Capturing Hyperprogressive Disease with Immune-Checkpoint Inhibitors Using RECIST 1.1 Criteria

Ignacio Matos[1,2], Juan Martin-Liberal[1], Alonso García-Ruiz[3], Cinta Hierro[1], Maria Ochoa de Olza[1], Cristina Viaplana[4], Analia Azaro[1], Maria Vieito[1], Irene Braña[1], Gemma Mur[5], Javier Ros[1], Jose Mateos[6], Guillermo Villacampa[4], Roger Berché[4], Mafalda Oliveira[1], Maria Alsina[1], Elena Elez[1], Ana Oaknin[1], Eva Muñoz-Couselo[1], Joan Carles[1], Enriqueta Felip[1,2], Jordi Rodón[1], Josep Tabernero[1,2], Rodrigo Dienstmann[4], Raquel Perez-Lopez[3], and Elena Garralda[1]

ABSTRACT

Purpose: Most hyperprogression disease (HPD) definitions are based on tumor growth rate (TGR). However, there is still no consensus on how to evaluate this phenomenon.

Patients and Methods: We investigated two independent cohorts of patients with advanced solid tumors treated in phase I trials with (i) programmed cell death 1 (PD-1)/PD-L1 antibodies in monotherapy or combination and (ii) targeted agents (TA) in unapproved indications. A Response Evaluation Criteria in Solid Tumors (RECIST) 1.1–based definition of hyperprogression was developed. The primary endpoint was the assessment of the rate of HPD in patients treated with ICIs or TAs using both criteria (RECIST and TGR) and the impact on overall survival (OS) in patients who achieved PD as best response.

Results: Among 270 evaluable patients treated with PD-1/PD-L1 inhibitors, 29 PD-1/PD-L1–treated patients (10.7%) had HPD by RECIST definition. This group had a significantly lower OS (median of 5.23 months; 95% CI, 3.97–6.45) when compared with the non-HPD progressor group (median, 7.33 months; 95% CI, 4.53–10.12; HR = 1.73, 95% CI, 1.05–2.85; $P = 0.04$). In a subset of 221 evaluable patients, 14 (6.3%) were categorized as HPD using TGR criteria, differences in median OS (mOS) between this group (mOS 4.2 months; 95% IC, 2.07–6.33) and non-HPD progressors ($n = 44$) by TGR criteria (mOS 6.27 months; 95% CI, 3.88–8.67) were not statistically significant (HR 1.4, 95% IC, 0.70–2.77; $P = 0.346$). Among 239 evaluable patients treated with TAs, 26 (10.9%) were classified as having HPD by RECIST and 14 using TGR criteria in a subset of patients. No differences in OS were observed between HPD and non-HPD progressors treated with TAs.

Conclusions: HPD measured by TGR or by RECIST was observed in both cohorts of patients; however, in our series, there was an impact on survival only in the immune-checkpoint inhibitor cohort when evaluated by RECIST. We propose a new way to capture HPD using RECIST criteria that is intuitive and easy to use in daily clinical practice.

Introduction

The introduction of immune-checkpoint inhibitors (ICIs) in the cancer therapeutic arsenal has been one of the most important advances in medicine in recent years. Several ICIs have already been approved for the treatment of different tumors. Most of these approvals have been based on phase III clinical trials that compared ICIs with chemotherapy or targeted therapies as standard treatments in a wide range of malignancies such as melanoma (1–3), non–small-cell lung cancer (NSCLC) (4–8), head and neck squamous-cell carcinoma (HNSCC; refs. 9, 10), urothelial carcinoma (11, 12), and renal cell carcinoma (RCC; refs. 13, 14), among others. In orphan tumors such as Merkel cell carcinoma, uterine cervical carcinoma, or microsatellite instability-high (MSI-H) tumors, their approval has been based on single-arm phase II clinical trials (15–19). Despite the widespread use of ICIs, response assessment to these drugs continues to be a challenge. New patterns of response such as pseudoprogression, with an estimated incidence of around 5% to 10% of cases (20), prompted revision of the classically used Response Evaluation Criteria in Solid Tumors (RECIST). Since then, disease progression needs to be confirmed in a second tumor assessment performed at least 4 weeks apart in clinically stable patients by means of new response criteria such as immune-related response criteria (irRC), immune-related RECIST (irRECIST), or immune RECIST (iRECIST; refs. 21–23).

Hyperprogressive disease (HPD) is a phenomenon described more recently with ICI treatment (24, 25). The actual concept of HPD, whereby patients experience significant increase of their disease burden right after ICI exposure, remains currently under discussion. In some phase III studies comparing ICIs versus chemotherapy, there is inferior progression-free survival (PFS) and/or overall survival (OS) during the first 3 to 6 months in the ICI arm, with later overcrossing of

[1]Department of Medical Oncology, Vall d'Hebron University Hospital. Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain. [2]Deparment of Medicine. Universidad Autónoma de Barcelona, Spain. [3]Radiomics Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain. [4]Oncology Data Science (OdysSey) Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain. [5]Clinical trials office, Vall d'Hebron Institute Oncology (VHIO), Barcelona, Spain. [6]Radiology Department. Imagen ensayos clínicos at Hospital Quiron Barcelona, Spain.

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

Corresponding Authors: Elena Garralda, Vall d'Hebron Institute of Oncology (VHIO), P. Vall d'Hebron 119-129, 08035 Barcelona, Spain. Phone: 34-61-641-5542; Fax: 34-91-224-6931; E-mail: egarralda@vhio.net; and Ignacio Matos, Medical Oncology Department, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), P. Vall d'Hebron 119-129, 08035 Barcelona, Spain. Phone: 34-93-4894350; E-mail: imatos@vhio.net

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Translational Relevance

This study of two independent cohorts of patients [270 in the immune-checkpoint inhibitor (ICI) cohort and 239 in the targeted agent (TA) cohort] observed a hyperprogressive disease (HPD) rate of 10.7% (29 patients) and 10.9% (26 patients) using RECIST criteria, respectively. Fourteen patients (6.3%) were classified as HPD in both cohorts defined by TGR criteria. However, significant overall survival difference was observed exclusively with RECIST in the ICI cohort; the HPD group had a significantly lower median overall survival (mOS) of 5.23 months when compared with the non-HPD progressor group, with an mOS of 7.33 months. We show that the radiologic definition of HPD following both TGR criteria and RECIST criteria occurs in both cohorts. However, in our cohort, HPD, whereby a specific treatment causes a worsening of survival, seems to occur with ICIs and not by TAs. Our study suggests HPD can be captured using RECIST criteria, streamlining the evaluation of this phenomenon in the clinic. Patients with HPD should not continue treatment beyond progression, and an alternative salvage therapy without anti–PD-1/PD-L1 should be recommended. Applying this definition to clinical trials performed so far could deepen our knowledge of the true incidence and implications of this event and could aid in the translational research being performed to discover predictive biomarkers of this new pattern of response.

survival curves, with improved long-term outcomes with anti–PD-1 antibodies (4, 7, 9–11, 26). These results in favor of the control arms in the first months have mainly been attributed to two potential explanations: (i) total lack of efficacy and (ii) HPD and early deaths with ICIs. Its incidence varies from 5% to 29% of patients, depending on the tumor type and definition (25, 27–29). Given the fact HPD implies a worsening due to a specific treatment, most classifications define it by using tumor growth rate (TGR), which compares the tumor growth of the target lesions during ICI treatment and a reference period immediately prior to ICIs (3 months to 2 weeks; refs. 24, 28–31). These methods have some clinically important limitations, such as (i) requiring a prior computed tomography (CT) scan, which can sometimes be difficult to retrieve, is not available or has been performed outside the established reference period; and (ii) the assessment of new lesions and nonmeasurable disease is not accounted in the definition of TGR; however, in certain tumor types, over half the patients with progressive disease have new lesions and progression due to an increase in the nontarget lesions (32, 33).

Given these difficulties, HPD still remains more of an intuition of the treating physician for an individual patient than a phenomenon that is evaluated and measured in a standardized way. To overcome these limitations, we explored if HPD could be identified using an adapted RECIST criterion in patients treated with ICIs in phase I clinical trials, in order to assess the concept in a more applicable way in the clinic. We also cross-compared patients with HPD captured by RECIST definition and by the original TGR criteria (increase in TGR of more than two times during ICI treatment vs. reference period; ref. 24). To determine if this phenomenon is exclusively seen with ICIs, we analyzed a control cohort of patients treated with targeted agents (TA) in phase I clinical trials (34). Finally, we investigated clinical, laboratory, and radiology parameters that could understand and predict HPD according to RECIST criteria.

Patients and Methods

Patients

Patients treated with anti–PD-1/PD-L-1 monoclonal antibodies as monotherapy or in combination with other immunotherapeutic agents exclusively, in phase I clinical trials at Vall d'Hebrón Institute of Oncology (VHIO) included between January 2012 and June 2018, were analyzed ($n = 287$). For the control cohort, we collected data from patients treated in phase I clinical trials with TAs in monotherapy or combination with other targeted drugs considered Tier 2 to 3 in the ESMO scale of clinical actionability for molecular targets (ESCAT; ref. 34) included between January 2011 and January 2018 ($n = 280$). We excluded from both cohorts patients without a complete first tumor response assessment or not evaluable by RECIST (Supplementary Figs. S1 and S2). There was no patient overlap in both cohorts and no patients in the TAs cohort were treated with ICIs subsequently.

All procedures followed were in accordance with the ethical standards of the responsible committee on human research (institutional and national) and with the Helsinki Declaration of 1964 and later versions. This study was approved by the institutional review board of Vall d'Hebrón University Hospital, and informed consent from participants was not required because of the retrospective nature.

Radiologic evaluation

CT scans were acquired at baseline and every 6 to 8 weeks as per clinical trial specifications. The baseline CT scan (performed up to 7 days before treatment initiation) and the first CT scan for response assessment (week 6 or 8 ± 7 days) were reviewed. In order to evaluate HPD by TGR criteria, CT scans performed between 3 months and 2 weeks previous to the baseline CT scan were also reviewed. The TGR was assessed according to the definition by Ferte and colleagues tumor growth (TG) is equal to $TG = 3\ \mathrm{Log}(Dt/D0)/t$, where D is tumor size defined as the sum of the longest diameters of the target lesions as per RECIST 1.1. TGR were expressed as a percentage increase in tumor volume during 1 month using the following transformation formula: $TGR = 100\ (\exp(TG) - 1)$, where exp(TG) represents the exponential of TG (31).

The specifications of the image acquisition protocol are summarized in Supplementary Table S1. Previous-to-baseline CT scans were considered for evaluation only when they fulfilled the image acquisition requirements as per RECIST, with at least 5-mm contiguous slice thickness.

Target lesions defined by RECIST for every patient were collected at baseline and after treatment. In the ICI group, patients with progressive disease (PD) as best response who were clinically stable could continue treatment until PD confirmation in a second assessment at least 4 weeks apart, as per clinical trial specifications. In order to assess the rate of HPD by TGR, the same target lesions were identified and measured at the previous-to-baseline CT scan by an experienced radiologist (R. Perez-Lopez). Diameters of the target lesions before starting treatment with the ICIs were collected. The dates of the CT scans were also collected to calculate time between scans. All CT scans were centrally reviewed by two independent radiologists from two different centers (J. Mateos and R. Perez-Lopez).

Definition of HPD based on RECIST criteria

We defined HPD based on RECIST as PD in the first 8 weeks after treatment initiation and minimum increase in the measurable lesions of 10 mm plus: (i) increase of $\geq$40% in sum of target lesions compared with baseline [which represents doubling in unidimensional target lesions compared with classic RECIST PD criterion (20%)]; and/or (ii)

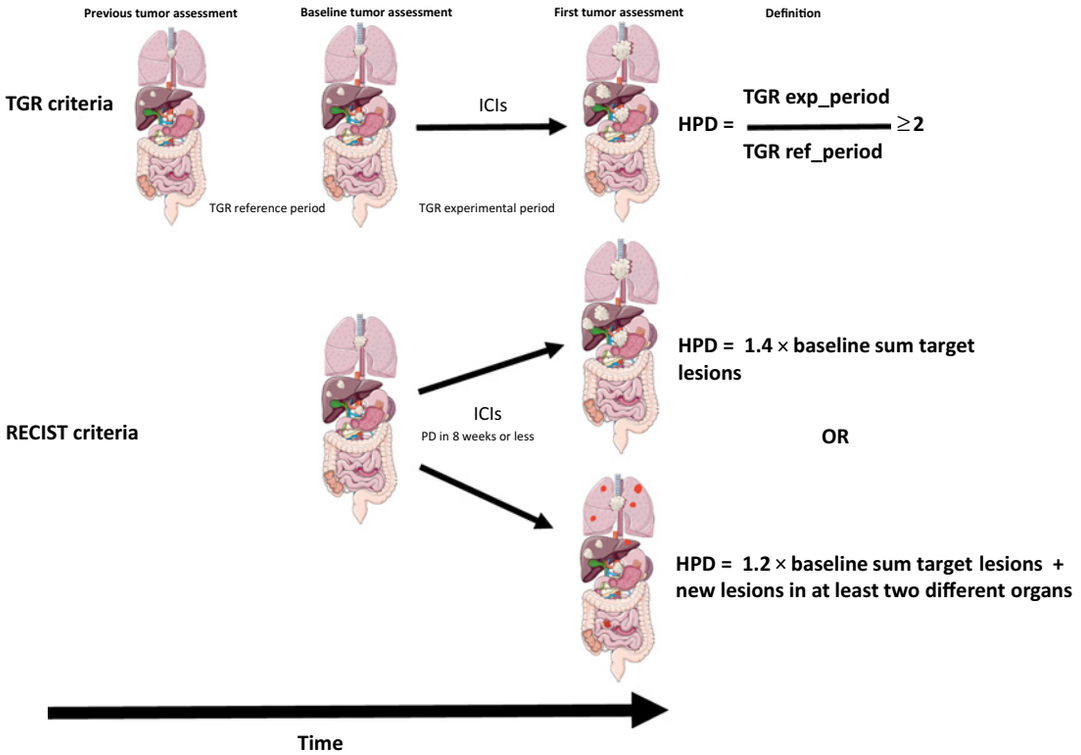

Figure 1.
Definition of HPD, according TGR criteria and RECIST criteria.

increase of ≥20% in sum of target lesions compared with baseline (the classic RECIST PD criterion) plus the appearance of new lesions in at least two different organs (**Fig. 1**). The reason to include both criteria (i and ii) as HP alternatives is that we noticed that some patients experienced progression that is largely driven by multiple new metastatic sites and not major target lesion growth. Importantly, the RECIST-based criteria to capture HPD were defined before the statistical analysis was performed, to avoid bias.

Statistical analyses

Survival analysis was calculated using the Kaplan–Meier method, and log-rank test was used for statistical comparison. Overall survival (defined as time from treatment initiation to death or last follow-up) and time from initial progression by RECIST to study discontinuation [in patients with treatment beyond progression (TBP)] of patients with PD as best response were evaluated according to their classification as HPD using RECIST and TGR criteria. The median follow-up was calculated using Kaplan–Meier reverse method. We performed a landmark analyses with OS calculated from the initial date of progression by RECIST to death or last follow-up. RECIST and TGR criteria were compared and analyzed to assess their performance using Fisher exact tests and concordance using kappa value. Univariate Cox proportional-hazard models were used to obtain hazard ratios (HR) with 95% confidence interval (CI). Statistical comparisons were performed using Student *t* test or Mann–Whitney–Wilcoxon test for continuous parametrical and nonparametrical variables. Chi-square or Fisher exact tests were used for categorical variables. All *P* values were two-sided, and values less than 0.05 were considered statistically significant. Statistical analyses were performed using a software program (SPSS for MAC, version 25.1; IBM Inc.).

Results

ICIs cohort

From January 2012 to June 2018, 287 patients with different tumor types received treatment in the context of a clinical trial with anti–PD-1/PD-L1 monotherapy (41.6%) or combination (58.4%) in the Early Drug Development Unit at VHIO. Seventeen (5.9%) patients experienced clinical progression or toxicity before the first tumor assessment as illustrated in the flowchart (Supplementary Fig. S1). A total of 270 patients were analyzed and evaluable for HPD. Clinical characteristics are described in **Table 1**. The median follow-up was 16.9 months (95% CI, 14.6–19.1 months). Median OS (mOS) was 10.93 months (95% CI, 8.52–13.34 months). No case of pseudoprogression as per iRECIST criteria was observed.

We independently analyzed patients with PD as best response ($n = 107$). Median time from cycle 1 day 1 to first CT scan was 6.5 weeks (95% CI, 6.2–6.9 weeks) in these patients. Overall, 29 patients (10.7%) were considered HPD by RECIST definition, representing 27.1% of the evaluable patients with PD as best response. In this population, patients with HPD had significantly lower OS as compared with the non-HPD group, with mOS of 5.23 months (95% CI, 3.97–6.45) versus 7.33 months (95% CI, 4.53–10.12), respectively (HR = 1.73; 95% CI, 1.05–2.85; $P = 0.04$; **Fig. 2**). Landmark analyses showed very similar results (HR = 1.73; 95% CI, 1.04–2.84; $P = 0.03$; Supplementary Fig. S3). When stratified by treatment line (second or third line), the

Table 1. Clinical variables in patients treated with ICIs.

Variable	Group	All patients ($n = 270$)	Non-HPD by RECIST ($N = 241$)	HPD by RECIST ($N = 29$)	*P* (Fisher exact test)	All patients[a] ($N = 221$)	Non-HPD by TGR ($N = 206$)	HPD by TGR ($N = 14$)	*P* (Fisher exact test)
Gender	Female	121 (44.8%)	112 (46.5%)	9 (31%)		98 (44.3%)	92 (44.7%)	6 (42.9%)	
	Male	149 (55.2%)	129 (53.5%)	20 (69%)		123 (55.7%)	115 (55.3%)	8 (57.1%)	
					0.114				0.908
Age (y)	<65	186 (68.9%)	167 (69.3%)	19 65.5%)		149 (67.4%)	142 (68.6%)	7 (50%)	
	≥65	84 (31.1%)	74 (30.7%)	10 (34.5%)	0.678	72 (32.6%)	65 (31.4%)	7 (50%)	0.236
Histology	Melanoma	55 (20.4%)	50 (20.7%)	5 (17.2%)		42 (19%)	41 (19.8%)	1 (7.1%)	
	NSCLC	32 (11.9%)	28 (11.6%)	4 (13.8%)		27 (12.2%)	26 (12.6%)	1 (7.1%)	
	Colorectal	24 (8.9%)	21 (8.7%)	3 (10.3%)		18 (8.1%)	15 (7.2%)	3 (21.4%)	
	Gastric	21 (7.8%)	21 (8.7%)	0 (0%)		17 (7.7%)	16 (7.7%)	1 (7.1%)	
	TNBC	21 (7.8%)	18 (7.5%)	3 (10.3%)		14 (6.3%)	13 (6.3%)	1 (7.1%)	
	H&N	20 (7.4%)	16 (6.6%)	4 (13.8%)		18 (14.3%)	16 (7.7%)	2 (14.3%)	
	Cervical	16 (5.9%)	16 (6.6%)	0 (0%)		13 (6.3%)	13 (6.3%)	0 (0%)	
	Bladder	14 (5.2%)	11 (4.6%)	3 (5.2%)		10 (4.8%)	10 (4.8%)	1 (7.1%)	
	Others	67 (24.8%)	60 (24.0%)	7 (24.1%)		57 (27.5%)	57 (27.5%)	4 (28.6%)	
					0.412				0.659
Lymphocyte count	≤1.9	205 (75.9%)	182 (75.5%)	23 (79.3%)		167 (75.6%)	155 (74.9%)	12 (85.7%)	
	>1.9	65 (24.1%)	59 (24.5%)	6 (20.7%)		54 (24.4%)	52 (25.1%)	2 (14.3)%)	
					0.652				0.526
Neutrophil count	≤4.9	172 (63.7%)	151 (62.7%)	21 (72.4%)		142 (62.8%)	130 (62.8%)	12 (85.5%	
	>4.9	98 (36.3%)	90 (37.3%)	8 (27.6%)		79 (37.2%)	77 (37.2%)	2 (14.3%)	
					0.302				0.083
dNLR	≤3	224 (83.3%)	199 (82.9%)	25 (86.2%)		190 (86.4%)	177 (85.9%)	13 (92.9%)	
	>3	45 (16.7%)	41 (17.1%)	4 (13.8%)		30 (13.6%)	29 (14.1%)	1 (7.1%)	
					0.796				0.699
Platelet count	≤300	177 (65.8%)	159 (66.3%)	18 (62.1%)		146 (66.4%)	135 (65.5%)	11 (78.6%)	
	>300	92 (34.2%)	81 (33.8%)	11 (37.9%)		74 (33.6%)	71 (34.5%)	3 (21.4%)	
					0.654				0.318
Albumin	<3.5	34 (12.6%)	29 (12.1%)	5 (17.2%)		28 (12.7%)	27 (13.1%)	1 (7.1%)	
	≥3.5	235 (87.4%)	211 (87.9%)	24 (82.8%)		192 (87.3%)	179 (86.9%)	13 (92.9%)	
					0.386				1
LDH	<375	72 (31.9%)	62 (30.8%)	10 (40%)		60 (33.1%)	56 (33.5%	4 (28.6%)	
	>375	154 (68.1%)	139 (69.2%)	15 (60%)		121 (66.9%)	111 (66.5%)	10 (71.4%)	
					0.354				1
No. of metastatic sites	≤2	141 (52.2%)	130 (53.9%)	11 (37.9%)		122 (55.2%)	118 (57%)	4 (28.6%)	
	>2	129 (47.8%)	111 (46.1%)	18 (62.1%)		99 (44.8%)	89 (43%)	10 (71.4%)	
					0.103				0.04
Liver metastasis	no	172 (63.7%)	157 (65.1%)	15 (51.7%)		146 (66.1%)	143 (69.1%)	3 (21.4%)	
	yes	98 (36.3%)	84 (34.9%)	14 (48.3%)		75 (33.9%)	64 (30.9%)	11 (78.6%)	
					0.156				0.001
IPI score prognosis	Good	103 (38.1%)	91 (37.8%)	12 (41.4%)		92 (41.6%)	88 (42.5%)	4 (28.6%)	
	Intermediate	135 (50%)	120 (49.8%)	15 (51.7%)		107 (48.4%)	98 (47.3%)	9 (64.3%)	
	Poor	32 (11.9%)	30 (12.4%)	2 (6.9%)		22 (10%)	21 (10.1%)	1 (7.1%)	
					0.677				0.470
MDA-ICI prognosis	Good	67 (24.8%)	59 (24.5%)	8 (27.6%)		57 (25.8%)	56 (27.1%)	1 (7.1%)	
	Intermediate	165 (61.1%)	147 (61%)	18 (62.1%)		136 (61.5%)	125 (60.4%)	11 (78.6%)	
	Poor	38 (14.1%)	35 (14.5%)	3 (10.3%)		28 (12.7%)	26 (12.6%)	2 (14.3%)	
					0.808				0.253
Previous ICI treatment	No	214 (79.6%)	192 (80%)	22 (75.9%)		177 (80.5)	165 (80.1%)	12 (85.7%)	
	Yes	55 (20.4%)	48 (20%)	7 (24.1%)		43 (19.5%)	41 (19.9%)	2 (14.3%)	
					0.602				1
Type of inhibitor	PD-1	174 (64.4%)	151 (62.7%)	23 (79.3%)		140 (63.3%)	130 (62.8%)	10 (71.4%)	
	PDL1	96 (35.6%)	90 (37.3%)	6 (20.7%)		81 (36.7%)	77 (37.2%)	4 (28.6%)	
					0.077				0.517
Combination of ICIs	No	114 (42.2%)	109 (45.2%)	5 (17.2%)		99 (44.8%)	97 (46.9%)	2 (14.3%)	
	Yes	156 (57.8%)	132 (54.8%)	24 (82.8%)		122 (55.2%)	110 (53.1%)	12 (85.7%)	
					0.004				0.018

[a]All patients evaluable for TGR criteria.

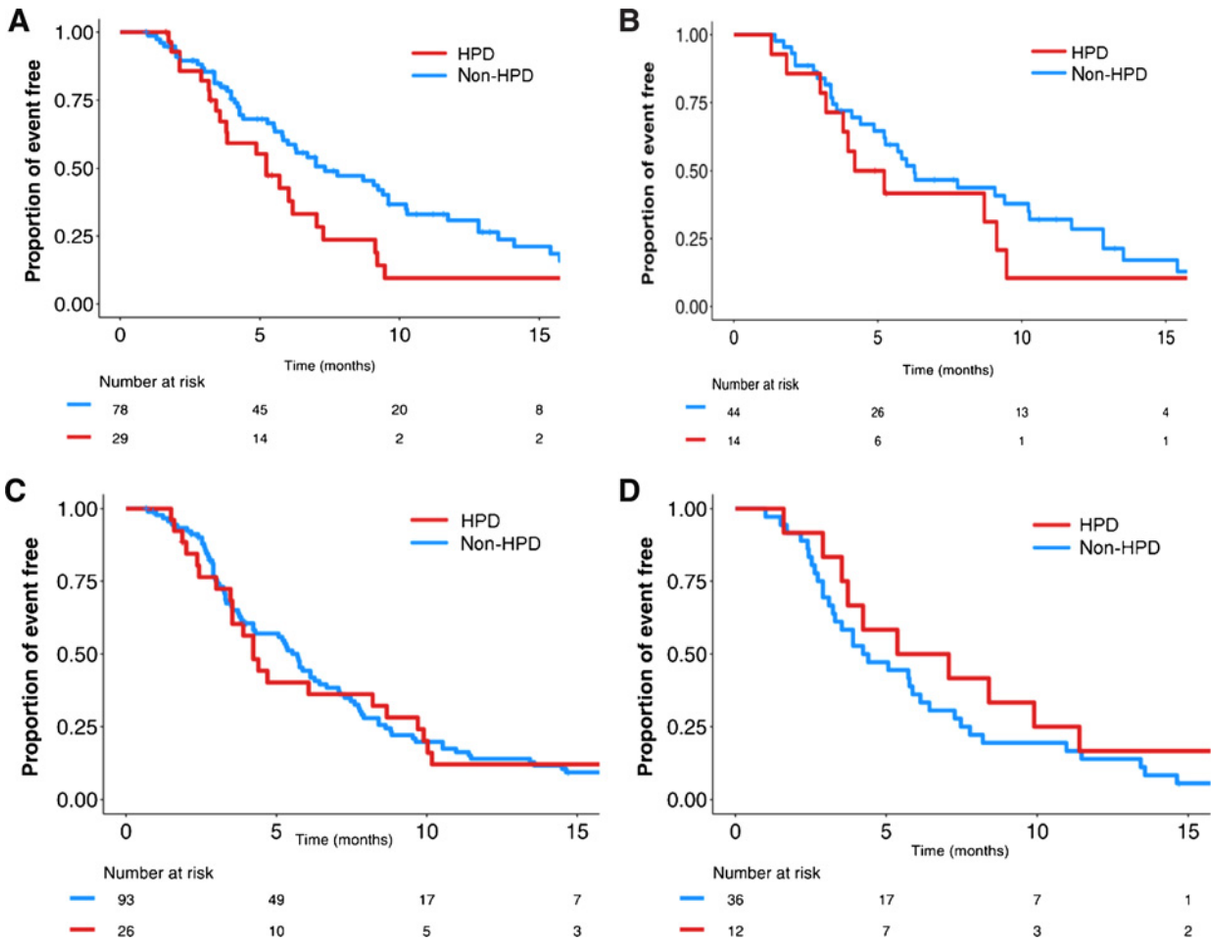

Figure 2.

OS for HPD compared with non-HPD progressors by RECIST and TGR criteria in the ICI and TA cohorts. **A,** RECIST criteria in the ICI cohort. **B,** TGR criteria in the ICI cohort. **C,** RECIST criteria in the TA cohort. **D,** TGR criteria in the TA cohort.

association between HPD and worsened outcomes was maintained (Supplementary Fig. S4).

In the multivariable analysis for OS in patients with PD as best response, including classically well-described prognostic factors [age, LDH, albumin, liver metastasis, more than two metastasis sites, derived neutrophils/(leukocytes minus neutrophils) ratio (ref. 35; dNLR) and count platelets], HPD using RECIST definition remained a significant prognostic factor together with low albumin, high LDH, and liver metastases (**Table 2**).

Overall, 34 patients continued treatment beyond progression by RECIST criteria. Time from initial progression to study discontinuation was 0.9 m (95% CI, 0.65–1.15) in the HPD group ($n = 10$) versus 1.4 months (95% CI, 1.14–1.46) in the non-HPD progressors (HR = 1.45; 95% CI, 0.67–3.10; $P = 0.34$).

TAs cohort

Overall, 239 patients treated with TAs were included in the HPD analysis. A total of 41 patients (17.2%) were excluded due to clinical progression or toxicity before the first tumor response assessment as indicated in the flowchart (Supplementary Fig. S2). Main characteristics of the 239 patients are listed in Supplementary Table S2. None of the patients had received prior ICI treatment. The median follow-up was 29.66 months (95% CI, 23.6–35.7 months) and mOS was 7.93 months (95% CI, 6.90–8.95 months). From 119 patients who had PD as best response, 26 (21.8%) were classified as HPD by RECIST criteria. No differences in OS were observed between HPD group

Table 2. Multivariate model in patients with progression disease as best response in the ICI group.

		Overall survival	
		Full analysis	
Variable		**HR (95% IC)**	***P* value**
***N* (events)**	**Level**	**107 (77)**	
Age	≥65(y)/<65	0.87 (0.46–1.65)	0.669
Lymphocyte count	≤1.9/>1.9	0.84 (0.42–1.69)	0.623
Neutrophil count	>4.9/≤4.9	1.06 (0.48–2.33)	0.881
dNLR	>3/≤3	1.27 (0.64–2.51)	0.495
Platelet count	>300/≤300	1.02 (0.50–2.08)	0.948
Albumin	≤3.5/>3.5	2.13 (1.02–4.46)	0.043
LDH	≥ULN/<ULN	2.80 (130–6.08)	0.009
No. of metastatic sites	>2/≤2	1.42 (0.79–2.55)	0.238
Liver metastases	Yes/no	2.03 (1.20–3.46)	0.009
HPD (RECIST)	Yes/no	2.02 (1.13–3.61)	0.018

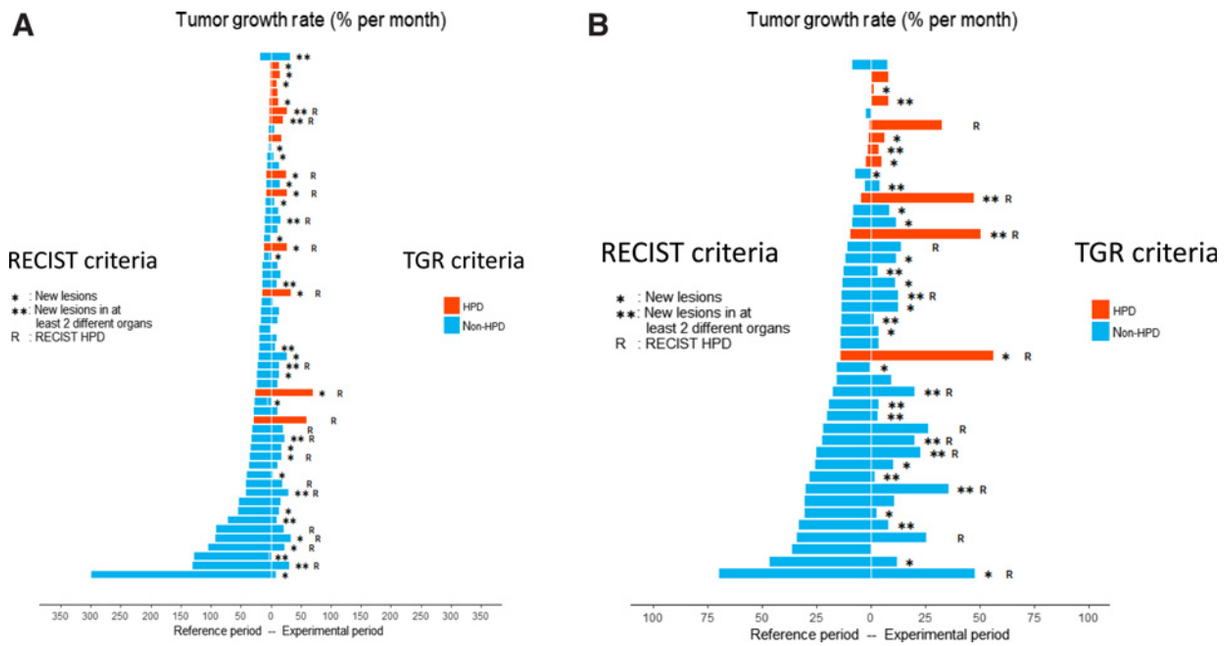

Figure 3.

Tumor growth rate during the reference and experimental periods of the patients included in the ICI and TA cohorts who were evaluable for HPD following both criteria. Patients with new lesions are also shown. Patients categorized as HPD following TGR are marked in red, patients categorized as HPD following RECIST criteria are marked with an R. **A,** ICI cohort. **B,** TA cohort.

(mOS 4.23 months; 95% CI, 3.42–5.04) and non-HPD progressor group (mOS 5.7; 95% CI, 4.99–6.4; HR 1.09, 95% CI, 0.7–1.7; $P = 0.70$), as seen in **Fig. 2**.

Comparison between HPD by RECIST definition versus TGR evaluation

HPD using TGR assessment was evaluated for every patient from the previously described ICIs cohort whenever possible. From a total of 107 patients with PD as best response, 32 (30%) could not be assessed for the previous-to-baseline CT scan: 22 (21%) did not have a previous-to-baseline CT scan and 10 (9%) had no measurable disease. From the 75 remaining patients, 17 (19%) had no available previous-to-baseline CT scan during the established reference period (within 3 months and 2 weeks before baseline). A total of 58 patients were evaluable following both definitions. The time between previous-to-baseline and baseline CT scans was 45.36 ± 20.98 days (mean ± standard deviation). The time between baseline and follow-up CT scans was 58.79 ± 11.20 days (mean ± standard deviation).

Fourteen patients (24.13% of patients with PD as best response and evaluable by TGR criteria) were categorized as HPD using TGR criteria. Differences in mOS between this group (mOS 4.2 months; 95% IC, 2.07–6.33) and non-HPD progressors ($n = 44$) by TGR criteria (mOS 6.27 months; 95% CI, 3.88–8.67) were not statistically significant (HR 1.4; 95% IC, 0.70–2.77; $P = 0.346$; **Fig. 3**). A landmark analysis did not detect differences in OS in HPD versus non-HP progressors as per TGR (Supplementary Fig. S3). In the multivariable analysis for OS in patients with PD as best response, using the same previous clinical prognostic factors, HPD by TGR criteria was not an independent prognosis factor (Supplementary Table S3).

The overall concordance rate between the two criteria was 70.7% (Supplementary Fig. S5), with a significant association and concordance between both definitions of HPD ($P = 0.047$). HPD using RECIST and not by an increase of TGR was observed in 11 patients (19%). Eight of these patients had new lesions in the first tumor assessment. In three of them, PD was based on increase in target lesions (49%, 46%, and 55%). We then compared mOS between two groups [HPD by RECIST combined with non-HPD by TGR definition ($n = 11$) versus non-HPD progressors by RECIST definition ($n = 39$)]. mOS was 3.43 months (95% CI, 2.70–4.15 months) and 8.7 months (95% CI, 4.73–12.66 months), respectively, which was statistically significant (HR 4.53; 95% CI, 1.92–10.67; $P = 0.001$). Six (10.3%) patients were categorized as HPD when assessing TGR dynamics and not by RECIST, and no patient had new lesions in at least two different organs (two patients had no new lesions, two patients had a single new lesion, and two patients had new lesions in a single organ).

In addition, we analyzed an initial subgroup of patients from the TA cohort with PD as best response ($n = 75$) for TGR criteria. Overall, 48 patients were included in this analysis. The reasons for exclusion were the following: 12 patients with unavailable CT scans prior to baseline and 15 patients had no available previous-to-baseline CT within the reference period. Twelve patients (25% of patients with PD as best response) were categorized as HPD when assessing TGR increase. We found no significant differences in outcome between HPD group and non-HPD progressors, with mOS of 5.37 months (95% CI, 0.55–10.12 months) and 4.23 months (95% CI, 2.42–6.041 months; HR 0.68, 95% CI, 0.34–1.36; $P = 0.27$), respectively (**Fig. 2**). The concordance rate between RECIST and TGR criteria in the TA cohort was 66.7%, but not statistically significant ($P = 0.695$).

Association between HPD and clinical, laboratory, and radiologic parameters

Next, we analyzed the association between HPD by each of the criteria and three different types of variables: (i) clinical variables, (ii)

radiologic parameters, and (iii) mechanism of action of the ICIs administered.

No clinical variables were associated with HPD using RECIST criteria, as summarized in **Table 1**. However, some clinical prognostic factors were associated with HPD using TGR assessment, such as the presence of liver metastasis ($P = 0.001$) and having more than two metastatic sites before treatment with ICIs ($P = 0.038$).

Regarding radiologic parameters in the ICI cohort, we analyzed the distribution of TGR in the reference period and in the experimental period (**Fig. 3**), and the sum of target lesions in the baseline CT scan and the first tumor assessment, for patients meeting each of the HPD definitions. We observed a lower TGR value in the reference period in patients defined as HPD when assessing the dynamics of TGR compared with the non-HPD progressor group ($P < 0.001$). In the experimental ICI treatment period, this variable was significantly reversed with higher TGR values in HPD patients ($P = 0.002$). We did not find differences in the total sum of the diameter of target lesions in either cohort, neither in the baseline CT scan ($P = 0.317$) nor in the first tumor assessment ($P = 0.158$). When evaluating those patients classified as HPD following RECIST criteria, TGR values during the experimental period were higher in the HPD group than in the non-HPD progressor group ($P < 0.001$). Finally, TGR values during the reference period and the total sum of the diameter of target lesions during any period were not different in HPD group by RECIST as compared with the non-HPD progressor group.

When evaluating the association between HPD and mechanism of action of the ICIs administered using RECIST criteria, we observed a clear trend for increased risk with anti–PD-1 treatment as compared with anti–PD-L1 antibodies ($P = 0.077$), not detected when evaluating TGR change ($P = 0.775$). The association with HPD was very strong for patients receiving ICI combinations using both RECIST criteria ($P < 0.01$) and TGR change criteria ($P = 0.019$) as compared with monotherapies. Of note, a total of 129 patients were treated with anti–PD-1 based combinations (representing 82.7% of the total patients treated in combination).

Discussion

The concept of HPD, where patients present clinical deterioration secondary to ICI treatment, is a new and controversial phenomenon, which has important clinical implications. Currently, there are no easily applicable criteria for routine use in the clinic. In this retrospective study of patients receiving ICIs in the context of phase I clinical trials, HPD was observed in 10.7% of the cases (29 of 270) using an adapted RECIST definition and in 6.3% (14 of 229) using TGR evaluation. If we analyze only those patients who obtain PD as best response in the first tumor assessment, the prevalence is quite similar with 27.1% (29 of 107) and 24.1% (14 of 58) of cases, respectively. These results are comparable with studies published by Champiat and colleagues, with 24.4% of HPD in the cases with PD as best response (12 of 49) in phase I patients receiving PD-1/PD-L1 ICIs (24) and by Ferrara and colleagues, observing a 32.9% (56 of 170) of HPD exclusively in non–small cell lung cancer patients (29).

When comparing both ways to evaluate HPD, the main discordance is seen in those patients who are categorized as HPD when assessed by RECIST and non-HPD using TGR. This is mainly due to the criterion that takes into account the appearance of multiple new metastases, which are not captured with TGR evaluation. Arguably this is an important limitation, as in our study most patients with PD as best response (72 of 107, 67.3%) had multiple new metastases, and importantly these patients had a similar poor prognosis independently of the TGR, with a clear negative impact in OS. Other clinical trials published have shown that around 40% to 50% of patients with PD had new lesions (32, 33). The slight increase of our series could be explained given the nature of phase I population.

Understanding the concept of HPD as tumor burden increase due to ICI exposure, one limitation of using RECIST could be overestimating the HPD phenomenon in cases with intrinsically rapid aggressive disease. It is worth noticing that despite this being potentially true, we did not find differences in the TGR values during the reference period between the HPD group and the non-HPD progressor group using RECIST, or with the baseline tumor burden, both expected to be higher in aggressive tumors. On the other hand, we did observe higher TGR values during the experimental period in the HDP group by RECIST, consistent with a rapid progression while receiving ICIs therapy.

Independent of the fact that assessing HPD by RECIST criteria could be capturing patients with a rapid progression (irrespective of it being caused by the treatment or by the intrinsic behavior of the disease), it is able to identify a subgroup of patients with lower OS when treated with ICIs, and this could already have a relevant impact in the clinic. Importantly, HPD by RECIST criteria remained an independent poor survival factor in a multivariable model adjusted for known prognostic factors. Furthermore, 38 patients with PD as best response in our ICI cohort continued treatment to confirm PD; however, the median time from initial progression to study discontinuation was less than 1 month. This implies that if a patient meets RECIST criteria of HPD in his first tumor assessment, PD should not be confirmed with a second tumor assessment and an alternative rescue therapy without anti–PD-1/PD-L1 should be recommended. Our cohort was based on patients receiving ICIs in the context of phase I clinical trials, and this could represent a bias, as there is a smaller prevalence of patients with very bad prognosis, being one of the most common inclusion criteria having a life expectancy of more than 3 months. However our definition has been assessed in independent cohorts of patients with gynecological and genitourinary tumors treated with ICIs at our institution, with similar results (36, 37).

Other than the already mentioned logistical difficulties to quantify TGR due to the need of a previous-to-baseline CT scan, assessing the kinetics through TGR can also have limitations to capture the biological impact of the treatment. Our results show that a lower TGR during the reference period is associated with higher chances of an HPD classification in the later period (both in the ICI and TA cohorts). This could underline the fact that in tumors with a lower TGR prior to treatment it will be easier to reach a doubling of the TGR independently of the kind of treatment received. For example, a tumor with a change from a 10% volume increase during the month prior to the experimental treatment to a 20% increase during ICI treatment would be classified as a HPD; however, with a change from 50% during the reference period to 70% during the experimental period, it would not be considered as an HPD, despite having a higher absolute increase in tumor burden than the previous situation.

One important question that remains to be answered is if HPD is really a novel way of response exclusive of ICIs (29, 38). In this regard, we also analyzed a similar cohort of patients treated with TAs. Targets that have already been approved, such as BRAF inhibitors in *BRAF*-mutated tumors, were excluded from the analysis. HPD by RECIST was observed in 10.8% (26 of 239) of all population and in a 21.8% (26 of 119) of patients with PD as best response. However, it had no impact in mOS. We observed similar results analyzing TGR with 25% (12 of 48) of patients having HPD without an impact in survival. Thus, in our cohort of patients, the radiologic definition of HPD is met with both types of treatments; however, the impact in patients' outcome appears

to be exclusively seen in the ICI cohort. This is in line with the previously described 14.2% (3 of 21) early PD seen in a chemotherapy cohort by Ferrara and colleagues. Understanding the limitations of the analysis, such as a selected patient population, heterogeneous tumor types, and previous treatments, with 20.4% having received previous ICIs, our results suggest the phenomenon of HPD (where the type of progression is not only a radiologic description but also has a biological impact with a worsening of survival) could be exclusive of ICIs. Given the fact that the half-life of ICIs is around 25 days, longer than most TAs (39–42), the deleterious effect of ICIs in some patients could be continued after stopping treatment, even Osa and colleagues demonstrated that PD-1–blocking antibody nivolumab persists in patients several weeks (>20 weeks) after the last infusion, bound to its receptor (43), which could explain in part this detrimental impact in mOS. To fully determine if the negative impact of survival seen in a subset of patients is exclusive of ICIs, this observation should be further evaluated in bigger cohorts of patients. Our definition based on RECIST criteria could be easily tested in the previously performed prospective clinical trials.

Finally, we analyzed if HPD was related with a specific ICI in our cohort. Using RECIST criteria we observed a clear trend of HPD in patients treated with anti–PD-1 therapies, and this association was very robust in patients treated with combinations based on an anti–PD-1 backbone. In most cases, the combination agent was an antibody against a lymphocyte receptor made with a $IgG4_{(S228P)}$ Fc subtype, similarly to the most common used anti–PD-1 agents (44, 45). Preclinical models have demonstrated that an anti–PD-1 $IgG4_{S228P}$ antibody can mediate cross-linking between $PD\text{-}1^+$ T cells and $Fc\gamma RI^+$ macrophages, resulting in macrophage-mediated phagocytosis of $PD\text{-}1^+$ T cells (46). This seems to be in line with the observation published by Lo Russo and colleagues, where they found tumor infiltration by M2-like $CD163^+CD33^+PD\text{-}L1^+$ clustered epithelioid macrophages in patients with HPD. Additionally, in patient-derived xenograft models, TG was enhanced by treatment with anti–PD-1, but not by anti–PD-1 F(ab)2-fragments punctuating the importance of the Fc section to cause the growth phenomenon (47). Interestingly, when analyzing the data presented in phase III clinical trials comparing ICIs with other therapies, the overcrossing of survival curves in the first months is more prominent in anti–PD-1 agents (4, 7, 9–11), and to our knowledge has not been described so far in positive clinical trials with anti–PD-L1 agents (6, 8, 48, 49). A potential hypothesis to explain HPD in some patients could be the fact that lymphocytes marked with these antibodies could interact with the immune system and be destroyed, causing a deleterious effect. $IgG4_{(S228P)}$ could activate macrophages through its FcγRI and FcγRIIb, producing antibody-dependent cell-mediated phagocytosis. This is only a hypothesis and should be further investigated in prospective studies.

Our study has several limitations. It is a retrospective study in a single institution, although the data were collected prospectively for patients participating in phase I clinical trials. Both the investigational and control cohorts include a multitude of tumor types and different treatment regimens both as monotherapy and combination; this heterogeneity might potentially influence the survival results, despite multivariate analysis. Given the population were all phase I participants, the nature of the disease could be more aggressive than in other settings such as first- or second-line treatment. Most importantly, as discussed previously, capturing HPD by RECIST criteria may overestimate the phenomenon in specific cases with an aggressive intrinsic behavior, and underestimate it in patients with a rapid clinical deterioration not allowing confirmatory scans to be performed. However this definition can be used easily by oncologists in current practice, helping in the decision-making process of discontinuing a treatment with ICIs and looking for alternative treatments (50).

Conclusions

Our study is the first to evaluate how HPD with ICIs therapy can be captured based on RECIST criteria. Using a control arm with patients treated with TAs and an investigational arm with patients receiving ICIs, we show that the radiologic definition of HPD following both TGR criteria and RECIST criteria occurs in both cohorts. However, in our series, significant OS difference was observed exclusively with RECIST criteria in the ICI cohort. We proposed new criteria to capture HPD that is intuitive and easy to use in daily clinical practice. Importantly, it correlates with poor mOS and represents a contraindication for treatment beyond progression.

Disclosure of Potential Conflicts of Interest

I. Matos reports receiving other remuneration in the form of an ESMO Research Fellowship - Translational Focus, sponsored by Roche. J. Martin-Liberal reports receiving speakers bureau honoraria from Astellas, Bristol-Myers Squibb, MSD, Novartis, Pierre Fabre, Pfizer, and Roche, is an advisory board member/unpaid consultant for Bristol-Myers Squibb, Novartis, Pierre Fabre, and Roche, and reports receiving other remuneration from Bristol-Myers Squibb, MSD, Novartis, Pierre Fabre, Pfizer, Roche, and Ibsen. C. Hierro reports receiving commercial research grants from Bayer, reports receiving speakers bureau honoraria from Ignyta and Lilly, and reports receiving other remuneration from Amgen, Merck and Roche. M. Vieto is an advisory board member/unpaid consultant for Debiopharma and Roche. I. Brana is an employee/paid consultant for MSD, reports receiving commercial research grants from AstraZeneca, Bristol-Myers Squibb, Gliknik, GlaxoSmithKline, MSD, Novartis, Pfizer, Shattuck Labs and Roche, and reports receiving speakers bureau honoraria from Bristol-Myers Squibb, AstraZeneca, and Merck Serono. J. Ros reports receiving speakers bureau honoraria from Amgen and reports receiving other remuneration in the form of a travel grant from Amgen. G. Villacampa reports receiving speakers bureau honoraria from MSD. M. Oliveira is an employee/paid consultant for Roche, GlaxoSmithKline, PUMA Biotechnology, AstraZeneca, and reports receiving speakers bureau honoraria from Roche and Seattle Genetics. M. Alsina reports receiving speakers bureau honoraria from Lilly, BMS, MSD, and Servier. A. Oaknin reports receiving speakers bureau honoraria from Roche, AstraZeneca, PharmaMar, Clovis Oncology, Tesaro, and Immunogen. E. Felip is an employee/paid consultant for AbbVie, AstraZeneca, Bergenbio, Blueprint Medicines, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, Guardant Health, Janssen, Medscape, Merck KGaga, Merch Sharp & Dohme, Novartis, Pfizer, Prime Oncology, Roche, Samsung, Takeda and Touchtime, and reports receiving other commercial research support from Fundacion Merck Salud and a grant for oncology innovation EMD Serono. J. Rodon is an employee/paid consultant for Peptomyc, Merck Sharp Dome, Kelund Pharma, Spectrum Pharmaceuticals, Roche, Certera, Bayer, and reports receiving other commercial research support from Bayer. J. Tabernero is an employee/paid consultant for Array Biopharma, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Chugai, Genentech, Inc., GenMab A/S, Halozyme, Imugene Limited, Inflection Biosciences Limited, Ipsen, Kura Oncology, Lilly, MSD, Menarini, Merck Serono, Merrimack, Merus, Molecular Partners, Novartis, Peptomyc, Pfizer, Pharmacyclics, ProteoDesign SL, Rafael Pharmaceuticals, F. Hoffmann-La Roche Ltd, Sanofi, SeaGen, Seattle Genetics, Servier, Symphogen, Taiho, VCN Biosciences, Biocartis, Foundation Medicine, HalioDX SAS, and Roche Diagnostics. R. Dientsmann reports receiving speakers bureau honoraria from Roche, MSD, Servier, Boehringer Ingelheim, Ipsen, Amgen, and Sanofi. E. Garralda is an employee/paid consultant for Roche/Genentech, Ellipses Pharma, Boehringer Ingelheim, Janssen, AstraZeneca, Seattle Genetics, Alkermes, and Neomed Therapeutics1, reports receiving commercial research grants from Novartis and Roche, and reports receiving speakers bureau honoraria from Bristol-Myers Squibb, Merck, Roche, and Thermo Fisher. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: I. Matos, J. Martin-Liberal, C. Hierro, A. Azaro, M. Vieito, J. Ros, J. Tabernero, R. Dienstmann, E. Garralda

Development of methodology: I. Matos, J. Martin-Liberal, C. Hierro, J. Ros, E. Elez, J. Tabernero, R. Dienstmann, R. Perez-Lopez, E. Garralda

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): I. Matos, J. Martin-Liberal, A. García-Ruiz, C. Hierro, M.O. de Olza, A. Azaro, M. Vieito, I. Braña, G. Mur, J. Mateos, M. Oliveira, M. Alsina, E. Elez, A. Oaknin, E. Felip, J. Rodón, J. Tabernero, R. Dienstmann, R. Perez-Lopez, E. Garralda

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): I. Matos, J. Martin-Liberal, A. García-Ruiz, C. Hierro, C. Viaplana, M. Vieito, I. Braña, G. Mur, J. Ros, J. Mateos, G. Villacampa, J. Rodón, R. Dienstmann, R. Perez-Lopez, E. Garralda

Writing, review, and/or revision of the manuscript: I. Matos, J. Martin-Liberal, A. García-Ruiz, C. Hierro, M.O. de Olza, C. Viaplana, A. Azaro, M. Vieito, I. Braña, G. Mur, J. Ros, J. Mateos, G. Villacampa, R. Berché, M. Oliveira, M. Alsina, E. Elez, A. Oaknin, E. Muñoz-Couselo, J. Carles, E. Felip, J. Rodón, J. Tabernero, R. Dienstmann, R. Perez-Lopez, E. Garralda

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): I. Matos, J. Martin-Liberal, A. García-Ruiz, C. Hierro, M.O. de Olza, C. Viaplana, A. Azaro, M. Vieito, I. Braña, G. Mur, J. Ros, M. Oliveira, M. Alsina, E. Elez, A. Oaknin, E. Muñoz-Couselo, J. Carles, E. Felip, J. Rodón, J. Tabernero, R. Dienstmann, R. Perez-Lopez, E. Garralda

Study supervision: A. García-Ruiz, C. Hierro, J. Ros, A. Oaknin, J. Carles, R. Dienstmann, E. Garralda

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References

1. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.
2. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23–34.
3. Schachter J, Ribas A, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet 2017;390:1853–62.
4. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015;373:1627–39.
5. Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387:1540–50.
6. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389:255–65.
7. Hellmann MD, Ciuleanu TE, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med 2018;378:2093–104.
8. Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med 2018;378:2288–301.
9. Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 2016;375:1856–67.
10. Burtness B, Harrington KJ, Greil R, Soulières D, Tahara M, De Castro JG, et al. LBA8_PRKEYNOTE-048: phase III study of first-line pembrolizumab (P) for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). Ann Oncol 2018;29(suppl_8):mdy424.045.
11. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee J-L, Fong L, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017; 376:1015–26.
12. Powles T, Durán I, van der Heijden MS, Loriot Y, Vogelzang NJ, De Giorgi U, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet North Am Ed 2018;391: 748–57.
13. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1803–13.
14. Motzer RJ, Tannir NM, McDermott DF, Aren Frontera O, Melichar B, Choueiri TK, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018;378:1277–90.
15. Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol 2016;17:1374–85.
16. Chung HC, Schellens JHM, Delord J-P, Perets R, Italiano A, Shapira-Frommer R, et al. Pembrolizumab treatment of advanced cervical cancer: Updated results from the phase 2 KEYNOTE-158 study. J Clin Oncol 2018;36(15_suppl):5522.
17. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372: 2509–20.
18. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357:409–13.
19. Diaz L, Marabelle A, Kim TW, Geva R, Van Cutsem E, André T, et al. 386P efficacy of pembrolizumab in phase 2 KEYNOTE-164 and KEYNOTE-158 studies of microsatellite instability high cancers. Ann Oncol 2017;28 (suppl_5):mdx367.020.
20. Chiou VL, Burotto M. Pseudoprogression and immune-related response in solid tumors. J Clin Oncol 2015;33:3541–3.
21. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15:7412–20.
22. Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res 2013;19:3936–43.
23. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017;18:e143–e52.
24. Champiat S, Ferrara R, Massard C, Besse B, Marabelle A, Soria J-C, et al. Hyperprogressive disease: recognizing a novel pattern to improve patient management. Nat Rev Clin Oncol 2018;15:748–62.
25. Borcoman E, Kanjanapan Y, Champiat S, Kato S, Servois V, Kurzrock R, et al. Novel patterns of response under immunotherapy. Ann Oncol 2019;30:385–96.
26. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016;375:1823–33.
27. Champiat S, Dercle L, Ammari S, Massard C, Hollebecque A, Postel-Vinay S, et al. Hyperprogressive disease is a new pattern of progression in cancer patients treated by anti-PD-1/PD-L1. Clin Cancer Res 2017;23:1920–8.
28. Saada-Bouzid E, Defaucheux C, Karabajakian A, Coloma VP, Servois V, Paoletti X, et al. Hyperprogression during anti-PD-1/PD-L1 therapy in patients with recurrent and/or metastatic head and neck squamous cell carcinoma. Ann Oncol 2017;28:1605–11.
29. Ferrara R, Mezquita L, Texier M, Lahmar J, Audigier-Valette C, Tessonnier L, et al. Hyperprogressive disease in patients with advanced non–small cell lung cancer treated with PD-1/PD-L1 inhibitors or with single-agent chemotherapy. JAMA Oncol 2018;4:1543–52.

30. Kato S, Goodman A, Walavalkar V, Barkauskas DA, Sharabi A, Kurzrock R. Hyperprogressors after immunotherapy: analysis of genomic alterations associated with accelerated growth rate. Clin Cancer Res 2017;23:4242–50.
31. Ferte C, Fernandez M, Hollebecque A, Koscielny S, Levy A, Massard C, et al. Tumor growth rate is an early indicator of antitumor drug activity in phase I clinical trials. Clin Cancer Res 2014;20:246–52.
32. Long GV, Weber JS, Larkin J, Atkinson V, Grob JJ, Schadendorf D, et al. Nivolumab for patients with advanced melanoma treated beyond progression: analysis of 2 phase 3 clinical trials. JAMA Oncol 2017;3:1511–9.
33. Escudier B, Motzer RJ, Sharma P, Wagstaff J, Plimack ER, Hammers HJ, et al. Treatment beyond progression in patients with advanced renal cell carcinoma treated with nivolumab in CheckMate 025. Eur Urol 2017;72:368–76.
34. Mateo J, Chakravarty D, Dienstmann R, Jezdic S, Gonzalez-Perez A, Lopez-Bigas N, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). Ann Oncol 2018;29:1895–902.
35. Mezquita L, Auclin E, Ferrara R, Charrier M, Remon J, Planchard D, et al. Association of the lung immune prognostic index with immune checkpoint inhibitor outcomes in patients with advanced non-small cell lung cancer. JAMA Oncol 2018;4:351–7.
36. Rodriguez Freixinos V, Garcia A, Fasani R, Castellvi J, Ruiz-Pace F, Viaplana C, et al. Immune profile and outcomes of patients (pts) with gynecological malignancies (GYN) enrolled in early phases immunotherapy (IO) trials. J Clin Oncol 2018; 36(5_suppl):5595.
37. Suárez C, Morales-Barrera R, Garcia-Ruiz A, Gonzalez M, Ligero M, Valverde C, et al. Hyperprogressive disease in patients with metastatic genitourinary tumors treated with immune checkpoint inhibitors. J Clin Oncol 2019;37(7_suppl):448.
38. Ferte C, Koscielny S, Albiges L, Rocher L, Soria JC, Iacovelli R, et al. Tumor growth rate provides useful information to evaluate sorafenib and everolimus treatment in metastatic renal cell carcinoma patients: an integrated analysis of the TARGET and RECORD phase 3 trial data. Eur Urol 2014;65:713–20.
39. Patnaik A, Kang SP, Rasco D, Papadopoulos KP, Elassaiss-Schaap J, Beeram M, et al. Phase I study of pembrolizumab (MK-3475; anti-PD-1 monoclonal antibody) in patients with advanced solid tumors. Clin Cancer Res 2015;21:4286–93.
40. Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol 2010;28:3167–75.
41. Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 2014;515:563–7.
42. Fairman D, Narwal R, Liang M, Robbins PB, Schneider A, Chavez C, et al. Pharmacokinetics of MEDI4736, a fully human anti-PDL1 monoclonal antibody, in patients with advanced solid tumors. J Clin Oncol 2014;32(15_suppl):2602.
43. Osa A, Uenami T, Koyama S, Fujimoto K, Okuzaki D, Takimoto T, et al. Clinical implications of monitoring nivolumab immunokinetics in non-small cell lung cancer patients. JCI insight 2018;3:pii: 59125.
44. Scapin G, Yang X, Prosise WW, McCoy M, Reichert P, Johnston JM, et al. Structure of full-length human anti-PD1 therapeutic IgG4 antibody pembrolizumab. Nat Struct Mol Biol 2015;22:953–8.
45. Wang C, Thudium KB, Han M, Wang XT, Huang H, Feingersh D, et al. In vitro characterization of the anti-PD-1 antibody nivolumab, BMS-936558, and in vivo toxicology in non-human primates. Cancer Immunol Res 2014;2:846–56.
46. Zhang T, Song X, Xu L, Ma J, Zhang Y, Gong W, et al. The binding of an anti-PD-1 antibody to FcgammaRIota has a profound impact on its biological functions. Cancer Immunol Immunother 2018;67:1079–90.
47. Lo Russo G, Moro M, Sommariva M, Cancila V, Boeri M, Centonze G, et al. Antibody-Fc/FcR interaction on macrophages as a mechanism for hyperprogressive disease in non-small cell lung cancer subsequent to PD-1/PD-L1 blockade. Clin Cancer Res 2019;25:989–99.
48. Horn L, Mansfield AS, Szczesna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 2018;379:2220–9.
49. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med 2017;377:1919–29.
50. Frelaut M, Le Tourneau C, Borcoman E. Hyperprogression under immunotherapy. Int J Mol Sci 2019;20:2674.