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Radiological response to nivolumab in patients with hepatocellular carcinoma: A multicenter analysis of real-life practice

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ABSTRACT

Background and aims: Immune-checkpoint inhibitors are effective in many advanced tumors. However, there is scarce information regarding the radiological response to these agents in hepatocellular carcinoma outside clinical trials. We aimed to describe the radiological response in a retrospective cohort of hepatocellular carcinoma patients treated with nivolumab and to analyze the radiological evolution according to tumor response at first post-treatment radiological assessment.

Methods: We reviewed pre-treatment and post-treatment images (CT or MRI) obtained at different time-points in patients with hepatocellular carcinoma treated with nivolumab outside clinical trials at seven Spanish centers, assessing the response according to RECIST 1.1 and iRECIST and registering atypical responses. We also analyzed the imaging findings on subsequent assessments according to tumor status on the first posttreatment imaging assessment.

Results: From the 118 patients with hepatocellular carcinoma treated with nivolumab, we finally analyzed data from 31 patients (71 % Child-Pugh A; 74 % BCLC-C). Median follow-up was 8.39 months [IQR 5.00–10.92]; median overall survival was 12.82 months (95 %CI 10.92–34.79). According to RECIST 1.1, the objective response rate was 16 % and according to iRECIST, the objective response rate was 22.6 %. Findings at the first post-treatment assessment varied, showing stable disease in 44.8 % of patients; findings during follow-up also varied widely, including 4 hyperprogressions and 3 pseudoprogressions.

Conclusion: Imaging findings during nivolumab treatment are heterogeneous between and within patients. Progression of disease does not always signify treatment failure, and surrogate end-points may not reflect

Abbreviations: ICIs, immune-checkpoint inhibitors; HCC, hepatocellular carcinoma; FRA, first radiological assessment; BCLC, Barcelona Clinic Liver Cancer; CT, computed tomography; MR, magnetic resonance; RECIST, Response Evaluation Criteria in Solid Tumor; iRECIST, immune Response Evaluation Criteria in Solid Tumor; AASLD, American Association for the Study of Liver Diseases; IQR, interquartile range; HR, hazard ratio; BOR, best overall response; OR, objective response.

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survival outcomes, making the management of hepatocellular carcinoma patients under immunotherapy challenging.

1. Introduction

Immunotherapy has emerged as an effective treatment option for a variety of cancer types. Immune-checkpoint inhibitors block the programmed death cell protein-1 (PD-1)/PD-L1 pathway, stimulating T-cell-mediated cytotoxicity and provoking an immune response against tumor cells. [1] Immunotherapy is promising in patients with hepatocellular carcinoma (HCC) because their livers overexpress the PD-1/PD-L1 complex and immune-suppressive molecules; moreover, HCC nearly always develops in the context of underlying chronic liver disease and chronic inflammation [2].

Phase III trials aimed at capturing overall survival failed to confirm immune-checkpoint inhibitors' superiority versus sorafenib as first-line monotherapy or versus placebo in sorafenib-experienced patients. [3,4] Recently, combination strategies yielded positive results in a phase III trial testing atezolizumab plus bevacizumab [5]. On the other hand, the anti-PD-1 agents nivolumab and pembrolizumab have shown encouraging results in phase I/II studies in HCC. Durable response rates of around 15%–20% led to approval of both drugs by regulatory agencies for sorafenib-experienced patients [6–8]. Earlier-phase trials also reported encouraging results for pembrolizumab plus lenvatinib [9] and nivolumab plus ipilimumab [10]. Consequently, immune-checkpoint inhibitors are being increasingly adopted in the management of HCC.

The response to PD-1 blockade is not well understood. The complex interplay between immune elements from the periphery of the tumor and elements from within the tumor results in atypical patterns on imaging. [11] The Response Evaluation Criteria in Solid Tumor (RECIST) [12] used to assess treatment response in clinical trials has severe shortcomings in assessing the response to immune-checkpoint inhibitors. For example, in some HCC patients who reap clinical benefits including increased survival on nivolumab, RECIST 1.1 criteria mistakenly classify findings as progression [13].

Beyond clinical trials, clinical imaging experience may provide insights into the response dynamics and patterns of progression in patients with HCC treated with immune-checkpoint inhibitors. These data may help clarify the mechanisms that mediate the immune response and provide complementary information to guide decisions in clinical practice. For these reasons, we analyzed the imaging findings over time and outcomes in a real-life cohort of HCC patients treated with nivolumab.

2. Patients and methods

2.1. Study design and patients

For this retrospective observational study, we surveyed Spanish hospitals with multidisciplinary teams dedicated to managing HCC to identify patients with histologically or radiologically confirmed HCC treated with nivolumab monotherapy outside clinical trials between June 1, 2016 and February 28, 2019.

We included patients diagnosed with HCC (by pathology or noninvasive criteria according to AASLD guidelines [14]) who were not candidates for resection, transplantation, or ablation; who had failed/recurred after loco regional treatment; who were treated with nivolumab monotherapy (but not in the context of a clinical trial); and who underwent pre- and post-treatment scans and periodic imaging and clinical follow-up until death or the end of the study.

2.2. Treatment and assessments

The decision to treat patients with nivolumab was made by multidisciplinary tumor boards at each institution. Nivolumab was infused intravenously at a dose of 240 mg every 2 weeks or 3 mg/kg every 2 weeks according to local protocols. Treating physicians determined the periodicity of clinical and imaging assessments, imaging modality (computed-tomography [CT] and/or magnetic resonance imaging [MRI]), infusion schedule, treatment delay, discontinuation, and supportive treatment for adverse events.

2.3. Data collection

We analyzed baseline clinical characteristics, radiological evaluation based on image interpretation at different timepoints, dermatologic adverse events during the treatment and the clinical outcomes at the last available assessment. All data were collected by local investigators and compiled by the central study coordinators. A single radiologist with 14 years' experience in HCC (JR) independently reviewed imaging studies, recording the number of lesions, size at each timepoint, and response evaluation.

2.4. Scan characteristics

All CT or liver MRI studies were collected from medical records by local investigators and then centrally reviewed. To be eligible for inclusion, CT or MRI studies had to include multiphase post-contrast injection acquisition including at least arterial and portal venous phase acquisitions obtained 35–40 s and 70–80 s after initiation of contrast medium injection, respectively.

2.5. Radiological criteria for baseline assessment and tumor response

On baseline scans, HCC lesions were classified as target or non-target lesions based on size and suitability for repeated accurate measurement. Target lesions had to measure ≥1 cm at the largest diameter; non-target lesions could be smaller. Non-hepatic lesions could be considered target lesions. Lymph nodes detected at the hepatic hilium were considered malignant if the shortest diameter measured ≥2 cm.

Portal or hepatic vein thrombosis was considered malignant if confirmed at biopsy and/or by arterial enhancement on CT, MRI, or contrast-enhanced ultrasound, and/or if it expanded the diameter of the portal or hepatic vein and had a close relation with HCC in the liver parenchyma. [15]

Following the recommendations in RECIST 1.1, we selected a maximum of two target lesions per organ and five target lesions in total. To be considered a new HCC, newly detected lesions had to measure ≥10 mm in the longest diameter and show arterial hypervascularization.

After each cycle of treatment, the tumor response was categorized as progressive disease, stable disease, partial response, or complete response according to the standard definitions in both RECIST 1.1 and iRECIST. [12,16] In addition, to detect significant changes in tumor burden at the first posttreatment imaging assessment beyond the standard definition in RECIST 1.1, we also analyzed changes ≥ 10 % compared to pretreatment measurements.

We also recorded atypical patterns of response and progression, including pseudoprogression, hyperprogression, and dissociated responses. Pseudoprogression was defined as an increase in tumor burden ≥20 % and/or presence of a new lesion that was not confirmed at the following radiologic assessment. [16–18] Hyperprogression was defined as an increase in tumor burden ≥40 %, or ≥20 % together with presence of new lesions at first posttreatment assessment. [19] Dissociated response was defined as a heterogeneous response in which some lesions improved and others worsened.

2.6. Ethical aspects

The study was performed in accordance with the good clinical practice guidelines of the European Medicines Agency. Patient data were recorded, stored, and analyzed in accordance with confidentiality regulations (EU 2016/679). The local ethics committee approved the study (identifier HCB/2018/1125) and waived the need for informed consent given its retrospective nature.

2.7. Statistical analysis

Continuous variables are reported as medians and interquartile ranges. Categorical variables are reported as absolute frequencies and percentages. Time-to-event variables were analyzed using the Kaplan-Meier method and are reported as medians and their 95 % confidence interval (95 %CI). To analyze the risk of death, we used time-dependent Cox regression models to estimate hazard ratios (HR) and their corresponding 95 %CI.

All tests were two-sided, and significance was set at 5%. Analyses were performed with SAS software version 9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Patients

Of the 10 centers contacted, 7 had a total of 118 HCC patients treated with nivolumab; of these, 31 [median age, 65.5 [58–71] years; 23 (74.2 %) male] fulfilled the inclusion criteria (Fig. 1). All 31 patients had pretreatment scans available. All scans had optimal image quality to be interpreted centrally and included pre-contrast phase and post-contrast arterial and venous portal phase. Delayed venous phase was also included in all but two CT scans. Table 1 summarizes the baseline characteristics of the 31 patients included. The predominant etiologies of HCC were chronic hepatitis C (64.5 %) and hepatitis B (6.5 %) infection. Barcelona Clinic Liver Cancer (BCLC) stage was C in 74 % and B in 26 %. Child-Pugh classification was A in 22 (71 %) and B in 6 (19.4 %); 3 (9.7 %) patients had no underlying cirrhosis. Nivolumab was administered as the first-line systemic treatment in 7 (22.6 %) patients, as the second-line treatment in 13 (41.9 %), and as the third-line treatment in 11 (35.5 %). Measurable lesions were present on pretreatment imaging assessments in 30 patients; 29 of these underwent the first posttreatment imaging assessment within 2 months after nivolumab initiation, and two patients died before the first radiological assessment.

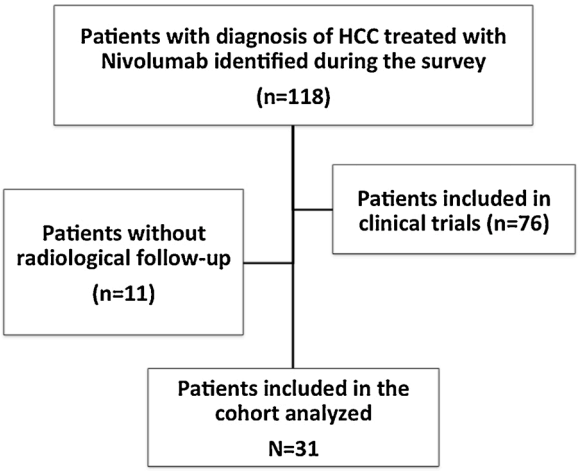

Fig. 1. Flowchart of the study.

Table 1
Clinical characteristics of patients included in the study.

Patients, (n = 31)	
Age (Years), median [IQR]	65.5 [58–71]
Gender (Male), n (%)	23 (74.2)
BCLC stage (C), n (%)	23 (74)
ECOG-PS (0–1), n (%)	9 (29)
Child-Pugh (B), n (%)	6 (19.4)
Etiology, n (%)	
- HCV	20 (64.5)
- HBV	2 (6.5)
- NASH	2 (6.5)
- Non-cirrhotic	3 (9.6)
- Others	4 (12.9)
Duration on nivolumab (months), median [IQR]	5.55 [2.9–8]
Follow-up (months), median [IQR]	8.39 [5–10.9]
Dosage, n (%)	
- 240 mg / 2 weeks	21 (67.7)
- 3 mg/kg / 2 weeks	10 (32.3)
First-line treatment, n (%)	
Nivolumab	7 (22.6)
Sorafenib	24 (77.4)
Second-line treatment, n (%)	
- NA	8 (25.8)
- Trial	1 (3.2)
- Nivolumab	13 (41.9)
- Regorafenib	9 (29)
DAE60 on first- or second-line (Yes), n (%)	14 (45.2)
Aspartate aminotransferase IU/L, median [IQR]	61 [39–98]
Alanine aminotransferase IU/L, median [IQR]	39 [32–58]
Alkaline Phosphatase IU/L, median [IQR]	137 [94–197]
Hemoglobin g/L, median [IQR]	13.4 [11.9–14.6]
Albumin g/L, median [IQR]	3.9 [3.5–4.1]

BCLC: Barcelona Clinic Liver Cancer; DAE60: dermatologic adverse events within 60 days; ECOG-PS: Eastern Cooperative Oncology Group performance status; HBV: hepatitis B virus; HCV: hepatitis C virus; NASH: non-alcoholic fatty liver disease; NA: not applicable.

3.2. Tumor burden evolution

After the first posttreatment imaging assessment (n = 29), the tumor burden assessed by RECIST 1.1 and by iRECIST (Fig. 2) changed heterogeneously over time.

Table 2 shows the changes in tumor burden over time. Tumor burden had increased ≥ 10 % at the first post-treatment imaging assessment compared to the pre-treatment measurement in 9 (31 %) patients; in 4 of these, tumor burden decreased in subsequent assessments. Tumor burden had decreased ≥ 10 % at first post-treatment imaging assessment compared to the pretreatment measurement in 7 (24.1 %) patients; the decrease was also seen in the following assessment, although within the first two treatment cycles, 2 of these patients died due to disease progression and 3 other patients developed new lesions. Tumor burden changed < 10 % between the pretreatment assessment and first post-treatment imaging assessment in the remaining 13 (44.8 %) patients; in subsequent assessments, tumor burden decreased in 4 of these and increased in 9.

3.3. Best overall response according to RECIST 1.1 and iRECIST

According to RECIST 1.1 criteria, the best overall response was classified as stable disease in 13 (42 %) patients and as an objective response in 5 (16 %) patients. According to iRECIST criteria, the best overall response was classified as an objective response in 7 (22.6 %) patients, including the 5 patients identified by RECIST 1.1 and 2 patients in whom the first post-treatment imaging assessment found unconfirmed progression of disease (iUPD) that was followed by subsequent partial response (iPR) and was therefore not confirmed according to iRECIST rules. [16] The best objective response was classified as progression of disease in 8 (26 %) patients according to RECIST 1.1 criteria and in 7 (22.6 %) according to iRECIST criteria.

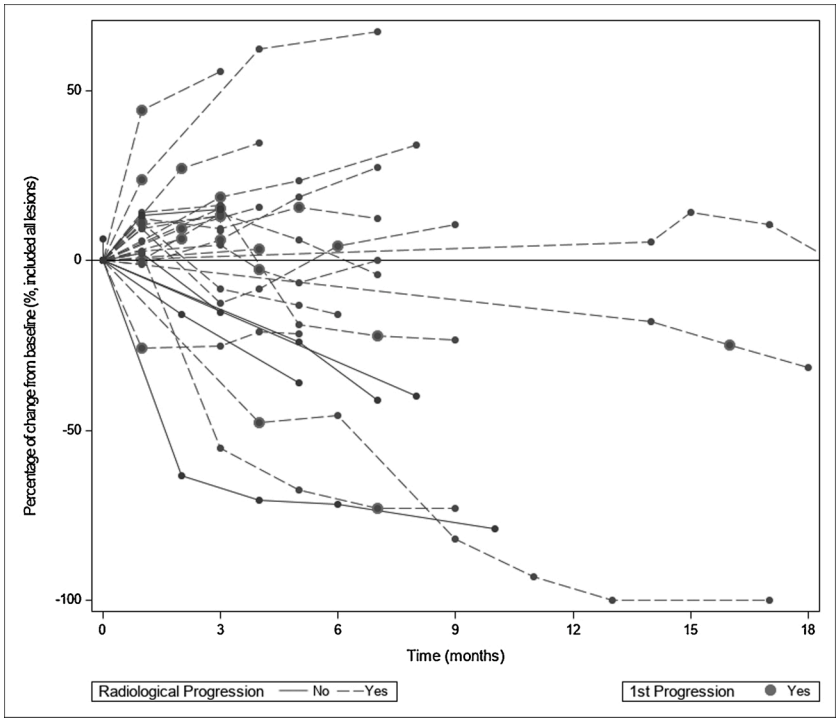

Fig. 2. Spider plot showing the radiologic evolution of tumor burden in patients with measurable lesions (n = 30).

3.4. Patterns of response and progression

During follow-up, progression of disease according to RECIST 1.1 criteria was seen in 21 patients (increase in size of target lesions in 10 (48 %), presence of new lesions in 9 (43 %), and both increased size of target lesions and new lesions in 2 (9%)). Median time to progression according to RECIST 1.1 was 3.68 (95 %CI: 2.3–6.87) months.

Of the 21 patients classified as having progression of disease according to RECIST 1.1, 16 were classified as having progression according to iRECIST; the reasons that progression was not confirmed in the remaining 5 patients was the absence of imaging follow-up after an initial unconfirmed progression of disease in 4 and death in 1. According to iRECIST, the objective response rate was 22.6 % and the median time-to-progression was 3.68 months (95 %CI 2.53–6.87).

Hyperprogression was observed in 4 (12.9 %) patients, all of whom had high tumor burden (burden 76−159 mm; 6–15 measurable lesions per patient) before treatment initiation. Pseudoprogression was observed in 3 (9.96 %) patients: one at the first posttreatment imaging assessment (Fig. 3) and the other two at the second posttreatment imaging assessment. Only one patient with pseudoprogression achieved a complete response (Fig. 4). Dissociated responses were observed in 8 (25.8 %) patients; in two of these, the dissociated response occurred where most lesions eventually decreased in size, but a few others showed a persistent increase in size.

3.5. Patient outcomes

During imaging follow-up, 11 (35.5 %) patients died due to tumor progression (Table 3). Among the 17 patients who continued follow-up after the first radiological progression according to RECIST 1.1, 11 (65 %) had a second radiological progression, including an increase in the size of target lesions >20 % alone (n = 4), an increase in the size of target lesions >20 % together with the detection of new lesions (at any location) (n = 3), detection of new hepatic lesions (n = 3), or vascular invasion (n = 1). The median time between the two progressions was 2.37 [2.07–3.32] months.

Overall survival was 12.8 months (95 %CI: 10.9–34.8 months).

Time-dependent Cox regression showed no differences in the risk of death according to radiological response as determined by RECIST 1.1 criteria (HR 0.62 [95 %CI 0.17–2.21]) or as determined by iRECIST criteria (HR 0.56 [95 %CI 0.16–2.04]).

4. Discussion

The response rate in this multicenter cohort of patients with HCC treated with nivolumab outside the context of clinical trials was similar to those published in prospective trials of check-point inhibitors in HCC. [6,7] Our study shows that the patterns of response and progression to nivolumab varied greatly, with some patients presenting hyperprogression, others pseudoprogression, and others heterogeneous patterns of progressive disease in which some lesions shrank while others grew. The heterogeneous response of the tumor over time indicates that the initial assessment of the effectiveness of treatment cannot be considered reliable.

In both clinical practice and research trials, the response to treatment is usually evaluated using conventional criteria such as RECIST 1.1, where the observation of progression or the absence of a response is interpreted as the absence of activity or treatment failure, calling for the discontinuation of treatment. Several research consortia and investigators have raised concerns about the validity of using these criteria to evaluate the response to check-point inhibitors. [20] RECIST 1.1 criteria were initially intended to assess the response immediately after chemotherapy or radiation therapy, and these criteria do not take into account events during follow-up.

Improving overall survival is the main objective in treating advanced HCC, but there is not enough evidence to support using time to progression or even progression-free survival as surrogates of overall survival in patients with HCC treated with immune-checkpoint inhibitors [20,21]; indeed, several trials found no relationship between the radiological response and overall survival [20,22,4]. Interpreting the response to immune-oncology agents is further complicated by the appearance of immune-specific responses, in particular pseudoprogression. For this reason, the RECIST working group developed iRECIST, which differs from RECIST 1.1. mainly in that it requires confirmation of

Table 2
Changes in target lesion tumor burden over time.

						Radiological assessments									
						1st		2nd		3rd		4th		5th	
Median [IQR], weeks						5 [4,5,6,7,8,9,10]		13 [12,13,14,15,16,17]		22 [20–32]		30 [28–34]		39 [39–58]	
ID	Number of intra-hepatic lesions	Number of extra-hepatic lesions	Location of extra-hepatic lesions	Total TL size (mm)	Up to 10 lesions size (mm)	TL (% change from baseline)	Up to 10 lesions (% change from baseline)	TL (% change from baseline)	Up to 10 lesions (% change from baseline)	TL (% change from baseline)	Up to 10 lesions (% change from baseline)	TL (% change from baseline)	Up to 10 lesions (% change from baseline)	TL (% change from baseline)	Up to 10 lesions (% change from baseline)
1	2	1	Lymph nodes	71	71	−63.38	−63.38	−70.42	−70.42	−71.83	−71.83	−78.87	−78.87		
2	2	2	Peritoneum	50	50	0	0	14	14	6	6	−4	−4		
3	5	0		94	154	15.96	14.29	14.89	16.23	−24.47	−18.83	−22.34	−22.08	−30.85	−23.38
4	2	3	Lung / Suprahepatic veins	122	122	6.56	6.56								
5	4	0		151	151	9.27	9.27	13.25	13.25						
6	≥5	0		42	76	14.29	10.53	14.29	13.16						
7	2	0		92	92	2.17	2.17	−15.22	−15.22						
8	4	0		83	110	−2.41	2.73	−14.46	4.55	−21.69	−2.73	−26.51	−6.36	−31.33	0
9	1	≥5	Lymph nodes / Bones	84	143	−9.52	−25.87	−10.71	−25.17	−2.38	−20.98	0	−21.68		
10	≥5	2	Peritoneum	53	80	0	−1.25	11.32	6.25	28.3	18.75	28.3	27.5		
11	3	1	Bones	135	159	8.15	9.43	−17.78	−12.58	−15.56	−8.18	−6.67	4.4	−12.59	10.69
12	≥5	1	Bones	207	280	17.87	15.36	8.7	8.93						
13	0	3	Peritoneum	24	32	16.67	12.5	16.67	9.38	20.83	15.63	16.67	12.5		
14	3	2	Lung / Suprahepatic veins	89	107	6.74	11.21	−23.6	−8.41	−33.71	−13.08	−37.08	−15.89		
15	4	2	Kidney / Peritoneum	152	186	9.87	13.44	9.21	15.05						
16	4	0		70	89	2.86	2.25	−42.86	−55.06	−58.57	−67.42	−65.71	−73.03	−65.71	−73.03
17	≥5	≥5	Lymph nodes / Portal Vein / Bones	200	314	−23	−17.83	−31	−24.84	−38.5	−31.53				
18	≥5	0		152	250	−26.32	−24	−43.42	−41.2						
19	2	1		56	56	5.36	5.36	14.29	14.29	10.71	10.71	−8.93	−8.93	−30.36	−30.36
20	0	4	Lymph nodes	56	85	8.93	5.88	23.21	18.82	30.36	23.53				
21*	2	0		67	67										
22	0	≥5	Lymph nodes	71	140	38.03	44.29	49.3	55.71						
23	≥5	0		77	159	22.08	27.04	49.35	34.59						
24	4	0		46	46	6.52	6.52								
25	≥5	2	Lymph nodes / Peritoneum	93	135	24.73	23.7	53.76	62.22	87.1	67.41				
26	≥5	0		34	44	−50	−47.73	−50	−45.45	−76.47	−81.82	−91.18	−93.18	−100	−100
27	≥5	5	Lymph nodes / Lungs	103	184	−18.45	−15.76	−38.83	−35.87						
28	≥5	4	Lymph nodes / Bones	168	215	−7.74	3.26								
29	1	≥5	Pancreas/ Lymph nodes / Lung	175	222	7.43	9.46	14.29	15.77						
30	≥5	0		144	208										
31	3	1	Peritoneum	55	70	−36.36	−40								

TL: Target lesion.
* Subject 21 died before the first radiological assessment.

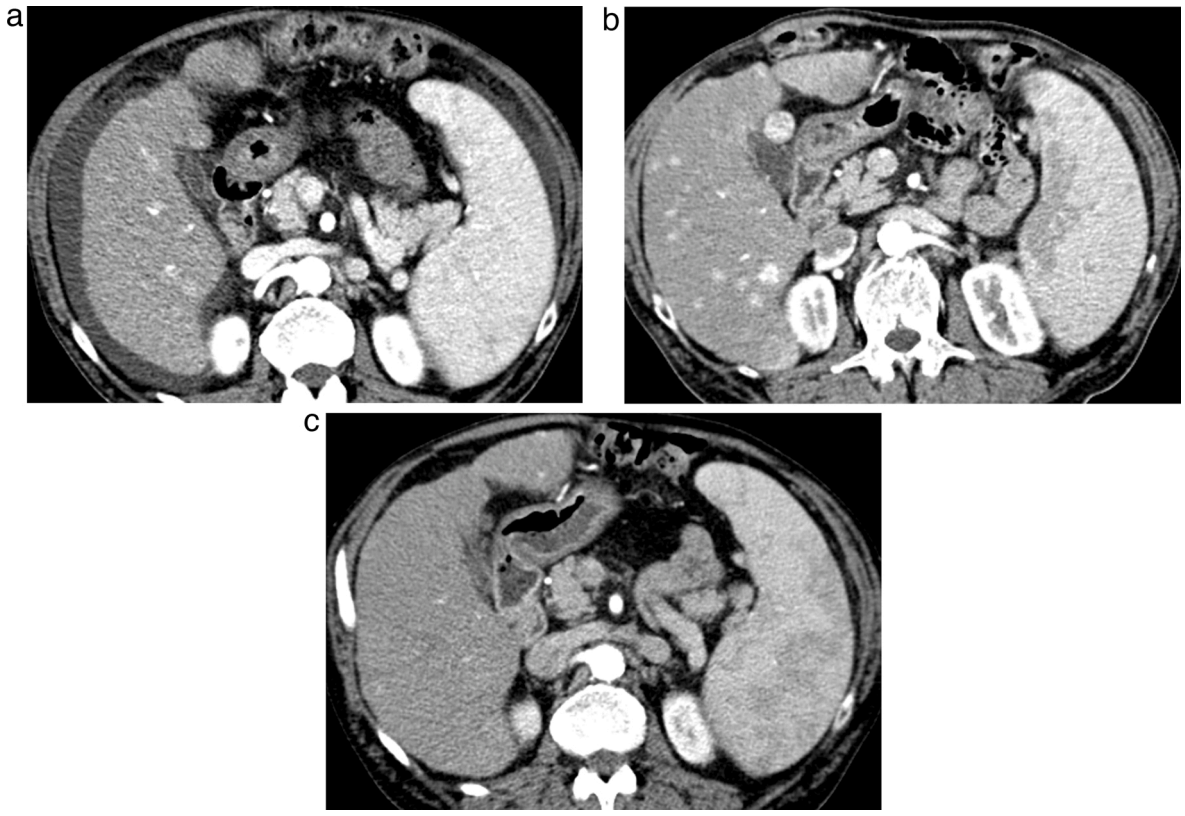

Fig. 3. Pseudoprogression in a 51-year old man with multifocal hepatocellular carcinoma. (A) Pretreatment arterial-phase liver CT scan shows multiple tiny hypervascular nodules scattered throughout the right hepatic lobe and segment IV, corresponding to multifocal hepatocellular carcinoma. (B) At the first imaging assessment after initiation of nivolumab treatment, the number and size of the lesions had increased. (C) CT 4-weeks afterwards shows the number and size of hepatic lesions had decreased.

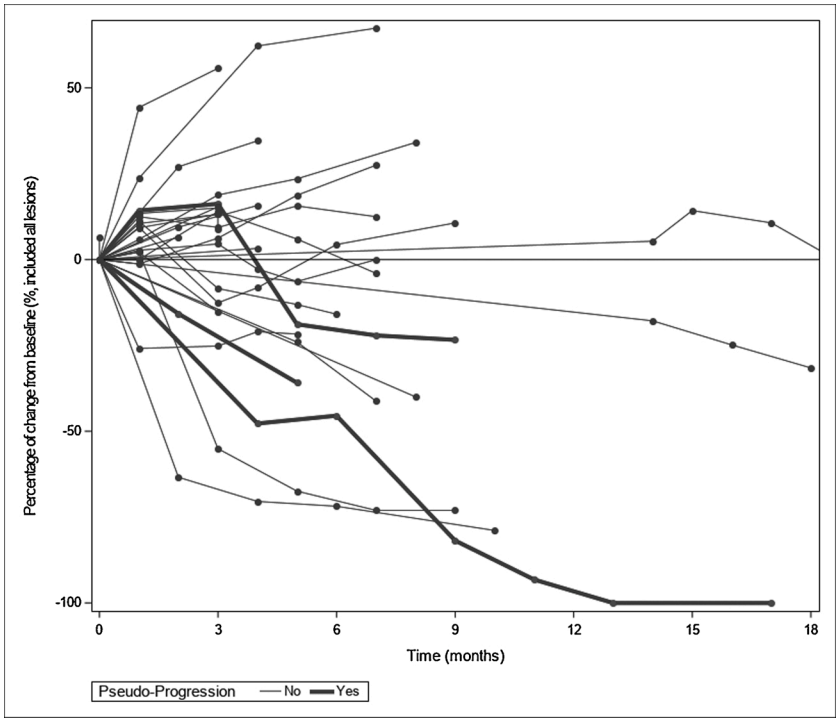

Fig. 4. Spider plot showing the evolution of radiologic tumor burden in patients who presented pseudoprogression (bold lines).

Table 3
Evolution of patients under nivolumab.

	Patients at risk	Events	Time (95 %CI)
TTP (months), median (95 %CI)	31	21	3.68 (2.30–6.87)
Time between first and second progression (months), median [IQR]		11	2.37 [2.07–3.32]

* Missing information for 1 patient.
TTP: time-to-progression according to RECIST 1.1.

progression after it is initially detected [16].

Given this scenario of uncertainty, we decided that it could be worth analyzing the imaging findings in patients treated with nivolumab outside clinical trials in Spanish centers with expertise in liver cancer management using the different criteria that are currently used in research. In that sense, while in most trials treatment is interrupted upon progression registration, this is not the case in clinical practice. Thereby, treatment may be maintained beyond progression if it is felt that the patient still enjoys benefits from treatment. According to RECIST 1.1, the response rate was 16 %; according to iRECIST, the response rate was 22.6 %. This is due to the fact that 2 of the 7 patients classified as having an objective response according to iRECIST did not meet the RECIST 1.1 response criteria. Three patients had pseudoprogression according to iRECIST, and two of these went on to show a sustained partial or complete response. The third patient went on to show progression again (new lesions and increased size of some persisting lesions) one cycle after the initial findings were classified as pseudoprogression. Thus, although pseudoprogression is uncommon, each radiological progression in HCC patients under immune-checkpoint inhibitors must be confirmed before deciding to discontinue treatment.

Another important finding of our analysis is that three patients showed hyperprogression after starting treatment with nivolumab. All three of these patients had a massive tumor burden involving different anatomical regions. These findings contradict those summarized in a recent review, which found that tumor burden was not associated with hyperprogression. [23] The concept of hyperprogression remains controversial, mainly due to the lack of controlled data to clarify whether rapid progression represents the natural history of tumor growth or acceleration of tumor kinetics induced by immune-checkpoint inhibitors. [23] Because we had no information about the pretreatment growth rate, our definition of hyperprogression was based on the available baseline and on-treatment imaging; nevertheless, the rapid and intense progression of disease in these 3 patients supports the hypothesis that hyperprogression is among the causes of early clinical deterioration, mainly in patients with high-volume disease at baseline.

We analyzed the behavior of each target lesion along the course of treatment separately, classifying the imaging response to nivolumab as dissociated in 8 patients. Interestingly, in 2 of these patients, the dissociated response occurred in the setting of pseudoprogression (Fig. 5), where we observed that the response after the initial pseudoprogression can be mixed, with most lesions decreasing in size or vanishing altogether, but with others persisting and eventually increasing in size. This observation suggests that the anti-tumor activity of immune cells may depend on local factors that can differ between tumors in the same individual. HCCs are heterogeneous on many different levels, [24] and our findings are in line with those from other studies in patients with lung cancer and mismatch-repair deficiency that described variable responses in different organ sites. [25]

Our study has some limitations. Our sample was small, in part

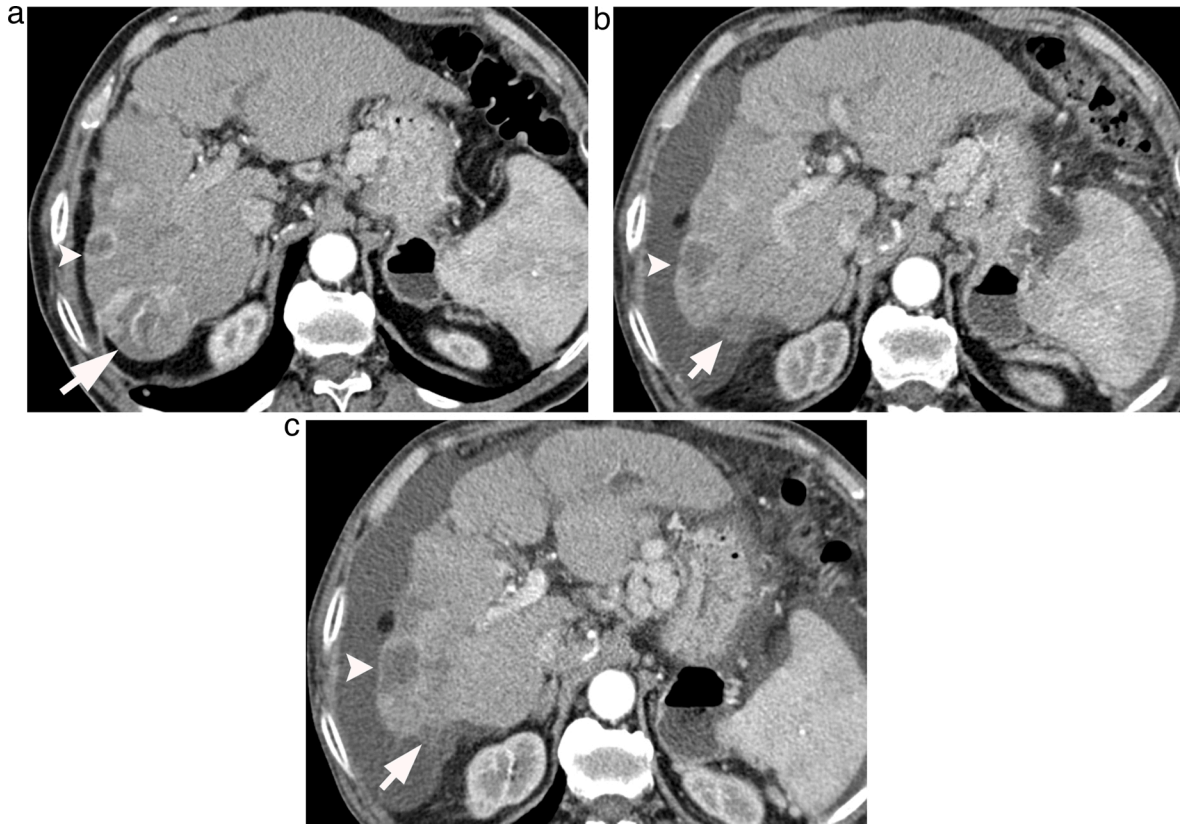

Fig. 5. A 62-year old male with multifocal HCC. Figure A corresponds to the arterial phase pre-treatment liver CT scan and shows two hypervascular nodules on the right hepatic lobe of different size (arrow and arrowhead). At 2nd cycle after treatment initiation with Nivolumab (Figure B), there was an increase in size of the smaller lesion (arrowhead) whereas the biggest lesion showed poor enhancement associated to a reduction of size. This dissociate response between two different lesions was also observed on the next radiologic assessment (Figure C).

because nivolumab is a relatively recent treatment option for advanced HCC and many patients (73 % of potential candidates) with advanced HCC treated with nivolumab were excluded because were enrolled in clinical trials. A larger sample might have allowed us to identify other radiological variables associated with clinically relevant outcomes. However, this study reflects the real – world clinical practice where different tumor boards decided the treatment of patients. The real-world clinical practice data is always associated to heterogeneous population. As said, the small sample size did not allow us to identify radiological predictors of OS, but we provide the proof of concept needed to prime larger investigations to delineate the imaging findings to be taken into account to properly interpret the imaging findings registered in patients under immune-oncology treatments. This should be seen as key to provide optimal care and avoid treatment interruptions that may not adequately serve the patients. Furthermore, our data should help understanding why central reading in research trials may not be concordant with the interpretation of the local investigators. At the end, the overall results may be coincidental [26] but in individual cases or small size trials, such discrepancies may become a major issue.

We acknowledge that this was a retrospective study, so that patients had received different treatments for advanced HCC before nivolumab and underwent radiological assessments at different timepoints depending on clinical symptoms and/or radiological evolution based on local interpretation. However, this approach reflects real-life clinical practice and does not impair the core of our findings about the existence of dissociate response under nivolumab.

In summary, our study underlines the heterogeneity of the patterns of response and progression in patients with HCC being treated with nivolumab, dispelling the myth that progression means treatment failure. This heterogeneity can lead to misinterpretation of results based on surrogate endpoints. The information provided by real-life studies such as ours can help clinicians decide when to declare treatment failure and can also help researchers refine the use of tumor-centered endpoints in the design of clinical trials.

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CRediT authorship contribution statement

Jordi Rimola: Conceptualization, Data curation, Investigation, Methodology, Resources, Supervision, Validation, Writing - original draft, Writing - review & editing. **Leonardo G. Da Fonseca**: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing - original draft, Writing - review & editing. **Víctor Sapena**: Formal analysis. **Christie Perelló**: Resources, Investigation. **Antonio Guerrero**: Resources, Investigation. **Maria Torner Simó**: Resources, Investigation. **Monica Pons**: Resources, Investigation. **Manuel De La Torre-Aláez**: Resources, Investigation. **Laura Márquez**: Resources, Investigation. **José Luis Calleja**: Resources, Investigation. **José Luis Lledó**: Resources, Investigation, Writing - review & editing. **Maria Varela**: Resources, Investigation. **Beatriz Mínguez**: Resources, Investigation. **Bruno Sangro**: Resources, Investigation, Writing - review & editing. **Ana Matilla**: Resources, Investigation. **Ferran Torres**: formal analysis, supervision. **Carmen Ayuso**: study design, supervision. **Jordi Bruix**: conceptualization, review & editing, supervision. **Maria Reig**: Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing - original draft, Writing - review & editing

Declaration of Competing Interest

J. Rimola Conflict with: Bayer, Roche; L. Da Fonseca Conflict with: Bayer, Ipsen; V. Sapena Conflict with: Bayer; C. Perelló: lecture fees from Bayer; A. Guerrero: None Declared; M. Torner Simó: None Declared; M. Pons: None Declared; M. De La Torre Conflict with: Bayer; L. Márquez Conflict with: Bayer, Gilead, Abbvie; J. L. Calleja Conflict with: Gilead science, Abbvie, MSD; J. L. Lledó Conflict with: Bayer; M. Varela Conflict with Gilead, Bristol-Myers-Squibb, SIRTEX, Bayer, IPSEN, Roche and BTG-Boston; B. Mínguez Conflict with: Bayer, Gilead; B. Sangro Conflict with: Terumo, Adapt immune, Astra-Zeneca, Bayer, BMS, BTG, Eisai, Eli Lilly, Ipsen, Onxeo, Roche, Sirtex, Novartis; A. Matilla Conflict with: Bayer; F. Torres: None Declared; C. Ayuso: None Declared; J. Bruix Conflict with: Bayer, BTG- Biocompatibles, Eisai, Terumo, Sirtex, Ipsen, Arqule, Novartis, BMS, Kowa, Gilead, Bio-Alliance, Roche, AbbVie, Merck, Astra-Medimmune, Incyte, Quirem, Adaptimmune, Lilly; M. Reig Conflict with: Bayer, BMS, Gilead, Roche, Ipsen, AstraZeneca and Lilly.

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