compared ICI with chemotherapy reported a higher proportion of early disease progression and death in the immunotherapy arm,<sup>5,6</sup> suggesting that a subset of patients may derive a detrimental effect from ICI.<sup>7</sup>

Since then, different publications have described the occurrence of HPD in patients with ICI-treated NSCLC, reporting rates that vary from 6% to 20%.<sup>8-11</sup> However, most studies included patients with different tumor types, different treatment lines, and different ICI agents. Furthermore, they rarely involved a control arm and used different measurements to define HPD.<sup>3,8-12</sup> Therefore, the true incidence of ICI-related HPD in NSCLC, compared with patients treated with chemotherapy, remains to be established. To fill this void, we investigate the incidence of HPD in patients with NSCLC treated with ICI or chemotherapy through three different methods (tumor growth rate [TGR], tumor growth kinetics [TGK], and Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST 1.1]).

## Material and Methods

### Patients and Treatment

We retrospectively analyzed 100 patients with stage IV NSCLC who had progressed to greater than or equal to one line of treatment and had received docetaxel or nivolumab, dividing them into two cohorts. Patients in the nivolumab cohort were treated between October 2015 and September 2017, whereas those in the docetaxel cohort were treated from April 2013 to September 2016. During the period of October 2015 to September 2016, patients included in our study with less than 1% programmed death-ligand 1 (PD-L1) expression in tumor cells, Eastern Cooperative Oncology Group performance status 1, and those with progressive disease as the best response to first-line therapy were not eligible for nivolumab treatment; hence, docetaxel therapy was initiated following the European Medicines Agency guidelines (European Public Assessment Report, EMA/246304).

### Ethics Approval

This project was approved by the local ethics committee (CEIC-PSMAR: 2015/6336/I), and all patients provided written informed consent.

### Radiologic Evaluation

At least two computed tomography (CT) scans before the start of treatment (at baseline and the most recent before baseline), and one CT scan during treatment were mandatory for radiologic evaluation ([Supplementary Fig. 1](#)). All CT scans were reviewed by senior radiologists (DR, ER, and FZ). The target lesions were defined in accordance with RECIST 1.1. The median time (mo) between CT scans was 2.8 months for the nivolumab cohort and 2.4 months for the docetaxel cohort ( $p =$  not significant, two-sided Mann-Whitney test).

### HPD Criteria

For each patient, we determined TGR, TGK, and RECIST 1.1, as previously described.<sup>4,12,13</sup> TGR was defined as the log-scale calibrated change in the sum of the volumes, whereas TGK was defined as the change in the sum of the longest diameters of the target lesions (defined according to RECIST 1.1 criteria) per month. HPD based on TGK or TGR was defined as at least a twofold increase in tumor growth during the experimental period with respect to the reference period. HPD based on RECIST 1.1 was defined as a 40% increase compared with the baseline sum of the target lesions, or an increase of 20% in the sum of target lesions and the appearance of new lesions in at least two different organs.

### Statistical Analysis

Statistical differences between categorical variables were evaluated using chi-square and Fisher's exact tests, whereas  $t$  tests were used for continuous variables. Associations between different HPD criteria and survival were assessed using Cox regression models. The Jaccard index was used to assess the similarity between the three methodologies. The overall survival (OS) was calculated as the time between the date of the beginning of nivolumab or docetaxel and the date of death.

## Results

### Comparison Between Different Methodologies to Define HPD

A total of 79 patients were included, 42 (53.2%) in the nivolumab cohort, and 37 (46.8%) in the docetaxel cohort ([Supplementary Fig. 1](#)). Except for the number of previous treatment lines (greater in the nivolumab cohort), no significant clinicopathologic differences were observed between the two cohorts ([Table 1](#)).

In the nivolumab cohort, we identified seven (16.7%), seven (16.7%), and six (14.3%) patients with HPD, and in the docetaxel cohort, three (8.1%), four (10.8%), and

**Table 1.** Clinicopathologic and Molecular Features for Nivolumab and Docetaxel Cohorts

Characteristic	Nivolumab (n = 42)	Docetaxel (n = 37)	p Value (t test or chi-square)
Age			0.439
Median (range)	67.5 (50-86)	68 (47-82)	
Sex			0.802
Female	6 (14.3)	7 (18.9)	
Male	36 (85.7)	30 (81.1)	
Smoking history			0.139
Never	2 (4.8)	0 (0)	
Former/current	39 (92.9)	37 (100)	
NA	1 (2.4)	0 (0)	
Pack-years smoking			0.586
<30	6 (14.3)	4 (10.8)	
≥30	28 (66.7)	31 (83.8)	
NA	8 (19)	2 (5.4)	
ECOG			0.802
0-1	36 (85.7)	34 (91.9)	
≥2	4 (9.5)	3 (8.1)	
NA	2 (4.8)	0 (0)	
Histologic diagnosis			0.421
Nonsquamous	26 (61.9)	27 (73)	
Squamous	16 (38.1)	10 (27)	
TNM stage, eighth edition			0.468
I	1 (2.4)	0 (0)	
II	4 (9.5)	1 (2.7)	
III	11 (26.2)	10 (27)	
IV	26 (61.9)	26 (70.3)	
Molecular features			0.77
KRAS mutation	10 (23.8)	7 (18.9)	
EGFR mutation	1 (2.4%)	1 (2.7)	
MET amplification	1 (2.4)	1 (2.7)	
BRAF mutation	1 (2.4)	0 (0)	
No driver mutation detected	13 (31)	18 (48.6)	
Not tested	16 (38.1)	10 (27)	
IHC PD-L1 in MCs, %			
<1	9 (21.4)	3 (8.1)	
1-49	7 (16.7)	0 (0)	
≥50	7 (16.7)	0 (0)	
NA	19 (45.2)	34 (91.8)	
Response rate			0.591
CR/PR	8 (19)	4 (10.8)	
Stable disease	18 (42.9)	18 (48.6)	
PD	16 (38.1)	15 (40.5)	
Best response to previous treatment			0.898
CR/PR	14 (33.3)	12 (32.4)	
Stable disease	17 (40.5)	15 (40.5)	
PD	9 (21.4)	10 (27)	
NA	2 (4.8)	0 (0)	
Treatment line			0.049
Second line	30 (71.4)	35 (94.6)	
Third line	7 (16.7)	2 (5.4)	
Fourth line	4 (9.5)	0 (0)	
Fifth line	1 (2.4)	0 (0)	
Number of sites of M1			0.157
≤2	29 (69)	23 (62.2)	
>2	9 (21.4)	14 (37.8)	
NA	4 (9.5)	0 (0)	
Liver metastasis			0.282
Yes	8 (19)	3 (8.1)	
No	34 (81)	34 (91.9)	

(continued)

Table 1. Continued

Characteristic	Nivolumab (n = 42)	Docetaxel (n = 37)	p Value (t test or chi-square)
Subsequent treatments			0.071
Yes	20 (47.6)	26 (70.3)	
No	22 (52.4)	11 (29.7)	
Corticoid treatment			0.87
Yes	19 (45.2)	16 (43.2)	
No	23 (54.8)	21 (56.8)	
Antibiotic treatment			0.285
Yes	20 (47.6)	23 (62.2)	
No	22 (52.4)	14 (37.8)	
Blood analysis			
Neutrophils			0.367
Mean (SD)	6500 (2400)	5920 (2560)	
Missing	4 (10.8)	14 (33.3)	
Lymphocytes			0.065
Mean (SD)	2070 (1950)	1390 (567)	
NA	4 (10.8)	14 (33.3)	
N/L ratio			0.297
Mean (SD)	4.48 (2.75)	5.47 (4.28)	
NA	4 (10.8)	14 (33.3)	
Median PFS (mo)	4.8	2.9	0.003
Median OS (mo)	13.3	8.4	0.39

Note: Values are given in number (%) unless indicated otherwise.

CR, complete response; ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry; M1, metastasis; MC, malignant cells; N/L, neutrophil/lymphocyte ratio; NA, not available; OS, overall survival; PD, progressive disease; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response.

five (13.6%) patients using TGR, TGK, and RECIST 1.1, respectively (Fig. 1A–C, Table 2). The proportion of HPD among patients with progressive disease (N = 16 in the nivolumab cohort and N = 15 in the docetaxel cohort) was higher in the nivolumab versus docetaxel cohort (43% versus 20%) when using TGR or TGK, although these differences were not statistically significant ( $p = 0.26$ ) (Table 2).

In the nivolumab cohort, 10 patients were identified as HPD by at least one method. We observed a complete overlap between the TGR and TGK methods for identifying patients with HPD (seven of seven, 100%). In contrast, of the six patients identified as HPD by RECIST 1.1, only three were also identified as HPD by TGR or TGK. In the docetaxel cohort, six patients were identified as HPD by at least one method, with a higher overlap for TGR and TGK (three of four patients [75%] identified by both methods) (Supplementary Fig. 2). Overall, the Jaccard index revealed a higher similarity between TGR and TGK (90.1%) than with RECIST 1.1 (31.3% and 37.5% with TGR and TGK, respectively) (Supplementary Table 1). No clinicopathologic differences were observed between patients with TGR-defined HPD and non-HPD (Supplementary Table 2).

### Survival Outcomes in the HPD Populations

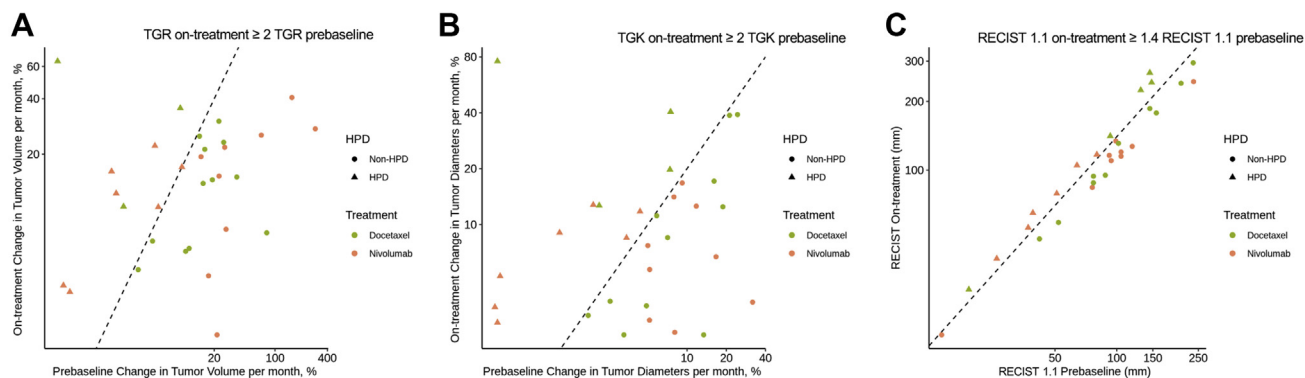
Survival analysis, using as the baseline time point the initiation of nivolumab or docetaxel, did not

exhibit any differences in OS (Supplementary Fig. 3). Specifically, using TGR, the median OS in the nivolumab cohort was 5.0 months and 6.7 months ( $p = 0.19$ ) for patients identified as HPD and PD, respectively. In the docetaxel cohort, we observed a median OS of 2.4 and 4.8 months ( $p = 0.0013$ ), respectively. Interestingly, three out of seven patients classified as HPD in the nivolumab cohort who received further treatment were alive 6 months after progression to nivolumab (Fig. 2).

## Discussion

Here, we compared three different methodologies to determine the incidence of HPD in patients treated with ICI or chemotherapy. In line with previous reports, we observed a higher incidence of HPD in patients treated with nivolumab compared with docetaxel-treated patients,<sup>10</sup> suggesting that this phenomenon is more frequent in the context of ICI therapies, although the differences were not statistically significant, probably because of the low frequency of HPD overall.

Several groups have recently used different methods to identify HPD, with some authors incorporating different clinical criteria to characterize this population.<sup>3,8–12</sup> However, the different methodologies used and the lack of reproducibility of the results between different studies lead to an increasing skepticism in the field regarding the occurrence of HPD.<sup>14</sup>



**Figure 1.** Identification of patients with HPD across three different methods and in both cohorts: (A) TGR; (B) TGK; (C) RECIST 1.1. Prebaseline refers to the period before initiation of nivolumab or docetaxel. On-treatment refers to the period of treatment with nivolumab or docetaxel. The dashed line represents the cutoff to define HPD. HPD, hyperprogressive disease; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TGK, tumor growth kinetics; TGR, tumor growth rate.

We evaluated patients with NSCLC that had progressed to at least one line of chemotherapy, treated with anti-programmed cell death protein-1 (PD-1) (nivolumab) or chemotherapy (docetaxel), and observed that TGR and TGK revealed a high concordance for the identification of patients with HPD. This stands in contrast with the observations made using RECIST 1.1, as reported recently in a cohort of patients with NSCLC treated with ICI.<sup>15</sup> These differences could be partially explained by the fact that TGR and TGK incorporate tumor growth dynamics (i.e., time is included as a variable), whereas RECIST 1.1 focuses only on the absolute change in tumor size. Consequently, HPD does not require a prebaseline radiologic evaluation, making this approach better suited for evaluating HPD in the first-line setting. Nevertheless, RECIST 1.1 does not provide insight as to the nature of HPD, whether it may be because of preexisting tumor-intrinsic properties or caused by treatment-related effects. Overall, the higher concordance between TGR and TGK suggests these should be used when at least three CT scans are

available, reserving the use of RECIST 1.1 for the remaining cases.

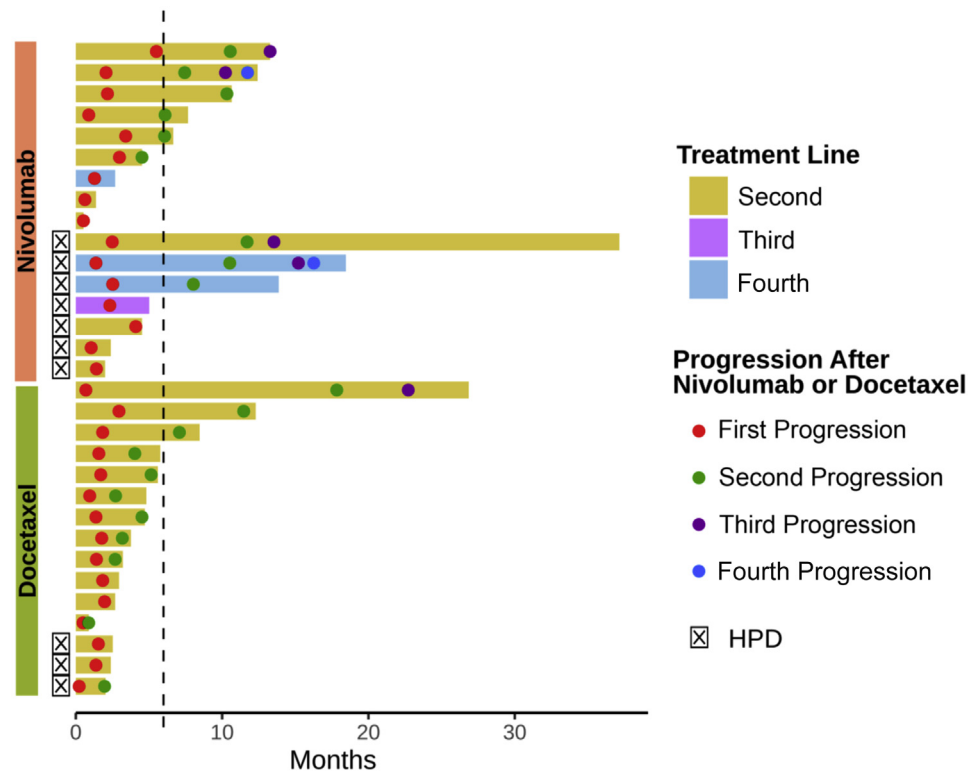
Although several clinicopathologic and molecular features (older age, number of metastasis, tumor burden, *EGFR* mutations, *MDM2/MDM4* amplifications, local radiotherapy)<sup>3,8,10,12</sup> have been associated with HPD, only *MDM2/MDM4* amplification has been confirmed in more than one study. In our study, we did not find any association of HPD with clinicopathologic or molecular features.

To the best of our knowledge, only one study reported the comparison of HPD in patients treated with ICI and a control arm.<sup>10</sup> Nevertheless, the comparison with historical cohorts introduces the time bias inherent in this kind of analysis. In our study, the docetaxel arm was treated during a period overlapping that of the nivolumab cohort, minimizing this bias. However, our study is not devoid of limitation, one of which is the reduced sample size; hence, our results should be taken with caution. In turn, we included only patients treated with nivolumab and a control

**Table 2.** Definitions and Methodologies Applied to Calculate HPD

Publication	Calculation Method	HPD Definition	HPD Nivolumab						
			N	%	% of PD	N	%	% of PD	p Value
Champiat et al., 2017 <sup>3</sup>	$TRG = \Delta \text{ tumor volume} / \Delta \text{ time (mo)}$	$TGR_{\text{post}} \geq 2 TGR_{\text{pre}}$	7	16.67	43.75	3	8.11	20.00	0.2574
Saàda-Bouzdid et al., 2017 <sup>12</sup>	$TGK = \Delta \text{ sum of tumor diameters} / \Delta \text{ time (mo)}$	$TGK_{\text{post}} / TGK_{\text{pre}} \geq 2$	7	16.67	43.75	4	10.81	26.67	0.4578
Matos et al., 2020 <sup>11</sup>	Sum of the target lesions by RECIST 1.1	1.4 × baseline sum target lesions or 1.2 × baseline sum target lesions and new lesions in at least two different organs	6	14.29	37.50	5	13.51	33.33	1

Δ, change in; HPD, hyperprogressive disease; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TGK, tumor growth kinetics; TGR, tumor growth rate.



**Figure 2.** Swimmer plot representing the patients that progressed in the first evaluation after receiving nivolumab (top) or docetaxel (bottom) (red circles), and HPD was assessed. Patients classified as HPD with the TGR method were identified as square boxes (seven patients in the nivolumab cohort and three patients in the docetaxel cohort). The vertical dashed line represents 6 months of the landmark after treatment initiation. At the time of analysis, all patients have died. HPD, hyperprogressive disease; TGR, tumor growth rate.

chemotherapy cohort treated in a similar period of time, making the population more homogeneous and comparable. Another potential source of bias is that we required at least three CT scans per patient, excluding those patients that died or progressed before the third CT scan, thus, potentially underestimating the true incidence of HPD and failing to account for early deaths that precluded the performance of the posttreatment CT. In addition, in NSCLC first-line setting, anti-PD-1 monotherapy (in tumors with PD-L1 expression  $\geq 50\%$ ) and chemotherapy plus anti-PD-1 (PD-L1) are now considered the standard of care; thus, our results should be further investigated in this setting, in which the addition of chemotherapy could potentially mitigate the incidence of HPD but might be still relevant for patients treated with pembrolizumab alone.

Overall, our results underscore the need for consensus in defining HPD and the need for predictive biomarkers to identify these patients upfront. Further studies in larger, prospective cohorts or detailed retrospective analysis of previous phase 3 trials represent potentially useful strategies in this context.

In conclusion, our results suggest that TGR and TGK can be used indistinctly for identifying patients with HPD

and that RECIST 1.1 should be reserved for those patients undergoing first-line therapy with ICI. Our results support that all patients that initiate ICI should be strictly monitored so that salvage therapy may be promptly initiated when HPD is identified.

## Acknowledgments

This work was supported by a grant from Instituto de Salud Carlos III-FEDER (PI19/00003).

## Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at [www.jtocrr.org](http://www.jtocrr.org) and at <https://doi.org/10.1016/j.jtocrr.2020.100115>.

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