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COMPARISON OF RADIOLOGICAL CRITERIA FOR HYPERPROGRESSIVE DISEASE IN RESPONSE TO IMMUNOTHERAPY

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Abstract:	Hyperprogressive disease (HPD) is a concerning paradoxical acceleration of cancer growth induced by immune drugs. The lack of standard radiological criteria makes its study challenging. We reviewed the literature and compared the main criteria for HPD proposed by Ferté, Le Tourneau, Garralda and Caramella to address this relevant unmet need in Immune-oncology. Among 182 consecutive patients with advanced cancer treated with immunotherapy in early-phase clinical trials, 71 with progressive disease at the first evaluation were eligible. HPD patients were studied regarding tumor growth dynamics and clinical impact. HPD occurred in 17 (23.9%), 17 (23.9%), 23 (32.4%) and 6 (8.4%) patients, as defined by Ferté, Le Tourneau, Garralda and Caramella, respectively. The strongest association was found between the Ferté and Le Tourneau criteria (Kappa=0.61), and the Jaccard similarity index varied from 55% (Ferté and Le Tourneau) to 21% (Le Tourneau and Caramella). The Ferté and Le Tourneau criteria showed statistically significant differences between pre-baseline and post-baseline tumor growth rate in patients with HPD, which could not be confirmed with the Caramella and Garralda criteria. Significant differences in progression-free survival were observed between non-hyperprogressors and hyperprogressors, with all criteria. The proportion of patients that could not receive additional lines of therapy was higher in the HPD group. HPD is an immunotherapy-related acceleration of tumor growth kinetics, with a consequent negative clinical impact. Pre-baseline CT scans and tumor growth rate evaluations are required to identify HPD. Our analysis favors the use of the Le Tourneau method, as it captures adequately the HPD phenomenon and is more convenient to use.
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CONFLICT OF INTERESTS STATEMENT

- Ana Luiza Gomes declares no potential conflicts of interest

- Maria de Miguel reports research funding from MSD, Pharmamar, Roche, Novartis, Abbvie, Array, Eisai, and Sanofi. Speaker´s Bureau: MSD, Janssen, Roche.

- José Miguel Cardenas declares no potential conflicts of interest

- Emiliano Calvo reports:

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HIGHLIGHTS

- Immuno-oncology (IO) drug-induced acceleration of some patients' disease is a clinically concerning phenomenon.

- Hyperprogressive disease (HPD) occurs in a meaningful percentage of patients.

- The Saâda-Bouzid radiological criteria to identify HPD are the preferable ones.

- Pre-baseline CT scans are needed to detect HPD.

- Important practical consequences in terms of assessment of toxicity to IO drugs and patients' safety are derived.

COMPARISON OF RADIOLOGICAL CRITERIA FOR HYPERPROGRESSIVE DISEASE IN RESPONSE TO IMMUNOTHERAPY

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ABSTRACT

Hyperprogressive disease (HPD) is a concerning paradoxical acceleration of cancer growth induced by immune drugs. The lack of standard radiological criteria makes its study challenging. We reviewed the literature and compared the main criteria for HPD proposed by Ferté, Le Tourneau, Garralda and Caramella to address this relevant unmet need in Immune-oncology.

Among 182 consecutive patients with advanced cancer treated with immunotherapy in early-phase clinical trials, 71 with progressive disease at the first evaluation were eligible. HPD patients were studied regarding tumor growth dynamics and clinical impact.

HPD occurred in 17 (23.9%), 17 (23.9%), 23 (32.4%) and 6 (8.4%) patients, as defined by Ferté, Le Tourneau, Garralda and Caramella, respectively. The strongest association was found between the Ferté and Le Tourneau criteria (Kappa=0.61), and the Jaccard similarity index varied from 55% (Ferté and Le Tourneau) to 21% (Le Tourneau and Caramella). The Ferté and Le Tourneau criteria showed statistically significant differences between pre-baseline and post-baseline tumor growth rate in patients with HPD, which could not be confirmed with the Caramella and Garralda criteria. Significant differences in progression-free survival were observed between non-hyperprogressors and hyperprogressors, with all criteria. The proportion of patients that could not receive additional lines of therapy was higher in the HPD group.

HPD is an immunotherapy-related acceleration of tumor growth kinetics, with a consequent negative clinical impact. Pre-baseline CT scans and tumor growth rate evaluations are required to identify HPD. Our analysis favors the use of the Le Tourneau method, as it captures adequately the HPD phenomenon and is more convenient to use.

KEYWORDS: hyperprogressive disease, immunotherapy, iRECIST, radiological criteria, immune-related toxicity.

INTRODUCTION

Immune-checkpoint inhibitors (ICIs) have been added to the therapeutic armamentarium for the treatment of many advanced cancers such as melanoma [1], non-small cell lung cancer (NSCLC)[2,3], renal cell carcinoma (RCC) [4], squamous cell carcinoma of the head and neck (SCCHN)[5] and urothelial carcinoma [6,7]. Various factors such as the status of the patient's immune system or the mechanism of action of immune-oncology (IO) drugs, are responsible for their characteristics regarding antitumor efficacy and toxicity [8].

With adequate modulation of the immune system, IO therapies can produce long-term responses in 10%-30% of patients, which translate into prolonged treatment-free survival and unprecedented improvements in overall survival (OS) [9]. Nevertheless, the radiological evaluation of patients receiving immunotherapies can be challenging, as different patterns of response, such as paradoxical pseudoprogressive disease (PPD), can appear and potentially hinder the benefit that patients may gain with these therapies. The proportion of patients who exhibit PPD is typically below 10%, but rates may differ among different tumor types [10]. To maximize the potential of IO therapeutics, the PPD concept has been incorporated into different immune-related radiological response criteria, thus allowing patients with progressive disease to continue treatment if they remain clinically stable and undergo an early reassessment of the disease.

On the other hand, there is accumulating evidence of a subset of patients who exhibit accelerated tumor progression as a consequence of their anti-PD1/PD-L1 treatment [11].

This proposed hyperprogressive disease (HPD) is a severe and even life-threatening condition that could lead to a drastic reduction in the patient's life expectancy as a result of IO treatment [12,13]. HPD differs from naturally rapidly growing disease in patients with aggressive, highly replicative tumors and a consequent poor prognosis independent of the therapy administered. In contrast, HPD refers to a change in the kinetics of tumor growth, which is accelerated as a result of the mechanism of action of the IO administered. No predictive factors have yet been identified and the biological underpinnings are unknown. Older age and a greater number of metastatic sites or molecular alterations, such as MDM2/MDM4 amplification or EGFR, might be related to HPD [14]. In randomized clinical trials, HPD might be responsible, in part, for the initial detrimental effect observed in the IO arm's comparative actuarial survival curves, which is followed by a crossover and longer-term benefit with the IO vs control arm drug [3]. Due in part to the lack of a standard definition and measurement criteria, high variability in the rate of HPD has been described; ranging from 9% in mixed solid tumors [12] to 14% in NSCLC [13] and 29% in SCCHN [15].

A key parameter for identifying patients with HPD is tumor growth rate (TGR), i.e., the increase in tumor volume over time. The analysis of TGR, as first described by Gómez-Roca et al. in 2011, combines the Response Evaluation Criteria in Solid Tumors (RECIST) sums of target lesions and the time between tumor evaluations, allowing for a dynamic and quantitative evaluation of tumor volume kinetics [16]. Later, Ferté et al. [12], from the same institution, first used TGR to define HPD related to IO, by exploring the difference in TGR between before and on immunotherapy. In their series, 9% of patients with solid tumors were identified to have HPD.

Caramella et al., from the same group, recently performed a comprehensive comparison of different HPD measurement criteria and proposed their own criteria that assume both

a large increase in tumor kinetics and a poor survival outcome in patients with NSCLC. They also considered a differential TGR, but with a threshold of greater than 100, and progressive disease by RECIST. In that study, HPD was found in 8.4% of patients [17].

Consistent with the concept of the comparison of tumor growth kinetics (TGK) before and during IO treatment, as first defined by Le Tourneau et al. in 2012 [18], researchers from the same institution simplified the definition of HPD later on, and based it only on changes in the bi-dimensional tumor dynamics over time. In this retrospective cohort study, HPD was present in 29% of patients with SCCHN [15].

These criteria may be challenging to use in daily practice, as pre-baseline imaging is not always available and, consequently, pre-IO tumor growth dynamics can be difficult to determine. Therefore, Garralda et al. recently calculated HPD as an increase in tumor size and/or the appearance of new lesions during IO treatment, without including any pre-baseline tumor evaluation. They reported an HPD rate of 10.7% in their series, without considering differential tumor growth rates or kinetics [19].

While many IO therapies have been approved or are in development, there are still no standard radiological criteria for the evaluation of HPD. The lack of a proper definition for HPD, and the major conceptual and practical differences between the reported criteria, make it difficult to determine the precise impact of this concerning paradoxical response to IO drugs. In this article, we retrospectively compared these reported HPD criteria in our own series of consecutive patients.

While other HPD criteria have been described, their perspectives have been similar to those discussed above, and thus they are not considered here. Kato et al. applied an HPD assessment derived from Ferté, but focused more on molecular predictive biomarkers than on HPD measurement criteria [14]. Two other studies were based on Gómez-Roca´s

definition of TGR, and therefore were very similar to the Ferté criteria for HPD. Ferrara et al. determined HPD as RECIST progressive disease on the first CT scan during treatment with an absolute increase in the TGR exceeding 50% per month [13]. Finally, Singavi et al. defined HPD as a doubling of the TGR and an increase in tumor size of 50%, albeit in a very small patient population [20]. These reports are included in the comprehensive comparison by Caramella et al., who proposed an improved measurement model, and therefore included as one of the comparators in our study [17].

PATIENTS AND METHODS

Patients

Consecutive advanced-cancer patients treated with single agents or combinations of immunotherapy within the Early Phase Clinical Drug Development program at START Madrid-CIOCC were retrospectively analyzed. All evaluable patients for HPD assessment had progressive disease (PD) as best response to the experimental IO treatment. In addition, three CT scans had to have been performed at the same institution at baseline (no more than 30 days before the first dose of IO treatment), pre-baseline (last image before baseline, which determines progressive disease in response to a previous line of therapy), and post-baseline (first reassessment while on experimental IO treatment). An independent RECIST 1.1 radiological evaluation was performed by two clinical researchers and a senior radiologist. Baseline RECIST 1.1 measurements were collected, and targets and non-target lesions in pre-baseline and post-baseline CT scans were identified. In post-baseline reassessments, new lesions were also collected. Tumor growth dynamics, i.e., TGR and TGK, were calculated for all patients at pre-baseline and

post-baseline. Patients with non-measurable disease only, as per RECIST 1.1 criteria, could not be assessed for TGR/TGK and were excluded from analyses.

HPD definitions

Ferté et al. [12]: Tumor growth was measured as $TG=3Log(D_t/D_0)/t$, where D_t is the sum of the diameters of the target lesions post-baseline, D_0 is the sum of the diameters at baseline, and t is time. TGR was expressed as the increase in tumor volume within one month: TGR = 100 [exp(TG) -1] [16,21] . HPD was defined as objective progressive disease by RECIST at the first on-IO evaluation, plus a two-fold or greater increase in the tri-dimensional TGR ratio during IO treatment in comparison with its pretreatment TGR.

Le Tourneau et al. [15]: The TGK rate pre-baseline (TGK_{pre}) was defined as the difference in the sum (S) of the largest diameters of the target lesions per unit of time (T) in months between pre-baseline and baseline imaging: $(S_0-S_{pre})/(T_0-T_{pre})$. Similarly, $TGK_{post}= (S_{post}-S_0)/(T_{post}-T_0)$. The TGK ratio (TGKR) was taken as the ratio of TGK_{post} to TGK_{pre}, and TGKR≥2 was considered to be HPD.

Garralda et al. [19]: HPD was defined as an increase in the measurable lesions of at least 10 mm, plus an on-IO treatment increase of ≥40% in the sum of target lesions compared to baseline and/or an increase of ≥20% in the sum of target lesions compared to baseline plus the appearance of new lesions in at least 2 different organs.

Caramella et al. [17]: HPD was defined as progressive disease according to RECIST 1.1 and a difference between pre-baseline and post-baseline TGR of greater than 100.

Statistical analyses

A survival analysis was performed using the Kaplan–Meier method and the log-rank test was used for statistical comparisons. Progression-free survival (PFS) was evaluated according to each of the four criteria (Ferté, Le Tourneau, Garralda and Caramella) in comparison to patients with objective PD as their best response. The Kuder-Richardson reliability coefficient (KR20), which is used to study the internal consistency of binary variables, was used; a value below 0.7 is associated with low consistency. A similarity matrix by the Jaccard method was used to evaluate agreement among the criteria. All criteria were compared with Fisher's exact tests and concordance was determined with Cohen's Kappa coefficient (K). Cohen's Kappa is a quantitative measure of agreement, where 0.01-0.20 is considered slight agreement, 0.21-0.40 is fair, 0.41- 0.60 is moderate, 0.61-0.80 is substantial, and 0.81-1.00 is near-perfect agreement. Data for continuous variables are expressed as means (standard deviations, SD). Categorical variables are reported as number and percentage, and analyzed using the Chi-squared test. Fisher's exact test paired samples T-test was used to compare TGR and TGK, both pre-baseline and post-baseline, between patients classified as HPD and non-HPD by the four criteria. Multivariate analysis was used to evaluate the correlations between variables and HPD. All p-values were 2-sided, and values less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS for Windows (version 24; IBM Inc., Armonk, NY), Stata software (version 15; StataCorp, College Station, TX) and Network Coincidence Analysis for a representative figure [22] under the supervision of two experienced biostatisticians.

The institutional review board approved this study, and all procedures followed the ethical standards of the responsible committee on human research (institutional and national) and the Helsinki Declaration of 1964 and later versions.

RESULTS

All 182 consecutive patients treated at our program in Phase 1 studies of IO drugs between January 2017 and December 2018 were included. They had different advanced tumor types and received treatment in the context of 27 immunotherapy clinical trials (Figure 1). We excluded 10 (5.4%) patients who stopped treatment due to clinical progression or toxicity before CT scan evaluation, two patients who withdrew their consent before the first reassessment, and one due to a lack of consistency in radiological techniques. Among the remaining 169 patients, 4 (2.3%) had pseudoprogressive disease, 27 (16%) had stable disease, 6 (3.5%) had partial response and 132 (78%) experienced progressive disease as their best response. A pre-baseline CT scan was not available for 58 of the 132 patients with PD (44%), and thus they had to be excluded from the comparative analyses. Neither TGR nor TGK could be calculated for 3 patients (4.1%) because the target lesions at baseline were not present in the pre-baseline evaluation. In table 1, clinical characteristics of the final 71 patients who were confirmed to be evaluable for the study goals are summarized. Table 2 shows the association of hyperprogressive disease (HPD) with tumor types and immunotherapies. Colorectal cancer was the most represented tumor type in both the total sample (56 of 182-30.8%) and evaluable sample (25 of 71-35.2%), which explains its predominance among HPD patients regardless of the criteria used. Also, most of patients received combinations of PD-1/PDL1 with other IO treatments. A multivariate analysis ruled out any correlation of clinical variables with HPD (including previously described prognostic factors such as age, lactate dehydrogenase (LDH), albumin, more than two metastatic sites, and Royal Marsden Hospital (RMH) score) (data not shown).

HPD evaluation and concordance between criteria

Of the 71 evaluable patients, 17 (23.9%), 17 (23.9%), 23 (32.4%) and 6 (8.4%) had HPD by the Ferté, Le Tourneau, Garralda and Caramella criteria, respectively. The median time from pre-baseline CT scan to baseline CT scan was 1.4 months (m) (range: 0.5m to 3.4m) and the time from baseline to post-baseline CT scan was 1.59 m (range: 0.2m to 2.5m).

The KR20 reliability coefficient for expressing the internal association among the four criteria was 0.68. This value reflecting low internal consistency was related to the Garralda criteria, since the coefficient increased to 0.71 when this HPD definition was excluded. Regarding Cohen´s Kappa, the Ferté and Le Tourneau criteria showed substantial concordance (K=0.61); 12 of 17 patients were equally classified by both. The Ferté and Garralda criteria showed the lowest concordance (K=0.17), with agreement in only 8 of 23 patients. Caramella showed a slightly better, but still low, concordance with Ferté (K=0.35, 5/17 patients), Le Tourneau (K=0.25, 4/17 patients) and Garralda (K=0.32, 6/23 patients). Finally, the Kappa value for Le Tourneau and Garralda was in the same range (0.24, agreement in 9/17 patients), which reflected low concordance between these definitions of HPD. In the same way, the Jaccard similarity matrix showed the strongest association between the Ferté and Le Tourneau criteria (55%), and the remaining criteria showed only weak agreement, in a range between 20% and 30% (Figure 2).

Acceleration of TGR

Pre-baseline and post-baseline TGR were calculated to determine the change in tumor volume kinetics in HPD and non-HPD patients with PD as best response. A paired-sample t-test was used to compare pre-baseline and post-baseline TGR in the evaluable

population and then stratified according to the HPD definition by the four criteria. No overall significant differences were observed between baseline and post-baseline TGR in the 71 study patients (pre-baseline=196.7, SD=565.3, vs post-baseline=78.8, SD=137.9, p=0.93). However, when patients with HPD according to the Ferté definition were selected, pre- and post-baseline TGR differences were statistically significant (pre-baseline=20.5, SD=36.7 vs post-baseline=112.4, SD=89.9, p<0.001). Similar results were observed for the Le Tourneau criteria, with statistically significant differences between before and during IO treatment (pre-baseline=47.2, SD=37.1 vs post-baseline=171.9, SD=242.4, p=0.04). On the other hand, for the Garralda and Caramella criteria, no differences were observed in TGR kinetics (Garralda pre-baseline=215.8, SD=436.4 vs post-baseline=177.3, SD=206.8, p=0.7; Caramella pre-baseline=41.3, SD=58.3 vs post-baseline=347.1, SD=357.7, p=0.07) (Figure 3).

HPD criteria and clinical impact

In patients with HPD by any of the four criteria, PFS was consistently shorter than that in non-HPD patients who had PD as their best response, and thus each of the criteria identified a subgroup of patients with a worse clinical course (Figure 4). Median PFS for the HPD population was 1.4 m by Ferté (p=0.04 95%CI 1.05 to 1.75m), 1.1 m by Le Tourneau (p=0.01 95%CI 0.73 to 1.60m), 1.4 m by Garralda (p=0.01 95%CI 1.08 to 1.71m), and 0.6 m by Caramella (p=0.01 95%CI 0.00 to 1.59m), compared to 1.6 m in the respective non-HPD populations.

New tumoral lesions in the post-baseline evaluation were present in 62.7% of patients. New lesions were present in almost all HPD patients by the Garralda (92.3%) and

Caramella criteria (100%), which reflects the identification of patients with aggressive and rapidly expanding disease. New metastatic disease was also confirmed in HPD patients by the Ferté and Le Tourneau criteria (76.5% and 66.7%, respectively), although to a lesser extent, since these definitions of HPD do not rely on the presence of new lesions or naturally aggressive disease.

HPD patients

Data about subsequent treatment lines reflect a trend towards worse outcomes for HPD patients. Patients with HPD that experienced ECOG performance status deterioration (from 0-1 to 2-3) received, in absolute numbers, additional lines in a lower proportion than non-HPD patients after disease progression. This occurred in 66.7% (4/6) of HPD patients by Caramella, 64.7% (11/17) by Ferté, and 76.5% (13/17) by Le Tourneau, which were higher than the values in the respective non-HPD patients (57%, 37/65; 56%, 30/54; and 52%, 28/54, respectively); however, these differences were not statistically significant, possibly limited by the number of total evaluable patients. On the other hand, 56% (13/23) of HPD patients and 58% (28/48) of non-HPD patients by the Garralda criteria, i.e., the same proportion of patients, could not undergo a new line of treatment after PD.

DISCUSSION

In this study, four radiological criteria for HPD identification were compared in the same set of advanced-cancer patients to determine their internal concordance as well as their ability to capture, in different ways (tumor growth dynamics and clinical impact), the biological concept of the acceleration of the patient's tumor due to the paradoxical

response to anticancer IO drugs. Three important conclusions can be derived from our study:

First, and most importantly, we further advanced the concept that HPD is a real and concerning phenomenon induced by IO drugs. To data regarding HPD from other series over the past few years [11–14,16,18,19], as well as the intriguing cross-over profile of the actuarial survival curves of randomized studies with IO drugs vs non-IO agents [1-4,8], here we add evidence regarding differences in TG dynamics before and during IO therapy in patients with HPD. This acceleration of tumor growth translates into their clinical deterioration due to this apparent IO-related toxicity, as reflected in shorter PFS and lower likelihoods of receiving rescue lines of additional therapies, compared to patients with progressive, but non-HPD status.

Our study identified subsets of patients with HPD according to the different criteria among patients with PD as best response, ranging from 8.4% (Caramella) to 23.9% (Ferté and Le Tourneau), consistent with other publications [11–14,16,18,19]. These are meaningful values, as they could relate to patients who have received a detrimental effect from IO therapy, which would usually be severe or even life-threatening if not taken into account in a proactive way. Regulatory agencies, pharmaceutical companies, oncologists and patient associations would then need to take action on this issue to protect cancer patients. In this regard, we would probably need to incorporate HPD assessment in IO clinical trials, include HPD as a grade 3 to 5 side effect of IO drugs in NCI-CTC AEs evaluation, inform patients before study entry or conventional IO treatment (through the consent process) of the potential for HPD, incorporate HPD as a new category of immune-related tumor measurements (iRECIST), and, when more precise analyses were performed, include this HPD information in the product labels of approved immune-modulating drugs. Pharmaceutical companies should then, in that apparent context,

describe the objective HPD rates for their IO drugs and lead prospective clinical trials to include this assessment as a secondary endpoint. Moreover, even though HPD would be an undesirable adverse event at any point of the disease, its consequences in the adjuvant setting could be particularly relevant in this curative intent, and challenging (since, by definition, there is no assessable disease in pre-baseline images), and patients and clinicians should be aware of this. In general, patients with IO therapy should be carefully followed-up, with a meticulous emphasis on early-onset symptoms or worsening that could suggest HPD, in order to re-evaluate their disease with CT scans as soon as possible in that context.

Secondly, our study highlights the need for mandatory pre-baseline CT assessments to enable the identification of HPD response to IO drugs. An important aspect of our evaluation was to assess how well these different criteria reflected the concept underlying HPD phenomenon as acceleration of the disease induced by IO drugs, instead of just a naturally rapidly growing disease unaffected by IO therapy. We found consistent results that favor the use of pre-baseline tumor measurements (i.e., Ferté, Le Tourneau, and Caramella criteria). These are the only criteria that reflect a significant change in tumor growth dynamics (figure 2). However, TGR increasing was statistically significant just by the Ferté and Le Tourneau definitions (p=0.00 and 0.04, respectively), as the differences observed by the Caramella criteria could not be confirmed probably limited by the low number of patients with HPD that this less sensitive method identifies. Furthermore, these three criteria that are based on pre-IO therapy assessments reflect a more pronounced deterioration of HPD patients, compared to their non-HPD counterparts, since more of these patients are unable to receive additional lines of therapy, which is consistent with prior reports [21].

Finally, of the criteria analyzed in our study, our results suggest that those reported by Le Tourneau [14] are preferable. Consistently, our study showed a much better agreement and concordance between the Ferté and Le Tourneau criteria (Cohen's Kappa and Jaccard indexes of 0.61 and 55%, respectively). This reflects the lack of pre-baseline tumor measurements in the Garralda criteria, which are essential for exploring the change in TGR that IO drugs must induce for HPD to occur. The Caramella criteria identify a highly selective and small subgroup of patients with HPD using a low-sensitivity method, which is derived from very restrictive HPD criteria based on a very large increase in tumor kinetics (with a TGR differential of greater than 100) and disease progression defined by a significant increase in the tumor burden; as a result, only a very small subgroup of patients satisfies these criteria for HPD, which makes intergroup comparisons difficult. Thus, the Caramella criteria fail to identify some HPD patients; and, in the field of oncology, diagnostic methods generally need to be highly sensitive. While the Le Tourneau and Ferté criteria seem to perform similarly well in detecting HPD, from a practical perspective, we found that it was easier to assess HPD based on 2-D estimations for TGK (Le Tourneau) than on 3-D estimations for TGR (Ferté).

This study has some limitations. This was a retrospective analysis, with consecutive and non-selected patients, and referred to an early-phase clinical trial program that usually included cancer patients with few therapeutic options, possibly with biologically more aggressive tumors, and who were receiving a variety of different IO treatments, including checkpoint inhibitors, agonists, and their combinations. Having said that, as this is not a therapeutic study, but, instead, it is focused on intraseries comparisons of different radiological criteria that are applied to all included patients, classical biases associated to a retrospective analysis would have a lesser negative effect on these results, as possible flaws would be similarly affecting all the comparisons here.

CONCLUSION

The acceleration of tumor kinetics related to IO therapy in a meaningful percentage of patients in our study reflects more a change in biological behavior associated with clinical deterioration and decreased progression-free survival, than just mere naturally occurring disease growth. However, even though we have shown, together with previous studies, that a concerning proportion of patients exhibit a detrimental response to IO, this is still not properly captured in clinical trials and consistently addressed. There is an urgent need to establish safety warnings or red flags during clinical research and in conventional therapy with IO drugs to protect patients from the potential harmful effects of HPD.

Our results highlight the need for mandatory assessment of pre-baseline CT scans to enable the identification of HPD in cancer patients with advanced disease. Among the criteria analyzed here that consider differential TGR dynamics, our data favor the 2-dimensional criteria proposed by Le Tourneau.

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TABLES

		Total Sample (n: 182)		*Evaluable Sample (n: 71)*	
		n	**Percent**	**n**	**Percent**
Sex	Female	92	50.5	35	49.3
	Male	90	49.5	36	50.7
Median Age (y)	Female	56		53	
	Male	57		55	
Smoking Status	Heavy smoker >15 cig/day	30	16.5	13	18.3
	Light smoker <15 cig/day	26	14.3	10	14.1
	Non-smoker	49	26.9	18	25.4
	Not available	77	42.3	30	42.3
Primary Site	Colorectal	56	30.8	25	35.2
	Lung	25	13.7	6	8.5
	Melanoma	13	7.1	2	2.8
	Breast	13	7.1	4	5.6
	Pancreas	12	6.6	6	8.5
	Biliary	10	5.5	6	8.5
	Gastric	8	4.4	4	5.6
	Head and Neck	7	3.8	3	4.2
	Ovary	6	3.3	3	4.2
	Endometrium	5	2.7	2	2.8
	Prostate	4	2.2	2	2.8
	Kidney	2	1.1	1	1.4
	Esophagus	2	1.1	2	2.8
	Anal Canal	2	1.1	1	1.4
	Bladder	1	0.5	0	0
	Other Mixed Types	13	7.1	4	7
Number of Prior Lines	1	29	16	10	14.1
	2	69	37.9	30	42.3
	3	43	23.6	14	19.7
	≥4	41	22.5	17	23.9

Type of Prior Lines	Immunotherapy	22	12.1	9	12.7
	Other Therapies	160	87.9	62	87.3
RMH score	Poor	18	9.9	45	63.4
	Intermediate	49	26.9	17	23.9
	Good score	115	63.2	9	12.7
Type of experimental treatment	PD1/PDL1 monotherapy	30	16.6	9	12.6
	PD1/PDL1 combinations	110	60.4	44	61.9
	Other Immunotherapies	42	23	18	25.3

Table 1. Main clinical characteristics

	Criteria for HPD							
	Ferté [12]		Le Tourneau [15]		Garralda [19]		Caramella [17]	
Primary Tumor	N:17	%	N:17	%	N:26	%	N:6	%
Colorectal	6	35%	5	29%	8	31%	3	50%
Lung	3	18%	4	23%	3	12%	1	17%
Breast	0	0%	0	0%	2	8%	0	0%
Melanoma	0	0%	0	0%	1	4%	0	0%
Pancreas	2	12%	1	6%	3	12%	0	0%
Gastric/GE Junction	0	0%	1	6%	4	15%	0	0%
Biliary	3	18%	2	12%	1	4%	1	17%
Head and Neck	1	6%	1	6%	1	4%	0	0%
Ovary	1	6%	1	6%	1	4%	0	0%
Endometrial	0	0%	0	0%	0	0%	0	0%
Prostate	0	0%	1	6%	0	0%	0	0%
Cervix	0	0%	0	0%	0	0%	0	0%
Mixed Types	1	6%	1	6%	2	8%	1	17%
Types of treatment								
PD1/PDL1 monotherapy	2	12%	7	39%	4	15%	1	17%
PD1/PDL1 combinations	10	59%	8	45%	19	73%	4	67%
Other Types of Immunotherapy	5	29%	3	17%	3	12%	1	17%

Table 2. Association of hyperprogressive disease (HPD) with tumor types and immunotherapies.

FIGURES

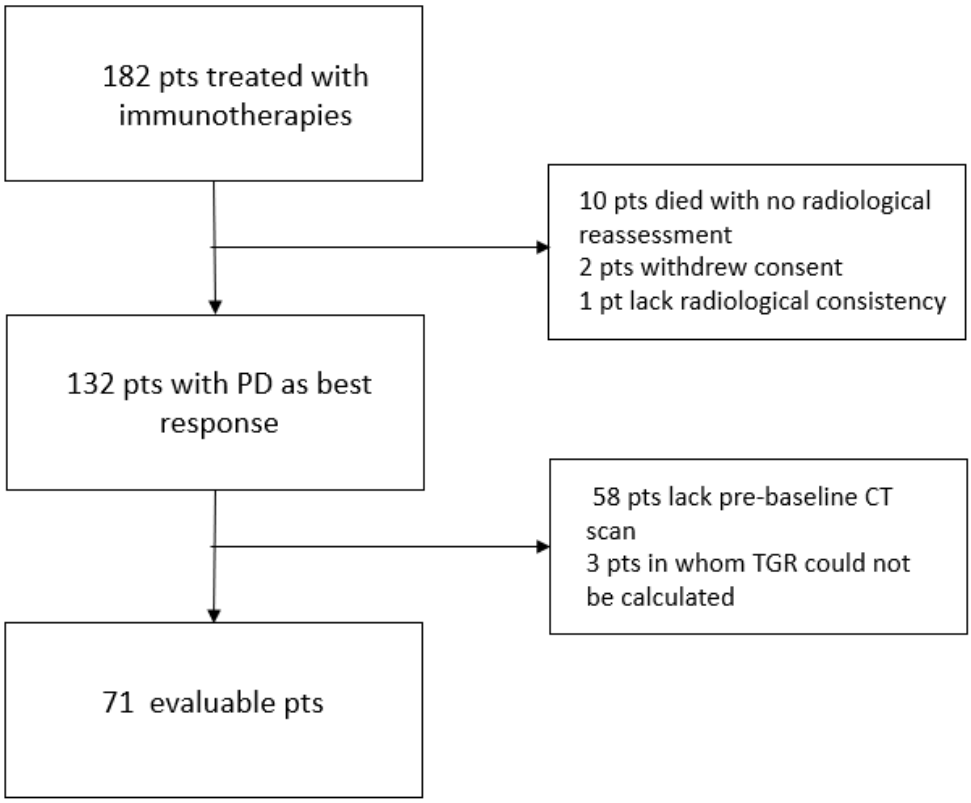


Figure 1. Patient CONSORT diagram.

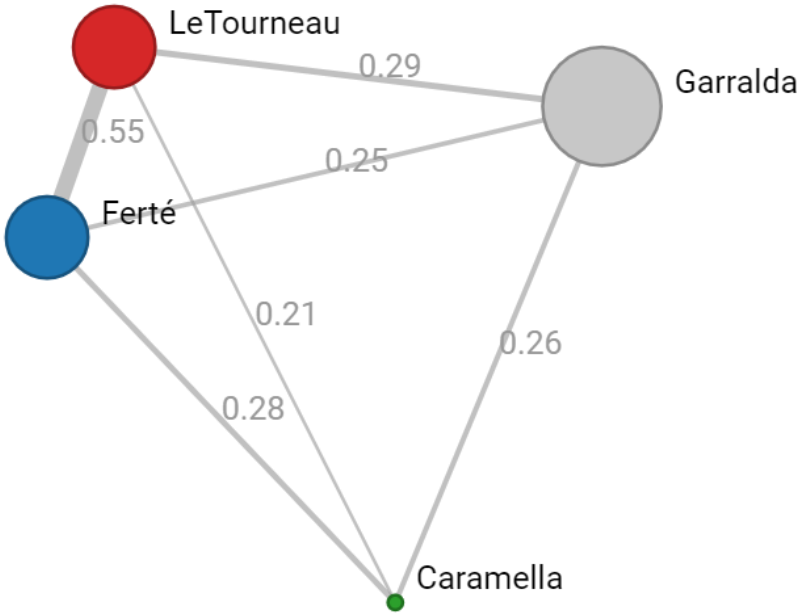


Figure 2: Schematic representation of the Jaccard associations between the different criteria. The size of the dots represents the percentage of HPD by the different definitions. The proximity and thickness of the lines represent the strength of the association.

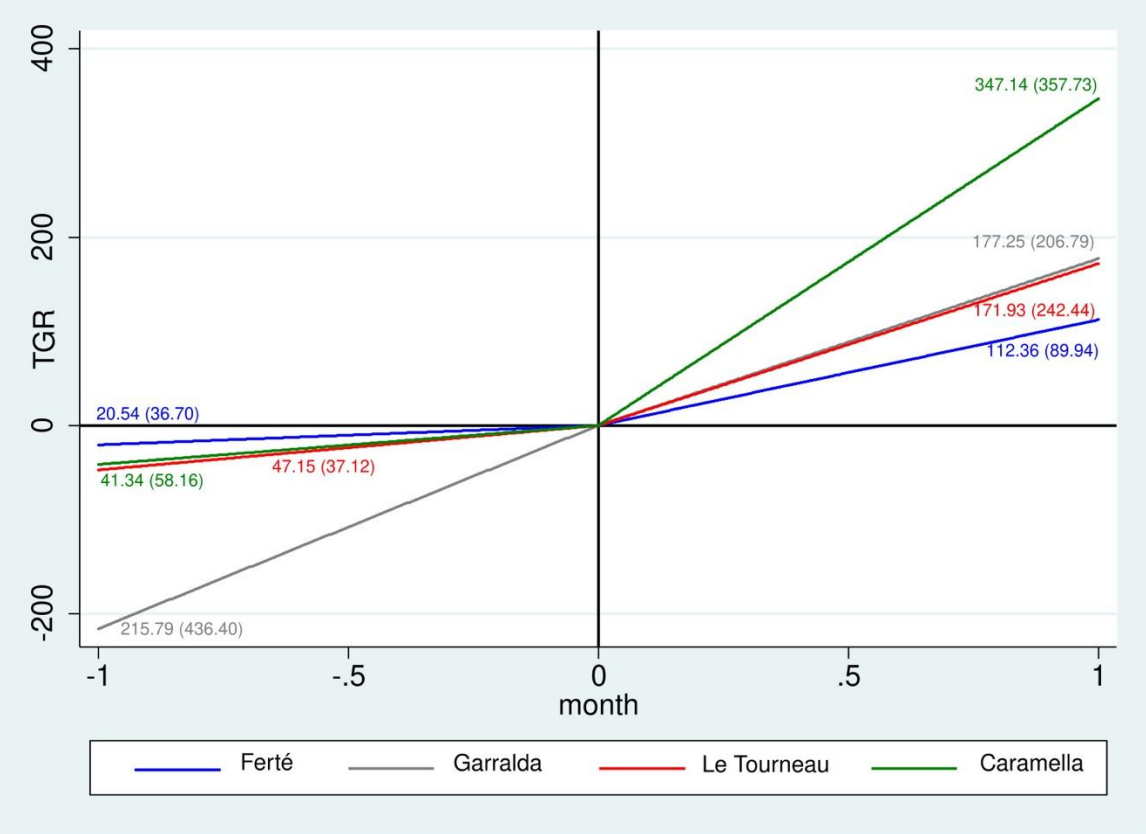


Figure 3. Representative comparison of pre-baseline and post-baseline TGR among patients considered to have HPD according to the different radiological criteria. Median TGR is expressed as the slope of the line and standard deviation in brackets.

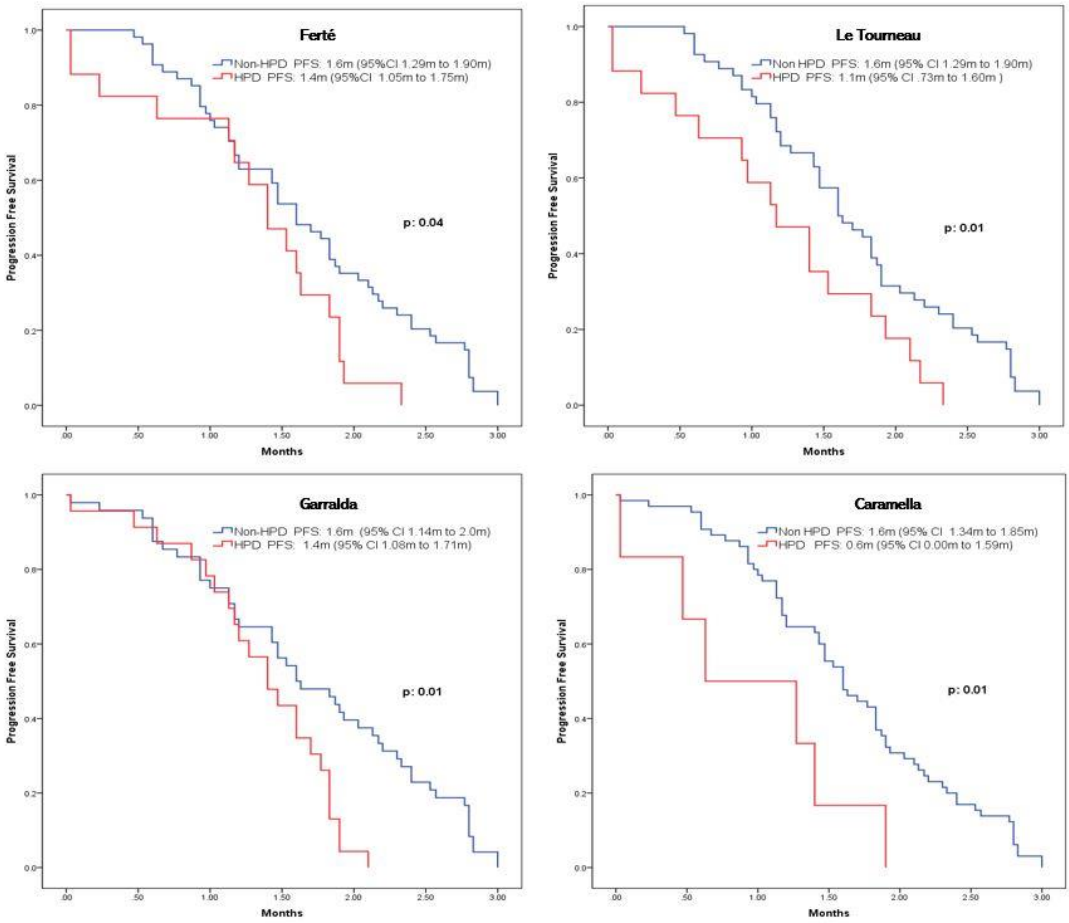


Figure 4: Progression free survival for the different HPD definitions.

POINT-BY-POINT RESPONSE TO THE REVIEWERS' COMMENTS

Reviewer #1:

The authors present a very important study that should definitely be published.

1. *To be fair, I guess what the authors name the "Saada-Bouzid" criteria should be replaced all along the manuscript and figures by the "Le Tourneau" criteria that were published initially in the British Journal of Cancer in 2012 as mentioned in the introduction. The senior author of the Saada-Bouzid paper was indeed Le Tourneau who designed the study.*

Response: We thank the reviewer for this comment and completely agree with the suggestion proposed. Therefore, "Saâda-Bouzid" has been replaced by "Le Tourneau" all along the manuscript. For consistency reasons, the rest of first authors have been also replaced by the manuscripts' senior/corresponding authors; "Matos" by "Garralda", "Champiat" by "Ferté", and "Kas" by "Caramella".

Reviewer #2:

I would like to thank the editors for the possibility of reviewing this article entitled "Comparison of radiological criteria for hyperprogressive disease in response to immunotherapy" by Gomes da Morais e al. I've read with great interest this manuscript as the topic proposed is of increasing relevance due to the wide use of checkpoint inhibitors or novel immunotherapies across several solid tumors. The abstract summaries the content of all the articles, both the introduction and method sessions are very well redacted and easily reading. The discussion arguments with detail all the addressed questions. The tables and figures are clear and well redacted. I do believe it is an interesting work and it could be considered helpful for clinicians. Nevertheless, the manuscript presents some minor weaknesses:

1. Table 2 shows the percentage of HPD positives in each tumor type but total number of tumor patients is not balanced and CRC is overrepresented. I would suggest the authors to underline this issue. The same effect is observed according to types of treatment.

Response: We agree with the reviewer about this interesting comment. Tumor types and type of IO treatment received show some disbalance towards CRC and PD-1/PD-L1 combinations, and this should be mentioned. We have added a new paragraph to explain it in the Results Section, page 12, lines 16-20.

2. *In the Acceleration of TGR, as only patients with HPD were analyzed, the sample in those tests is small. Did normality/homoscedasticity assumptions hold true? If so, p value for Champiat definition would be incorrect, it is not probable to have a p value equal to 0.00.*

Response: This is, in fact, a very interesting point. T-test for paired samples was used to study pre-baseline and post-baseline TGR. However, this is just one group of patients at two different timepoints, and so, homoscedasticity could not be applied because in this case we are not comparing two groups.

The Champiat/Ferté HPD patient´s group showed however normality of the TGR difference variable, as it can be observed in the Kolmogorov-Smirnov and Shapiro-Wilk tests below, where there are no significant differences in distribution.

Normality tests

Champiat	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Estadístico	gl	Sig.	Estadístico	gl	Sig.
Non-HPD	,346	54	,000	,388	54	,000
HPD	,131	17	,200[*]	,940	17	,320[c]

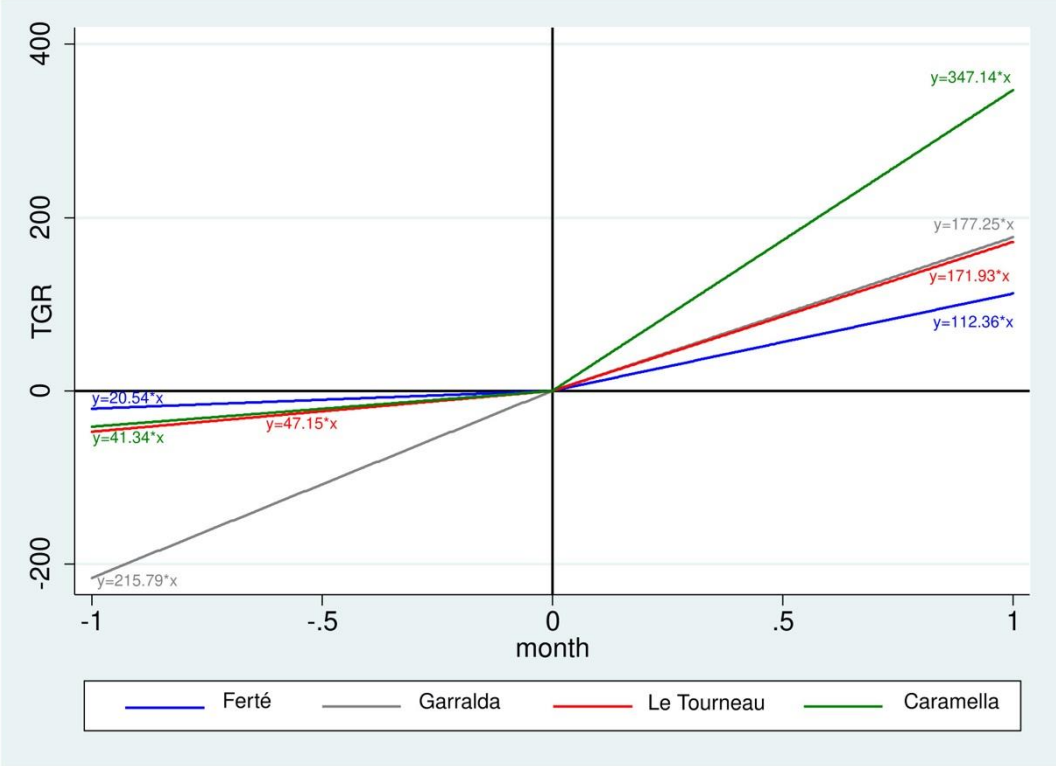
But, even in the case that normality could not be assumed because of small numbers, this fact has been also confirmed with the non-parametric test for paired Wilcoxon samples, with result of a p value <0.001 (below). In order to avoid misunderstanding with a p value of absolute zero, it has been modified in the text as p<0.001, page 14, seventh line.

Wilcoxon

Champiat		TGRPosbaseline - TGRBaseline
Non-HPD	Z	-4,909[b]
	Sig. asintót. (bilateral)	,000
HPD	Z	-3,621[c]
	Sig. asintót. (bilateral)	,000

3. *Figure 3 is misleading, maybe a paired boxplot (one for each definition) would be of better use.*

Response: We thank the reviewer for this comment and agree that adding a boxplot might be of interest for this review. However, although in our opinion a boxplot could be better to observe medians and dispersion of the data, it would not be accurate to show inter- and intra-criteria kinetic changes after IO. In this regard, as we agree that standard deviation is relevant for this kind of figures, figure 3 showed median TGR and standard deviation in brackets. Other way to show the increasing in TGR is as below with the formula of the slope of the line. Also, due to the journal space constraints we would not able to add a new figure to the manuscript, as there are already 6 tables and figures in total. Having said that, if the reviewer believes a boxplot is needed here, we would be more than happy to proceed with it and add it, accordingly.



4. *Please, include the confidence interval in the first paragraph of HPD criteria and clinical impact.*

Response: Indeed, we agree with the reviewer´s comment and confidence intervals for all criteria have been added to the text, page 14, last paragraph.

5. *I would like the authors to further describe the following claim: "Most patients with HPD could not receive additional lines of therapy after disease progression in response to IO experimental treatment due to their deteriorating performance status" as, in my opinion, there are not sufficient data to support it in this analysis.*

Response: We thank the reviewer for this comment and agree there are not sufficient data to support that statement in our analysis. In fact, as stated in the manuscript, the statistical analysis did not show statistically significant differences between the HPD and non-HPD groups across all criteria, with this regard. However, just considering the absolute numerical values in our population, patients with HPD had a relevant lower chance to receive a subsequent line of treatment due to clinical deterioration. Only the Matos/Garralda criteria showed no relevant differences between both groups as this criterion does not seem to be adequate to select patients with HPD. This has been clarified in the text, in the abstract section (third paragraph) and page 15, second paragraph.
