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Key Points

Question Are the different definitions used to assess hyperprogressive disease during immunotherapy for non–small cell lung cancer representative of the same tumoral behavior?

Findings For this multicenter cohort study of 406 patients with advanced non–small cell lung cancer treated with programmed cell death 1/programmed cell death 1 ligand inhibitors, the 5 disease definitions assessed resulted in diverse incidences, different patient characteristics, and different associations with survival outcomes. A new criterion of difference in tumor growth rate of greater than 100 showed more accuracy in assessing hyperprogressive disease.

Meaning These findings suggest that the 5 definitions assessed are not representative of the same tumoral behavior.

ABSTRACT

Importance Hyperprogressive disease (HPD) is an aggressive pattern of progression reported for patients treated with programmed cell death 1 (PD-1)/programmed cell death 1 ligand (PD-L1) inhibitors as a single agent in several studies. However, the use of different definitions of HPD introduces the risk of describing different tumoral behaviors.

Objective To assess the accuracy of each HPD definition to identify the frequency of HPD and the association with poorer outcomes of immune-checkpoint inhibitor (ICI) treatment in patients with advanced non–small cell lung cancer (NSCLC) and to provide an optimized and homogenized definition based on all previous criteria for identifying HPD.

Design, Setting, and Participants This retrospective cohort study included 406 patients with advanced NSCLC treated with PD-1/PD-L1 inhibitors from November 1, 2012, to April 5, 2017, in 8 French institutions. Measurable lesions were defined using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria on at least 2 computed tomographic scans before the initiation of ICI therapy and 1 computed tomographic scan during treatment. Data were analyzed from November 1, 2012, to August 1, 2019.

Exposures Advanced NSCLC and treatment with PD-1/PD-L1 inhibitors.

Main Outcomes and Measures Association of the definition with the related incidence and the HPD subset constitution and the association between each HPD definition and overall survival. All dynamic indexes used in the previous proposed definitions, such as the tumor growth rate (TGR) or tumor growth kinetics (TGK), were calculated before and during treatment.

Results Among the 406 patients with NSCLC included in the analysis (259 male [63.8%]; median age at start of ICI treatment, 64 [range, 30-91] years), the different definitions resulted in incidences of the HPD phenomenon varying from 5.4% (n = 22; definition based on a progression pace >2-fold and a time to treatment failure of <2 months) to 18.5% (n = 75; definition based on the TGR ratio). The concordance between these different definitions (using the Jaccard similarity index) varied from 33.3% to 69.3%. For every definition, HPD was associated with poorer survival (range of median overall survival, 3.4 [95% CI, 1.9-8.4] to 6.0 [95% CI, 3.7-9.4] months). The difference between TGR before and during therapy (ΔTGR) was the most correlated with poor overall survival with an initial plateau for a larger number of patients and a slower increase, and it had the highest ability to distinguish patients with HPD from those with progressive disease not classified as HPD. In addition, an optimal threshold of ΔTGR of greater than 100 was identified for this distinction.

Conclusions and Relevance The findings of this retrospective cohort study of patients with NSCLC suggest that the previous 5 definitions of HPD were not associated with the same tumor behavior. A new definition, based on ΔTGR of greater than 100, appeared to be associated with the characteristics expected with HPD (increase of the tumor kinetics and poor survival). Additional studies on larger groups of patients are necessary to confirm the accuracy and validate this proposed definition.

Key words: hyperprogression, HPD, immune checkpoint inhibitors, immunotherapy, NSCLC, TGR, TGK

INTRODUCTION

Immune-checkpoint inhibitors (ICI) have been one of the major developments in cancer therapy in the past decade, being now approved for various tumour types such as melanoma, Non-Small Cell Lung Cancer (NSCLC), Renal Cell Carcinoma (RCC) or Head and Neck Squamous-Cell Carcinoma (HNSCC) **[1-4]**. ICI differ from conventional cytotoxic treatments and molecularly targeted agents in their mechanism (restoring an efficient T-cell response) as well as in the response patterns they are associated with.

Indeed, immunotherapy has demonstrated survival benefits that can include long-term remissions and has also been associated with novel patterns of responses such as pseudoprogression, defined as an initial increase in the tumour burden followed by a later response **[5]**. More concerning, several studies have reported a possible deleterious effect that ICI may induce on a subpopulation of patients causing a dramatic tumor growth right after the initiation of the therapy, called hyperprogressive disease (HPD) **[12]**. This phenomenon is clinically defined as an unexpected acceleration of the tumor kinetics that can be measured on imaging via to dynamic parameters.

In order to define and quantify the incidence of this phenomenon, several parameters have been used: Tumour Growth Rate (TGR), Tumour Growth Kinetics (TGK), or Time to Treatment Failure (TTF), but the different studies are still not based on a consensual definition of HPD and the risk of describing different tumoral behaviours exists.

The objectives of the present article are to achieve an advanced comprehensive comparison of the different definitions of HPD applied on a NSCLC cohort of patients in order to evaluate the influence of the defintion on the related incidence, the HPD subset constitution, and the association between each HPD definition and overall survival.

MATERIALS AND METHODS

Patients

Data from Non-Small-Cell Lung Carcinoma (NSCLC) patients treated with PD-1/ PD-L1 inhibitors (ICI) from November 2012 to April 2017 in eight French institutions were retrospectively collected and analyzed. Only patients over the age of majority with confirmed stage III or IV NSCLC and for whom CT-scans were available for radiological evaluation were included. The complete characteristics of the patients have previously been published in [6].

In order to evaluate the tumor evolution and to assess the dynamic indexes needed to define HPD, at least 2 CT-scans before the beginning of the ICI therapy and 1 CT-scan during the treatment were required. The baseline CT-scan was performed in the 6 weeks preceding the initiation of ICI treatment and a minimum of 2 weeks between different CT evaluations was expected resulting in the inclusion of N = 406 patients in the final cohort **(Figure 1)**. All CT-scans were centrally and independently reviewed by two senior radiologists.

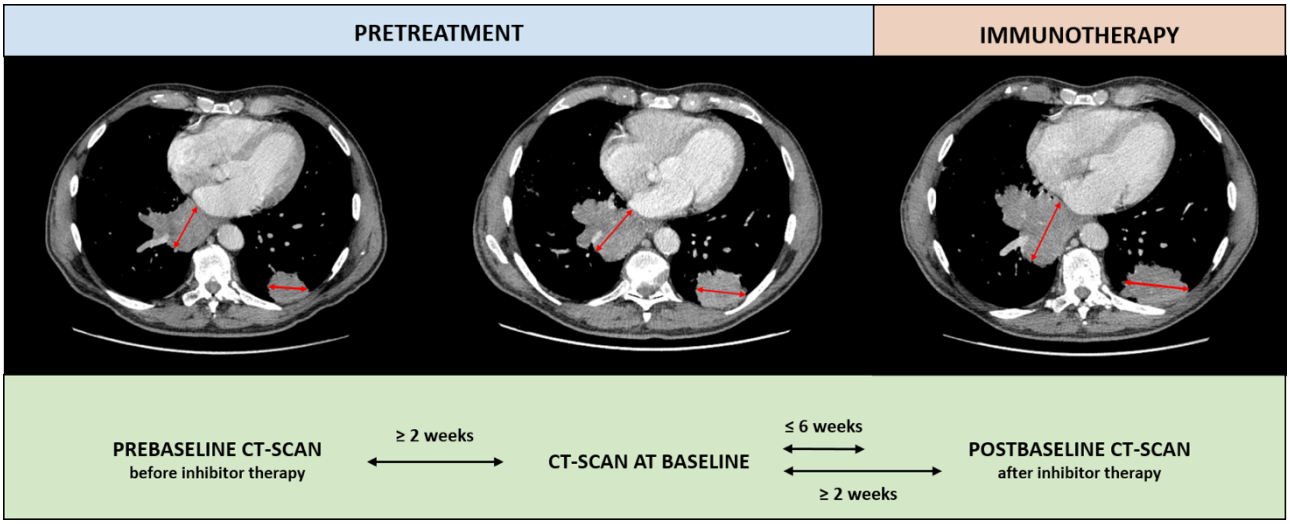


Figure 1: Case study of a patient with hyperprogressive disease. At least 3 CT-scans were required to assess the dynamic indices allowing us to define HPD since variations of size and volume were calculated both before and during the PD-1/PD-L1 therapy. The baseline CT-scan needed to be performed within 6 weeks before the initiation of the immunotherapy.

Definitions of tumor dynamics

In the recent litterature, hyperprogressive disease (HPD) has been defined in different studies using 5 different criteria as already emphasized in [7]. Recently, due to the difficulty of collecting pre-baseline CT-scans to assess dynamic parameters. [8] A summary of existing definitions is available in **Table 1**.

For a better understanding, in the sequel, a distinction between the terms “definition” and “index” has been established, “indices” refering to the mathematical parameters like Tumour Growth Rate (TGR) or Tumour Growth Kinetics (TGK) that are combined and used with thresholds to define HPD.

Overall Survival (OS) was defined as the time between the initiation of the ICI therapy and the death of the patient from any cause and Time-to-Treatment-Failure (TTF) as the duration between the beginning and the discontinuation of the treatment for any reason including toxicity, progression, patient will or death.

The Tumor Growth Rate (TGR) is defined in **[9]** as the percentage increase in the tumor volume per month following $TGR = 100\,[\exp(TG) - 1]$ where $TG = 3\,\mathrm{Ln}\,(S_t/S_0)$ and where S_t and S_0 are the tumor sizes at times t and t_0, defined as the sum of the longest diameters of the target lesions as per the RECIST 1.1 criteria **[10]**.

The Tumor Growth Kinetics (TGK) is defined as the change in the tumor size per unit of time as reported in **[11]**: $TGK = (S_t - S_0)/(t-t_0)$. Both these indices were calculated before and during treatment to evaluate any change in the tumor kinetics.

For both indices and for every patient, the RECIST sum was computed with the target lesions defined at baseline of ICI.

To ease reading, each of these definitions will be named using letters from A to E as summarized in **Table 2**.

	Champiat et al. Nov 2016 [12]	**Kato et al. Mar 2017 [13]**	**Saâda-Bouzid et al. Apr 2017 [14]**	**Singavi et al. Sep 2017 [15]**	**Ferrara et al. Nov 2018 [6]**	~~**Gandara et al. Dec 2018 [8]**~~
Letter	A	B	C	D	E	~~Fast Progression - FP~~
Definition	RECIST progression *&* $TGR_{EXP}/TGR_{REF} > 2$	TTF < 2 months *&* RECIST > 50 % *&* Progression pace > 2	$TGK_{EXP}/TGK_{REF} > 2$	RECIST progression *&* RECIST > 50 % *&* $TGR_{EXP}/TGR_{REF} > 2$	RECIST progression *&* TGR_{EXP} - TGR_{REF} > 50	~~RECIST > 50% *or* OS < 12 weeks~~
Reported HPD incidence	9 % (12/131)	4 % (6/155)	29 % (10/34)	5 patients	13.8 % (56/406)	~~44 patients~~
Histological types	Various (Melanoma, 34%. Lung, 10%)	Various (Melanoma, 33%. NSCLC, 25%)	Head and Neck Squamous-Cell Carcinoma (HNSCC)	Various	NSCLC	~~NSCLC~~

Table 1: Main different definitions of hyperprogression according to previous studies. TGR_{REF}, TGR_{EXP} being respectively the values of TGR before and during ICI andTGK_{REF}, TGK_{EXP} the values of TGK before and during ICI.

Out of these 5 definitions, 3 rest upon the hypothesis of a natural exponential growth of the tumor volume with time. Assuming that at time t, the volume V_t can be expressed $V_t = V_0 \exp(TG.t)$, this hypothesis leads directly to the use of TGR as HPD index. Nevertheless these 3 definitions are not strictly equivalent:.

- Champiat et al. (def. A) **[12]** defined hyperprogressive disease as a ≥ 2-fold increase of the TGR between the therapy and the reference periods : $TGR_{EXP}/TGR_{REF} \geq 2$. In other words, HPD patients are characterized by a twice as high percentage increase in volume per month during immunotherapy compared to before.
- A later study **[15]** by Singavi et al. (def. D) takes the same definition as A adding a condition on the RECIST percentage increase under ICI treatment > 50%.
- The study by Ferrara et al. (def. E in **[6]**) assumes that hyperprogressive disease is characterized by a difference (and not a ratio) greater than 50 % between TGR_{EXP} and TGR_{REF} suggesting that the increase in volume per month during IO must be 50 % higher that expected with the increase before treatment

Saâda-Bouzid et al. definition (C) of HPD **[14]** relies on the use of Tumor Growth Kinetics (TGK) which does not take into account the hypothesis of the natural exponential growth of the tumour and uses the diameters rather than the volume.

Finally, Kato et al. (def. B) defines HPD using three conditions : one on the tumor kinetics (progression pace ≥ 2, being equivalent to $TGK_{EXP}/TGK_{REF} \geq 2$ on a 2-month basis), one on the RECIST percentage (increase in the tumor burden under ICI treatment > 50%) and one on the treatment ongoing (TTF ≤ 2 months) **[13]**.

In what follows, Tumor Burden at prebaseline, baseline and postbaseline evaluations will be noted S_{PRE}, S_{BL}, S_{POST}.

Statistical analysis

Concordance between the constitutions of the HPD groups for the different definitions was evaluated using the similarity Jaccard index. The influence of each definition on the designation of HPD patients was then further theoretically analyzed as a function of the RECIST percentage before immunotherapy and the RECIST percentage during immunotherapy. To do so, we represented the 3 mathematical criteria ($TGK_{EXP}/ TGK_{REF} > 2$, $TGR_{EXP}/TGR_{REF} > 2$, $TGR_{EXP} - TGR_{REF} > 50$) under the form of isolines and compared the respective positions of the curves. For an identical RECIST percentage before immunotherapy, the above curve corresponds to the definition that requires a higher RECIST percentage during therapy to assess HPD and that is therefore more restrictive.

To investigate the association between HPD status and survival outcomes, patients with an initial progressive disease as defined per RECIST 1.1 were divided into two classes: Progressive Disease with HPD and Progressive Disease without HPD. Landmark survival analysis were performed using the Kaplan-Meier method **[16]** and the log-rank test was used for comparison : p-values less than 0.05 were considered statistically significant.

To evaluate the prognostic value of each index, we divided the progressive patients into two groups : the N patients with the highest values of the index on the one hand and the other progressive patients on the other hand. We then computed the median OS as a function of the number N, or in other words as the threshold chosen to distinguish progressive and hyperprogressive patients (as explained in **Figure 2**). Studying the influence of N on the landmark analysis, our objective was to determine which indices showed a clear ability to distinguish patients with both acceleration of the tumour growth and poor survival and therefore to determine which index and threshold led to the most significant distinction between the two groups.

All the statistical and mathematical analyses were carried out using the Python software package (Python version 3.0).

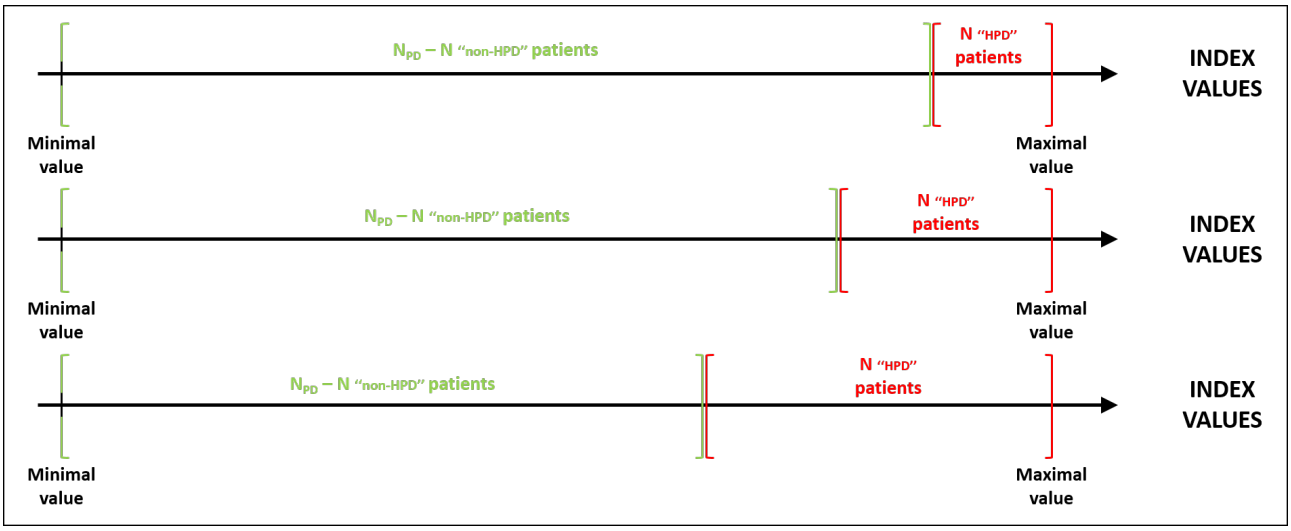


Figure 2: Evaluation method of the prognostic value of each index. N_{PD} being the number of PD patients at first evaluation, for each index, patients were categorized into two groups according to their index value. On the one hand, the N patients with the highest value and on the other hand the other N_{PD} – N patients. We first set N = 10 and then increased its value until it reaches half the number of PD patients. A comparative landmark analysis was performed on these two groups for each value of N.

RESULTS

Patient caracteristics have been already reported (REF FERRARA). Briefly, XXXX . All patients received ICI alone, without chemotherapy.

Out of 406 patients, 207 patient disease were classified progressive (PD) under ICI therapy at first evaluation according to RECIST 1.1 criteria :

- 143 of them due to an increase in TL > 20% (with or without an increase of NTL or the appearance of NL)
- 64 of them only due to a non target lesions increase or NL appearance

19 PD patients were retrospectively assessed as pseudoprogressors and were excluded from the analysis.

Influence of the definition on the incidence (Table 2).

Applying the different definitions of HPD to the 406-patient cohort analysis, HPD incidence varies from 5.4 % to 18.4 % of the patients.

Definition B of hyperprogressive disease appears to be the most restrictive, i.e. with the smallest incidence (5.4 %) being comparable to the incidence of their 4 % out of 155 patients [13].

Definitions A and E computed on a same cohort displayed quite similar incidences (12.8 % and 13.8 % respectively).

Table 2: Incidence of hyperprogressive disease according to the different definitions. In parentheses, the number of HPD patients / the total number of patients

	Definition A	Definition B	Definition C	Definition D	Definition E	~~Fast Progression~~
Incidence	12.8% (52/406)	5.4% % (22/406)	18.4 % (75/406)	6.2 % (25/406)	13.8% (56/406)	~~24.1 % (98/406)~~

Influence of the definition on the HPD subset constitution

19 patients were assessed HPD by all 5 definitions A, B, C, D and E and the maximum value of the similarity index was 69.3 %, reached for definitions A and C **(Table 3)** meaning that individual patients defined as HPD are dependent on the definition.

Table 3: Similarity between the different definitions of hyperprogressive disease

	A (N=52)	B (N=22)	C (N=75)	D (N=25)	E (N=56)	~~FP (N=98)~~
A						
B	34.5 % (19)					
C	69.3 % (52)	27.6 % (21)				
D	48.1 % (25)	67.9 % (22)	33.3 % (25)			
E	68.8 % (44)	34.8 % (23)	59.8 % (49)	47.4 % (24)		
FP	29.3 % (34)	22.4 % (22)	32.1 % (42)	25.5 % (25)	40.0 % (44)	

Table 3: Similarity between the different definitions of hyperprogressive disease. Values of Jaccard similarity index for each pair of definitions. In parentheses is the number of common HPD. The Jaccard index value corresponds to the proportion of HPD patients in common among all patients assessed HPD by either one definition or the other. For instance, definitions A and E assessed 44 HPD patients in common but other 20 patients were assessed HPD by only one of the two definitions (52 – 44 = 8 in A and 56 – 44 = 12 in E) leading to a similarity index of 44/64 = 68.8%.

In order to understand which patients are classified as HPD by each defintion, the characteristics of HPD patients for definitions A, C, D and E as regard the RECIST percentages before and during ICI therapy has been modelized in **Figure 3**. Of note, definition B and Fast Progression that do not only rely on considerations on the tumor size and kinetics could not be included in this comparison.

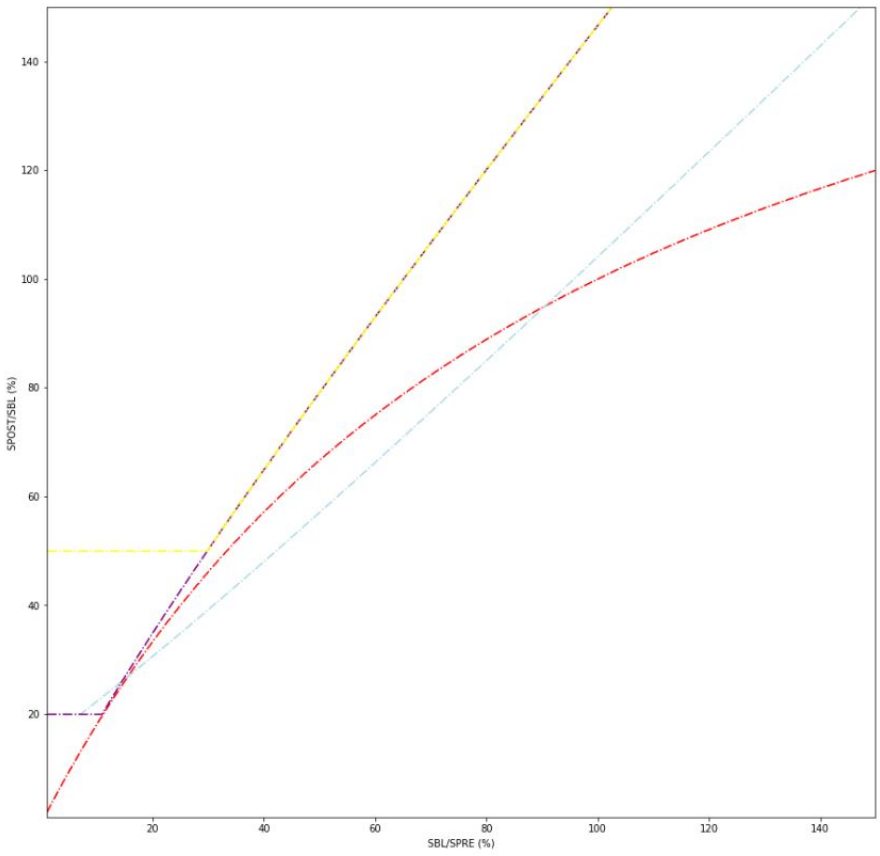


Figure 3: Areas of HPD incidence according to RECIST percentage before (x-axis) and during PD-1/PD-L1 therapy (y-axis) for $S_{BL}/S_{PRE} > 1$. Isolines for the definitions A (purple curve), C (red curve), D (yellow curve) and E (lightblue curve) mark the frontier between PD and HPD patients. For each definition, patients in the above area are assessed HPD whereas patients in the below area are not. These isolines were drawn in the ideal case of a period of 1 month between two CT-scans.

Two cases were distinguished : first, a pretreatment increase of the RECIST sum (i.e. $S_{BL}/S_{PRE} > 1$) and secondly a pretreatment decrease (i.e $S_{BL}/S_{PRE} < 1$).

$S_{BL}/S_{PRE} > 1$: (**Figure 3**)

For a pre-therapy increase of the target lesions'size, definitions based on the TGR or the TGK tend to associate HPD with high values of the RECIST percentage under ICI therapy (above areas). However, the corresponding curves do not overlap and 3 situations have to be distinguished. The definition C (red curve) based on the TGK ratio is mathematically more likely to diagnose HPD among patients with a pretreatment between 1 and 15% (Stable Disease according to RECIST) and among patients with a high pretreatment progression > 90%.

Definitions A (purple curve) requires the highest RECIST percentage during therapy to define HPD patients. Definitions D (yellow curve) that is based on the same index as definition A but adds the condition RECIST percentage > 50 % is even more restrictive than definition A until a pretreatment increase of 40% and then both curves overlap.

Finally, the definition E (lightblue curve) tends to diagnose more HPD among patients with a pretreatment progression with a RECIST percentage between 15 % and 90%, compared with other definitions.

$S_{BAS}/S_{PRE} < 1$:

For a pre-therapy decrease of the target lesions size, the difference between definitions is even more substantial. Using the mathematical ratios (with TGR or TGK) of definitions A, B and D, no patient with $S_{BAS}/S_{PRE} < 1$ can ever be considered as HPD : the three conditions $S_{BAS}/S_{PRE} < 1$, $S_{POST}/S_{BAS} > 1.2$ and $TGR_{RATIO} > 2$ (or $TGK_{RATIO} > 2$) cannot be satisfied at the same time. However, using a mathematical substraction like definition C and E allows patients with a small S_{BAS}/S_{PRE} and a high S_{POST}/S_{BAS} to be assessed HPD.

These patients were nonetheless declared PD during pretreatment period because of the appearance of new lesions only, which are not taken into account in any of the definitions.

Association between HPD definitions and OS

For each of the 5 definitions, the landmark survival analysis signals a worse outcome for the patients with HPD compared to the patients with progressive disease. The gap between the median OS of the two groups varied from 0.2 month (def. C) to 5.6 months (FP), thus highlighting a disparity in the correlation of the different HPD definitions with prognosis.

Log-rank test were then computed to test the statistical significance of the differentiation between PD with-HPD and PD-without HPD. The two definitions B and FP demonstrate a significant distinction (respectively 3 and 5.6 months, p-values < 0.001), but these definitions used one condition on OS or TTF to define HPD.

	A	B	C	D	E	~~Fast Progression~~
median OS HPD	5.1 months	3.4	6.0	5.1	4.0	~~2.4~~
median OS PD non HPD	6.3 months	6.4	6.2	6.2	6.4	~~8.0~~
p-value	p = 0.45	p < 0.001	p = 0.62	p = 0.59	p = 0.14	~~p < 0.001~~

Table 4: Median Overall Survival for Hyperprogressive Disease (HPD) compared with Progressive Disease without HPD for the different definitions

Prognostic value of the different indexes

In order to study the prognostic values of the different indices (TGK_{EXP}/TGK_{REF}, TGR_{EXP}/TGR_{REF} and TGR_{EXP}-TGR_{REF}) on the two groups gathering the N highest values and the 207 – N other values (207 being the number of patients with progressive disease at First Evaluation), we obtained the curves of **Figure 4**.

Figure X: Overall survival for hyperprogressive disease compared to progressive disease without HPD according to the threshold

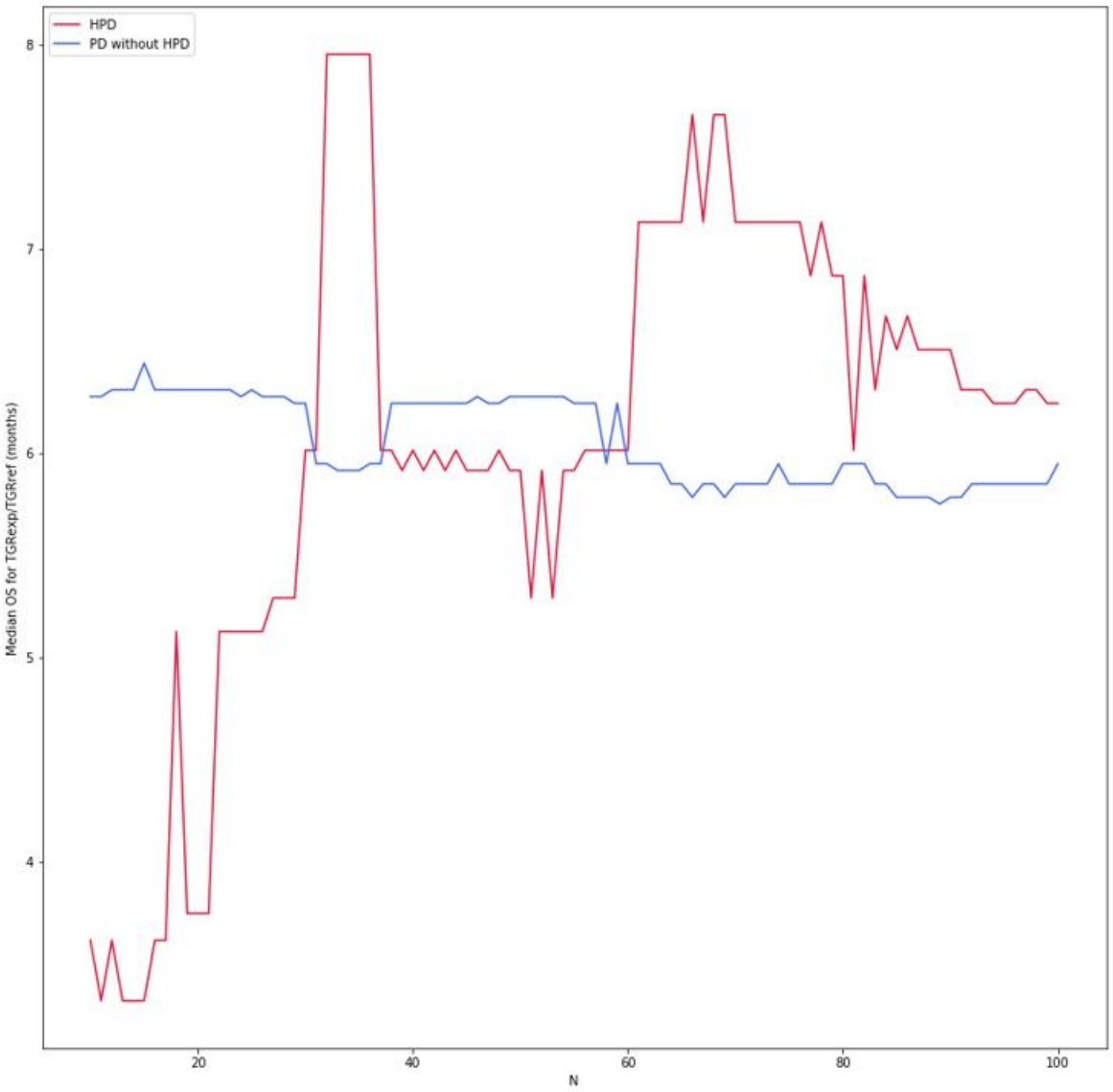
Median OS for both groups as a function of the number N of patients considered HPD. In red, median OS of the HPD group, in blue median OS of the PD without HPD group. A: median OS curves for the TGR_{EXP} – TGR_{REF} index. B: median OS curves for the TGR_{EXP} /TGR_{REF} index. C: median OS curves for the TGK_{EXP} /TGK_{REF} index.

For all three indices, the highest values (i.e. the highest increases of tumour kinetics during therapy) tend to be associated with the poorest survival outcomes. However, the curves of **Figure 4** show differences in the size of the population associated with these characteristics and in the amplitude and the stability of the gap between the median OS of both groups.

The curves of TGR_{EXP}/TGR_{REF} and TGK_{EXP}/TGK_{REF} appear to be very similar, highlighting a similar distribution of the values among patients (in other words, ranking patients according to their values of TGR_{EXP}/TGR_{REF} or of TGK_{EXP}/TGK_{REF} leads to a similar result). Both curves show an initial plateau up to 20 patients, but emphasize an important instability followed by a sharp increase of the median OS that even overtakes the one of progressive patients for a larger number N.

The curve of $TGR_{EXP} – TGR_{REF}$ also reveal an initial plateau for a larger number of 40 to 50 patients and a slower increase until both curves intersect, demonstrating a greater ability to correlate with OS.

To confirm the relevance of these distinctions between the two groups, we further investigated whether a log-rank test is significant for the different indexes and the different thresholds N. All 3 indexes locally reach a significant p-value less than 0.05 for a small N. However, only the $TGR_{EXP} – TGR_{REF}$ p-value remained below 0.05 for a range of N, both other indexes p-values oscillating between significant and non-significant values while N increasing. $TGR_{EXP} – TGR_{REF}$ p-value remained significant until a maximum number N = 34 of patients in the first group (**Supplementary**) corresponding to a threshold $TGR_{EXP} – TGR_{REF} > 102$.


HPD
PD without HPD
Median OS for TGRexp/TGRref (months)
N
8
7
6
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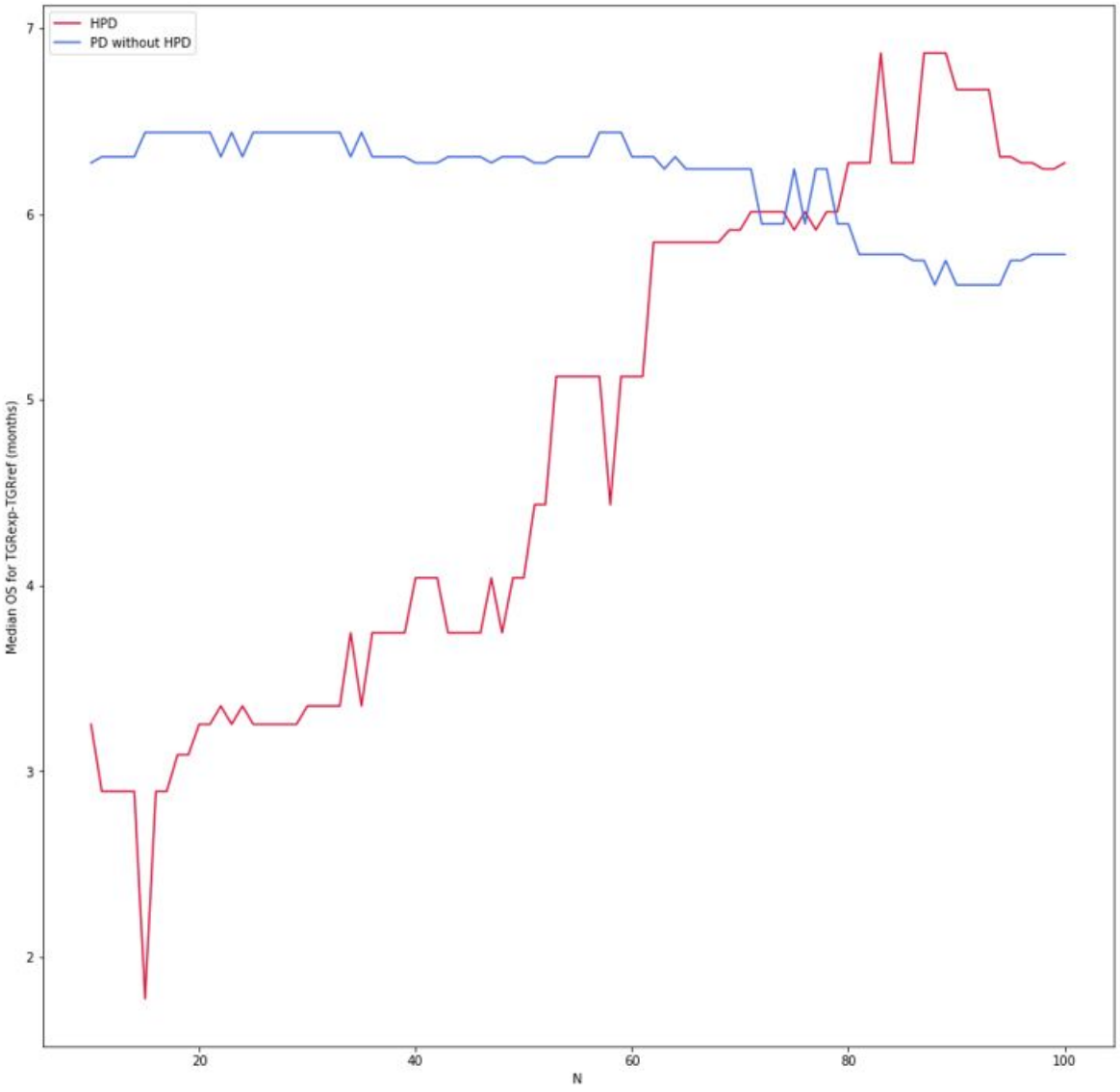
HPD
PD without HPD
Median OS for TGRexp-TGRref (months)
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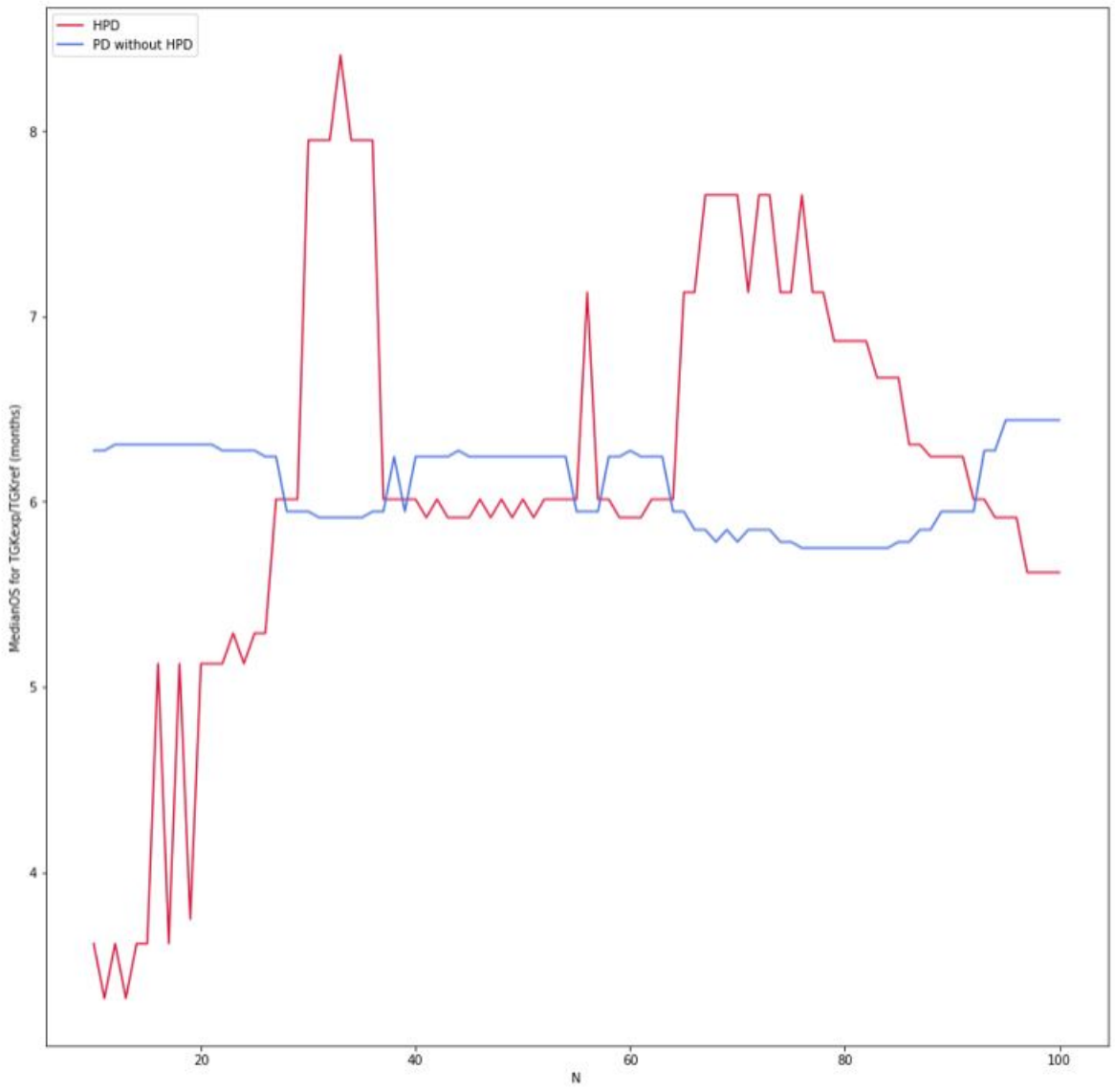
HPD
PD without HPD
MedianOS for TGKexp/TGKref (months)
N
4
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100

DISCUSSION

Previous studies on hyperprogressive disease (HPD) under immunotherapy reported different incidences of the phenomenon, varying from 4% to 29%. The causes for such a disparity might include the diversity in cancer histology as well as the size and source of the study cohort constitution **(Table 1)**. However, as already emphasized by Kim et al. **[17]**, the metrics used for HPD assessment could also be a major explanation for this inconsistency. To our knowledge, our study is the first to offer a detailed analytical comparison of all the definitions that have been used so far to assess this phenomenon.

In this study, the rates of HPD with the different definitions applied to a single NSCLC cohort appear to be concordant with the previously reported studies, with the exception of definition C in **[14]** that showed a smaller incidence of HPD patients in our cohort (18.4% *vs* 29%). No reasoned explanation can be given for such a gap at this stage but the influence of the patients' characteristics and the histology (NSCLC *vs* RSCCHN) on such a result should be further analysed. However, definition C is the only one based on the diameter of the lesions, the other being based on volume.

The results of the present study first and foremost point out the high disparity in HPD incidences due to the definitions themselves, with a number of HPD patients that can vary from 1 to 5 on the same cohort (22 patients for definition B compared to 98 patients for the so-called surrogate "Fast Progressor"). The choice of the definition seems therefore to be a major reason for the diversity observed among previous studies. Beyond the question of incidences, these results also highlight the fact that the groups of HPD patients appear to be different from one definition to another, with only 19 patients in common to all definitions. More precisely, the similarity measures show that the so-called HPD patients for different definitions are not representative of the same tumoral behaviour.

Consequently, the definitions do not correlate in the same way with OS. Most of them proved no ability to establish a clear distinction between the OS of HPD patients compared to PD without HPD patients. Indeed, only two definitions appeared to be (statistically) significantly correlated with a worse OS outcome for HPD patients. This result should however be moderated by the fact that the small OS is itself a criterion taken into account in both of these definitions.

Trying to extract thresholds to align the "worse progressive" patients with the "worse survival prognosis", we showed that only the index $TGR_{EXP} - TGR_{REF}$ appeared to be likely to distinguish subsets of patients with the characteristics expected with HPD status: acceleration of the tumour growth during treatment combined with a poor OS. For this index, the significance of the distinction between HPD patients and PD without HPD patients in terms of median OS was reached for a number N = 34 patients smaller than in the previous studies using $TGR_{EXP} - TGR_{REF}$ and corresponding to an approximate threshold $TGR_{EXP} - TGR_{REF} > 100$.

In summary, the definition that appears to be the most relevant according to the previous results would be:

- RECIST percentage under therapy > 20 % ($S_{POST}/S_{BAS} > 1,2$)
- $TGR_{EXP} – TGR_{REF} > 100$

Limitations

Some limitations to our study should be pointed out. First, whereas HPD behaviour was initially evaluated in a mixed oncologic population [X], in NSCLC or in RSCCHN [X], our model includes only patients with NSCLC. To date, no such phenomenon was ever described in other ICI target populations such as melanoma or renal cell cancer patients. Studies with larger groups of patients with varying characteristics would be necessary to confirm the accuracy of this definition of HPD, which was empirically determined.

Secondly, the characterization of HPD remains difficult on a routine basis since pre-treatment imaging is required. Alternative definition without pre-treatment imaging have been proposed, such as Fast Progression **[8]** but he latter is not a surrogate for HPD because it is not directly related to an acceleration of the tumour growth under ICI. Moreover, all definitions of HPD are based on the measurement of target lesions following RECIST 1.1 criteria, thus not taking into account the “unequivocal progression” of non-target lesions or the appearance of new lesion, which also define a disease as progressive. This might have lowered the incidence of HPD. On the other hand, our study artificially excluded patients who died before having the requisite post treatment imaging, making it impossible to associate their death to HPD and possibly leading to an underestimation of the phenomenon.

In conclusion, we observed the existence of an increase of kinetics of some NSCLC patients under ICI, named hyperprogression. Previous definitions of HPD were arbitrarily proposed and our study aimed to compare them and suggest a more relevant definition. However, a biological explanation and surrogate are urgently needed in order to identify as soon as possible HPD patients under ICI.

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