Complete Response Under Sorafenib in Patients With Hepatocellular Carcinoma: Relationship With Dermatologic Adverse Events

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The clinical benefit of sorafenib in patients with hepatocellular carcinoma (HCC) has been undervalued due to the absence of complete responses, even though patients who develop early dermatologic reactions have shown to have a positive outcome. In addition, sorafenib is described as an antiangiogenic drug, but it also acts on immunological cells. Thus, the goal of this study was to assess the complete response rate in a retrospective cohort of HCC patients treated with sorafenib and to describe the profile of the patients who achieve complete response for identifying factors related to this event and their connection with the immunological profile of sorafenib. Ten Spanish centers submitted cases of complete response under sorafenib. The baseline characteristics, development of early dermatologic reactions, and cause of treatment discontinuation were annotated. Radiological images taken before starting sorafenib, at first control, after starting sorafenib, at the time of complete response, and at least 1 month after treatment were centrally reviewed. Of the 1119 patients studied, 20 had been classified as complete responders by the centers, but eight of these patients were excluded after central review. Ten patients had complete disappearance of all tumor sites, and two had just a small residual fibrotic scar. Thus, 12 patients were classified as complete responders (58% HCV, median age 59.7 years, 83.4% Child-Pugh class A, Eastern Cooperative Oncology Group performance status 0 91.7%, and Barcelona Clinic Liver Cancer stage C 83.3%). The median overall survival and treatment duration were 85.8 and 40.1 months, respectively. All but one patient developed early dermatologic reactions, and seven patients discontinued sorafenib after achieving complete response due to adverse events, patient decision, or liver decompensation.

Conclusion: Complete response affects 1% of patients with HCC who are treated with sorafenib. The association of complete response with early dermatologic reactions supports the role of a specific immune/inflammatory patient profile in the improved response to sorafenib. (HEPATOLOGY 2018;67:612-622)

Sorafenib is the first-line systemic treatment for patients who are diagnosed with hepatocellular carcinoma (HCC). Patients who develop early dermatologic adverse events (eDAEs) defined as dermatological adverse events developed within the first 60 days after starting sorafenib and need sorafenib dose modification due to this reason present better overall survival than patients who start sorafenib but do not develop these reactions (18.2 months versus 10.1 months, respectively).1,2 This association can be explained by the biological link between hypoxia (which could be enhanced by sorafenib) and
inflammation. Thus, even though sorafenib is presented as an antiangiogenic and antiproliferative drug, the exact mechanism of action is unknown.

Sorafenib has proven to be effective in patients who may not benefit from options of higher priority such as surgery, ablation, or transarterial chemoembolization. However, the clinical benefit of sorafenib treatment for HCC patients is frequently undervalued because the rate of objective response according to conventional criteria is low, both in pivotal trials and cohort investigations. By contrast, interventions that reduce tumor burden through resection or induction of tumor necrosis (ablation, chemoembolization, radioembolization) offer such results, although they may not offer better survival or may even provide a shorter life expectancy according to published data.

Interestingly, during the last 9 years, several clinical cases and case series of HCC patients have described objective responses under sorafenib as well as complete response (CR). These are described in Table 1, but the response criteria used to evaluate the patients in those publications is heterogeneous (Response Evaluation Criteria in Solid Tumors [RECIST] 1.0, modified RECIST [mRECIST], and/or World Health Organization). Thus, we decided to retrospectively evaluate CR to sorafenib treatment in a multicenter study in Spain.

Patients and Methods

This was a multicenter retrospective study including HCC patients treated with sorafenib between October 2007 and March 2014, with the aim of evaluating patients who achieved CR according to RECIST 1.1 plus SHARP trial criteria amendments that were implemented to properly define additional nodules in the setting of cirrhosis and avoid the registration of ascites and pleural effusion as progression if not proven by cytology. We did not consider the use of necrosis according to European Association for the Study of the Liver criteria.

All patients who were treated with sorafenib in each center, regardless of whether they achieved CR, represented the initial study cohort. Each center submitted the cases that had been classified locally as complete responders, but only those patients who were confirmed to have achieved CR after central review were considered in our final cohort.

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### TABLE 1. Clinical Cases and Cohort Studies of Patients Treated With Sorafenib Who Developed Complete Radiological Response

| Author, Journal, Year | n | Etiology        | Child-Pugh Class | Portal Vein Thrombosis | Metastases | ECOG Performance Status | BCLC Stage | Dermatologic Adverse Events | DAE60 | Tumor Response Criteria |
|-----------------------|---|-----------------|------------------|-------------------------|------------|------------------------|------------|---------------------------|-------|------------------------|
| So BJ, et al., J Hematol Oncol 2008 | 1 | Hemochromatosis  | NR               | No                      | Lung       | 2                      | D          | No                        | NR    | NR                     |
| Wang SX, et al., Target Oncol 2010 | 1 | HCV             | A                | Yes                     | NR         | NR                    | C          | No                        | NR    | NR                     |
| Kudo M, et al., Oncology 2010    | 2 | HBV             | A                | Yes                     | Lung       | NR                    | NR         | Pathologic                | NR    | NR                     |
| Chiles L, et al., Med Oncol 2011 | 1 | HBV + HIV       | No LC            | No                      | No         | 0                     | C          | Yes                       | NR    | NR                     |
| Inuzuka T, et al., Oncology 2011 | 1 | HCV             | A                | No                      | Lung       | 1                     | C          | No                        | NR    | NR                     |
| Sacco R, et al., BMC Gastroenterol 2011 | 1* | HCV             | A                | Yes                     | No         | 0                     | C          | Yes                       | NR    | RECIST                 |
| Abbadesse G, et al., World J Gastroenterol 2011 | 1 | HCV             | A                | Yes                     | NR         | 0                     | C          | Yes                       | Yes   | NR                     |
| Mizukami H, et al., Case Rep Oncol 2012 | 1 | HCV             | NR               | No                      | Lymph      | NR                    | C          | Yes                       | Yes   | RECIST                 |
| Ahn SY, et al., Dig Dis Sci 2013 | 1 | HBV             | A                | Yes                     | NR         | NR                    | C          | NR                        | NR    | NR                     |
| Gerardi A, et al., Oncol Lett 2013 | 1 | HCV             | A                | Yes                     | No         | NR                    | C          | Yes                       | NR    | RECIST                 |
| Higihara A, et al., Intern Med 2013 | 1 | HCV             | B                | Yes                     | Lung       | 3                     | C          | No                        | NR    | NR                     |
| Kee KM, et al., Onco Targets Ther 2014 | 1 | Cryptogenic     | A                | Yes                     | NR         | NR                    | NR         | Yes                       | Yes   | RECIST                 |
| Shiozawa K, et al., Oncol Lett 2014 | 1 | HCV             | A                | Yes                     | NR         | NR                    | C          | Yes                       | Yes   | RECIST                 |
| Shibata S, et al., Hepatol Res 2014 | 18 | HCV, 83.3%; HBU, 16.7% | A, 88.8%; B, 11.2% | 17% | 44%; 0, 77.8%; | NR | 83%; NR | mRECIST |
| Moroni M, et al., Future Oncol 2015 | 1 | HCV             | A                | Yes                     | No         | 0                     | C          | Yes                       | NR    | NR                     |
| Shinoda M, et al., World J Surg Oncol 2015 | 1 | Cryptogenic     | A                | Yes                     | Lung       | NR                    | NR         | No                        | RECIST |                     |
| Azmi AN, et al., J Dig Dis 2015 | 1 | HCV             | A                | Yes                     | No         | 2                     | NR         | Si                        | NR    | NR                     |
| Katafuchi E, et al., Case Rep Gastroenterol 2015 | 1 | HCV             | A                | No                      | Lung       | NR                    | NR         | No                        | No    | RECIST                 |
| Park JS, et al., Clin Mol Hepatol 2015 | 7 | HBV, 57.1%; HCV, 28.6%; OH + HBV, 14.3% | A, 57.1%; B, 42.9%; Y, 85.7%; | 14.3%; | 0 | C | No | mRECIST |
| Maida M, et al., J Gastrointestin Liver Dis 2016 | 1 | OH              | A                | Yes                     | No         | 0                     | C          | No                        | No    | mRECIST + |
| Simao A, et al., Acta Med Port 2016 | 1 | OH + VHB + VHC | A                | Yes                     | Lung + adrenal | NR         | C          | No                        | No    | mRECIST                 |
| Waidmann O, et al., Z Gastroenterol 2017 | 1 | HCV             | NR               | Yes                     | No         | NR                    | C          | NR                        | NR    | NR                     |
| Kim TS, et al., Clin Mol Hepatol 2017 | 1 | HCV             | A                | Yes                     | No         | 1                     | C          | Yes                       | NR    | mRECIST                 |

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; DAE: Dermatologic Adverse Events; DAE60, dermatologic adverse events within the first 60 days; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LC, liver cirrhosis; mRECIST, modified Response Evaluation Criteria in Solid Tumors; NR, not reported; OH, Alcohol; RECIST, Response Evaluation Criteria in Solid Tumors.

*Information was available for only one of four patients.
†Lymph nodes, 22%; lung, 39%.
‡Hand/foot skin reaction, 83%; rash, 34%; alopecia, 56%. 
The inclusion criteria were 1) HCC diagnosed by either pathology or by noninvasive criteria according to American Association for the Study of Liver Diseases guidelines and European Association for the Study of the Liver guidelines (15) and 2) patients under sorafenib treatment or patients who discontinued sorafenib treatment due to adverse events but who had not received an additional treatment after complete radiological response under sorafenib according to RECIST 1.1. (4)

The exclusion criteria were 1) concomitant oncologic treatment before CR, 2) absence of complete radiological response according to RECIST 1.1 criteria, (12,17) and 3) HCC treatment after CR achieved under sorafenib.

**RADIOLOGICAL CRITERIA FOR BASELINE ASSESSMENT AND TUMOR RESPONSE**

At the time of diagnosis, HCC lesions were divided as target and nontarget lesions following RECIST 1.1 criteria. (4) Portal or hepatic vein thrombosis was considered malignant if it was biopsy-proven and/or displayed arterial enhancement on either computed tomography (CT), magnetic resonance imaging (MRI), or contrast-enhanced ultrasound and/or if it expanded the diameter of the portal or hepatic vein and had close relation with HCC in the liver parenchyma.

The criteria used for assessing radiological CR have been summarized before, and the two central radiologists validated its presence. Because some patients may present residual lesions after CR, we also registered CR when observing 1) the persistence of a small (<2 cm) residual lesion replacing the initial infiltrative HCC showing a scar-like appearance (peripheral, nonarterial enhancement pattern but non- or minimal late enhancement, wedge-shaped and with capsular retraction) or 2) unequivocal reduction of extension and diameter of the thrombus with persistence of a thin, residual, chronic, fibrotic-like, hypodense nonenhancing thrombus. Furthermore, to be considered residual these lesions had to remain stable for a period of 2 years, ensuring its nonmalignant behavior.

**DATA COLLECTED FOR THE ANALYSIS**

The variables collected for the analysis were baseline demographic patient characteristics, radiological images at four time points (before starting sorafenib, first control after starting sorafenib, at the time of CR, and at least 1 month after CR), presence of dermatologic adverse events within the first 60 days of sorafenib treatment, (1) reason for sorafenib discontinuation and status at the end of follow-up (death/alive). Additionally, we registered the presence of arterial hypertension and diarrhea within the first 60 days of sorafenib treatment.

The definition of eDAEs was established according to the criteria published by Reig et al. (1) in 2014. This definition takes into consideration the time of appearance of the dermatologic adverse events (within the first 60 days after starting sorafenib) as well as the degree of the event (grade ≥ 2 according to Common Terminology Criteria for Adverse Events (CTCAE) v3.0 and which also requires sorafenib dose modification).

The radiologic evaluation including number of lesions, size at each time point, and response evaluation according to RECIST 1.1 (4) was performed centrally by two independent radiologists with more than 10 years of experience each in the field of HCC (J.R. and A.D.).

**ENDPOINTS OF THE STUDY**

The primary endpoint of this study was to evaluate the rate of CR in this multicenter Spanish cohort and analyze the profile of patients who achieved CR under sorafenib treatment, including the development of eDAE days of treatment during sorafenib treatment.

**TREATMENT**

The starting sorafenib dose and dose adjustments were made according to the clinical practice recommendations (15,16,18,19) that closely parallel those of the manufacturer.

**STATISTICAL ANALYSIS**

Categorical variables are described as frequencies and percentages and continuous variables as median and ranges. Survival rates and curves were determined using the Kaplan-Meier method. Last date for data collection was October 14, 2016. Analysis was performed censoring survivals at the time of last follow-up or at the time of starting an additional HCC treatment. All calculations were performed with SPSS v22 (SPSS Inc., Chicago, IL).

**Results**

Between October 2007 and March 28, 2014, 1119 HCC patients were treated with sorafenib in 13...
referral centers across Spain. Ten of these centers had at least one patient with CR according to their local radiological evaluation, so that 20 patients were initially registered locally as CR. However, eight of these patients were excluded either because of a lack of fulfillment of diagnostic criteria such that no conclusive diagnosis could be made before treatment (n = 3), target lesion treated simultaneously with radiofrequency or resection (n = 2), and unconfirmed CR at central radiology review according to RECIST v1.1 (n = 3) (Fig. 1). One of these two patients had iso-enhancing lesions on MRI dynamic sequences, but lesions were still identified on T2 and pre-gadolinium T1 sequences. The second patient had hypoenhancing lesions on CT examination as an effect of sorafenib and was classified at his center as having achieved CR because of potential full necrosis, thus he was considered a complete responder when applying mRECIST criteria. Of the remaining 12 patients, 10 had complete resolution of all malignant lesions according to RECIST v1.1 (Fig. 2), and two additional patients had one small peripheral residual lesion stable for a period of at least 2 years. At baseline, these patients had large infiltrative tumors measuring 11 cm and 4.3 cm with tumoral portal vein thrombosis and, after treatment with sorafenib, imaging displayed small areas (21 and 12 mm in size) without contrast enhancement that were classified as residual fibrotic areas (Supporting Figs. S1 and S2).

The baseline characteristics of the 12 patients with confirmed CR are summarized in Table 2. Regarding HCC treatment before starting sorafenib, three of the 12 patients had been treated before with surgery, two with radiofrequency and one with chemoembolization. The other four patients received no previous treatment.

Nine of the patients were men (75%) and three were women (25%). The median age was 59.7 years (range, 49.8-78 years). The most common cause of underlying liver cirrhosis was hepatitis C virus (58.3%), followed by hepatitis B virus (16.7%), alcohol-induced liver disease (16.7%), and other causes (8.3%). Liver function was preserved in most of the patients: 83.4% corresponded to Child-Pugh class A, 8.3% were Child-Pugh class B, and 8.3% were not assessable because of absence of cirrhosis. In terms of symptoms, 91.7% were asymptomatic (ECOG performance status 0) and 8.3% presented mild cancer-related symptoms (ECOG performance status 1). In terms of tumor stage, two patients corresponded to Barcelona Clinic Liver Cancer (BCLC) stage B and 10 corresponded to BCLC stage C (83.3%). Vascular invasion was identified at CT or MRI in 66.7% of patients, and 16.7% presented with extrahepatic spread.

**RADIOLOGICAL EVALUATION**

The baseline radiological characteristics of the 12 patients finally included in the study are summarized in Table 3. Five patients had nodular type HCC at baseline, three of which were the infiltrative type, and the remaining four patients had both infiltrative lesions on one hepatic lobe and a nodular type on the other. Among the patients with nodular lesions, the number of lesions in the liver ranged from zero (extrahepatic metastatic spread) to eight (median, one lesion). The tumor size of nodular lesions ranged from 19 to 75 mm (median, 32 mm).

The seven patients with infiltrative HCC had expansive vein thrombosis, whereas in those patients with a nodular type, only one had portal vein thrombosis. Only two patients had extrahepatic disease, one with lung metastasis and another with peritoneal recurrence after surgery on the right subphrenic region after right hepatectomy without residual lesions on the liver. No patient had radiological signs of lymph node invasion according to the criteria used for the SHARP trial.  

The median time between baseline CT scan and the achievement of radiological CR was 6 months (range, 1.4-16.1 months).

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**FIG. 1.** Study flow chart. Abbreviations: CR, complete response. HCC, hepatocellular carcinoma.
ANALYSIS ACCORDING TO RECIST v1.1 PLUS PROTOCOL AMENDMENT

In two of the 20 patients (10%) initially sent for central evaluation, both central readers identified the presence of small residual scar-like lesions in the subcapsular region of the liver which remained stable over a period of 2 years while the patients were under sorafenib treatment. The first patient had at baseline a nodular lesion of 110 mm that decreased in size (21 mm) but persisted as such small lesion together with the presence of new peripheral calcification. The second patient had at baseline a 43-mm nodular lesion, infiltrative HCC, and an expansive portal vein thrombosis. In addition to the 12-mm residual scar-like lesion, a residual nonexpansive portal vein thrombosis was also identified (Supporting Figs. S1 and S2).

According to RECIST v1.1 criteria, these patients cannot be classified as CR, but the radiological characteristics and morphological changes of these lesions, and

FIG. 2. Computed tomography of an ill-defined infiltrative HCC located on segments IV and VIII of the liver. (A,B) The arterial phase shows areas of heterogeneous enhancement (A, arrowheads) with scattered areas of washout on portal venous phase (B, arrowheads). (C) There was an expansive portal vein thrombosis, better seen on coronal reconstruction (arrows). (D,E) During sorafenib treatment, the mass vanished, leaving a wedge-shaped area of arterial enhancement (D, arrowheads) with no washout related to residual nonexpansive portal vein thrombosis (E, arrow).
especially their stability over time, favors the classification of these patients as complete responders.

**CLINICAL OUTCOME, TREATMENT DURATION, AND OVERALL SURVIVAL**

Sorafenib was initiated at a full dose (800 mg/day) in the entire cohort except in one patient, whose attending physician started at a half dose because of concerns about potential interaction with concomitant anticoagulant treatment.

At the time of CR registration, four patients (33.4%) were treated at 800 mg/day, one (8.3%) was treated at 400 mg/day, one (8.3%) was treated at 200 mg/day, and three (25%) received no treatment due to definitive interruption per patient decision.

The median overall survival was 85.8 months (95% confidence interval, 67.8-103.8). The median treatment duration and median time from sorafenib initiation to documented CR was 40.1 months (range, 7.6-83.6 months) and 13.3 months (range, 0.9-33.3 months) respectively.

At the end of the follow-up, four patients continued on treatment and did not present tumoral recurrence, and seven discontinued sorafenib after achieving CR (three due to vascular events, two as a result of patient decision, and two due to liver decompensation). Five of those who discontinued developed HCC recurrence after sorafenib interruption, and the other two continued under CR. The median time since sorafenib discontinuation and tumoral recurrence was 16.9 months (range, 8.5-73 months). Regarding the pattern of recurrence in these patients, one presented extrahepatic spread involving lymph nodes and lung metastasis, another developed intrahepatic spread and tumoral portal vein thrombosis and three of them presented with intrahepatic spread. One patient developed HCC recurrence after 28.02 months of achieving CR under sorafenib. None of the patients in our cohort received other treatments such as chemoembolization and transarterial infusion chemotherapy after achieving CR. Supporting Table S3 describes the outcome of the five patients who developed HCC recurrence after discontinuing sorafenib.

Nine of the 12 patients had increased alpha-fetoprotein (AFP) baseline levels. In eight of these patients, the levels returned to normal, whereas in one patient the AFP levels decreased from 3100 ng/dL to <150 ng/dL. Regarding the two patients with residual fibrotic lesions that would have been registered as CR despite not fully fitting into the RECIST criteria, the AFP data were as follows: one had increased AFP levels at baseline (155 ng/dL), achieving normalization when complete response was documented (4.4 ng/dL), and the other had normal AFP levels at baseline (6 ng/dL) and AFP levels remained normal when CR was achieved (4 ng/dL) (Fig. 3).

**ADVERSE EVENTS**

All but one (91.6%) of the patients developed dermatologic adverse events within the first 60 days of treatment. The patient without eDAEs corresponds to the one that initiated sorafenib at half dose.
Only one patient presented with diarrhea within the first 60 days after starting sorafenib; however, no dose modification was needed for that adverse event, and none of the 12 patients developed arterial hypertension within the first 60 days after starting sorafenib.

One patient developed an impairment of arterial hypertension beyond the first 60 days after starting sorafenib, which was controlled with enalapril without needing to modify the sorafenib dose. That patient was the same patient who developed diarrhea within the first 60 days after starting sorafenib, but again, no dose modification was required for this adverse event. Finally, another patient developed diarrhea beyond the 60 days after starting sorafenib and before achieving CR. Supporting Table S2 presents the Early Adverse Events (eAE) (within 60 days of starting sorafenib) and adverse events beyond the first 60 days of starting sorafenib for each patient.

**Discussion**

This multicenter observational study conducted after a nationwide survey in Spain, which considered 1119 patients treated with sorafenib, describes the clinical and radiological characteristics of 12 HCC patients that achieved CR while on treatment. It is worth noting that our cohort included patients with advanced disease as reflected by their BCLC stage.

The main issue in the CR evaluation is the criteria used for that evaluation. It is already known that the rate of radiological tumor progression in patients under sorafenib or regorafenib treatment is similar between the different criteria used. However, these criteria differ in the rate of patients classified as having CR, partial response, or stable disease. Thus, to rule out the risk of a false-positive diagnosis of CR, we performed a central revision and excluded 15% of the original cohort (three of the 20 patients evaluated) due to unconfirmed CR at central radiology review according to RECIST 1.1 even when considered as complete responders by the local center.

CRs were not registered in the sorafenib pivotal trials, but several reports have described such positive evolution in a small number of patients (Table 1). Our study offers a 1.07% CR rate that fits into an event that is not frequent but that may occur in some individuals.
Shiba et al.\textsuperscript{(23)} reported a 0.6% CR rate in their countrywide Japanese study including 3047 patients.

The main differences between our study and the study by Shiba et al.\textsuperscript{(23)} were the definition of CR and the rate of patients who started sorafenib with half dose. Shiba et al. proposed that the initial dose was one of the factors associated with CR. However, according to our data, it is not possible to validate this proposal, because only one patient started with a half dose. Shiba et al. defined as complete responders patients with absence of contrast uptake within the tumor at dynamic imaging (mRECIST criteria). Although necrosis can be recognized easily after ablation or chemoembolization, it is more challenging and controversial to do so under sorafenib treatment. For these reasons, we decided to adhere to RECIST 1.1 and avoid criteria that consider tumor density as a reflection of necrosis. Overall, if we apply the mRECIST definition for CR, the prevalence of CR would be higher than it actually is. Indeed, reliable definition of response is one of the controversial points in the Lencioni et al. study testing the value of CR would be higher than it actually is. Indeed, reliable definition of response is one of the controversial points in the Lencioni et al. study testing the value of mRECIST in the brivanib second-line trial.\textsuperscript{(24,25)}

Sorafenib is a powerful vasoconstrictor, as is the case with all antiangiogenics. This implies a reduction in hepatic artery blood flow that may result in hypodensity within the tumor nodules. Although a correlation between supposed necrosis at radiology after ablation and pathology findings does exist, no such study is available for systemic therapy and specifically, for sorafenib.

In addition to the cases fitting into the RECIST 1.1 definitions, we registered as complete responders two additional patients in whom all radiology findings and follow-up monitoring strongly supported the achievement of complete tumor eradication. If these two patients were not included, the CR rate would decrease to 0.9% but would still be informative and key to increasing our understanding.

In the present study, in all but one of our patients (92%), the clinical record registered the emergence of eDAEs. In the study by Shiba et al.,\textsuperscript{(23)} the prevalence of dermatologic adverse events in patients with CR was lower (45%) but was still significantly higher than that for patients without CR (i.e., patients who exhibited partial response, stable disease, or progression [3%; \(P < 0.001\)]).

Thus, on-target sorafenib toxicity may have a predominant but underestimated role in the prediction of outcome. In this regard, we reported that dermatologic adverse events within the first 60 days is a predictor of better overall survival, and Branco et al.\textsuperscript{(3)} externally validated these data. Indeed, the median risk of death reduction in patients who developed eDAE is 42% higher than that reported in the entire cohort of the SHARP trial (35%). However, the role of the eDAEs is even more important if we consider the absence of correlation between Time to progression and overall survival in the SHARP\textsuperscript{(5)} and Asian-Pacific data.\textsuperscript{(6)} In this regard, the impact of eDAEs is maintained regardless of the radiological tumor progression.

Thus, our results reinforce the association between eDAEs and better outcome; even more importantly, they can be a link between clinical events and the understudied sorafenib mechanism of action.

The mechanism for the benefits associated with dermatologic adverse events is unknown but is very likely related to an immune modulation induced by any of the targets affected by sorafenib. This drug may modulate the stromal cell population, which may prime several molecular events due to direct action or be mediated by reduced blood flow reaching tumor cells.\textsuperscript{(26)} Hypoxia increases the production of tumor necrosis factor \(\alpha\), a proinflammatory cytokine, but simultaneously attenuates apoptosis. Additionally, interactions between hypoxia and inflammation are seen as a regulatory component of NF-\(\kappa B\) and of the regulation of hypoxia-inducible factor 1\(\alpha\) (HIF-1\(\alpha\) transcription by NF-\(\kappa B\) before and during inflammation.\textsuperscript{(3)} Thus, members of the NF-\(\kappa B\) family of transcription factors regulate inflammation and score the immune responses and tissue homeostasis.\textsuperscript{(27,28)} HIF-1\(\alpha\) regulates several functions of myeloid-derived suppressor cells\textsuperscript{(29)} and allows myeloid cells to generate adenosine triphosphate in oxygen-deprived tissues. Lei et al.\textsuperscript{(30)} evaluated the change of the peripheral blood immune pattern and its correlation with prognosis in patients with liver cancer treated with sorafenib. They reported a higher ratio of B cells and regulatory B cells in peripheral blood mononuclear cells of patients in the response group (stable disease or CR) than in that of the nonresponse group.

Interestingly, recent phase 1-2 data using different immune modulators blocking immune checkpoints have offered promising data regarding antitumoral activity and primed a major expectancy in the success of such therapies that needs to be confirmed in adequately powered phase 3 trials. In fact, a 2% CR rate has been reported in the preliminary data with nivolumab in a cohort of 262 patients.\textsuperscript{(31)} In addition to rates of 3.3% (1/30 patients) in HCV, 2.3% in HBV (1/43 patients), and 0% in uninfected patients (0/72 patients),\textsuperscript{(32)} which is very similar to the rate reported in the present study.
However, if hope is the driver for decision making, the rate offered by our results and those by Shiba et al.\textsuperscript{(23)} should confirm that the expectation for long-term, disease-free survival is not absent with sorafenib. It could be argued that the CRs observed could simply be spontaneous regressions of HCC, as has been reported previously.\textsuperscript{(33)} The rate is higher than that observed when summing up all the placebo control arms of the different trials that have been performed in recent years. This exercise shows a 0.008% rate of CRs in the placebo arm (Supporting Table S1), hence the rate for sorafenib treatment appears higher. Furthermore, the same favorable spontaneous evolution could be suggested in those patients with encouraging long-term outcome after resection or transarterial chemoembolization. Hence, despite the low rate of CR in our cohort, we believe that the eDAE is the only on-target sorafenib toxicity associated with CR. Because none of our patients developed arterial hypertension and only one developed diarrhea within the first 60 days, these events cannot be proposed to have the same value as eDAEs. Additional studies may externally validate our data and establish eDAE as a predictor of improved survival expectation and even potential CR under sorafenib treatment.

Our cohort encompassed a heterogeneous group of patients with different radiological patterns of HCC, including nodular, infiltrative, or mixed HCC lesions. Interestingly enough, 66.7% (8/12) presented with expansive portal vein thrombosis and two out of 12 presented with extrahepatic lesions, but this was not a limitation to achieving CR. Unlike the study of Shiba et al.,\textsuperscript{(23)} no patient from our cohort presented pathological lymph nodes at baseline CT/MRI. Thus, the clinical relevance of existing metastatic lymph nodes for achieving CR with antiangiogenic drugs may deserve further attention. Interestingly, the combined analysis of the two seminal sorafenib versus placebo trials has shown that patients without extrahepatic spread have a significantly higher treatment benefit from sorafenib compared with those with dissemination.\textsuperscript{(25,34)}

Thus, the main question in clinical practice is whether sorafenib should be stopped upon detection of CR or if treatment should be kept in place without time limits. There is no answer to this question, but our data suggest that clinicians should be very careful and critically assess all aspects. The first issue is to ensure that initial diagnosis is 100% accurate and CR is reliable. In our study, we discarded three cases because of the absence of a target lesion and three additional cases because local readers initially classified them as complete responders based on transient lack of enhancement during antiangiogenic treatment interpreted as necrosis. This was due to application of the mRECIST criteria, which have not been validated at all for systemic therapy, and may be faulty to register necrosis. In such cases, the follow-up data showed disease progression in the next 3–6 months after registering the supposed CR. Hence, it is likely that such assessment was an overestimation. In that regard, we observed that in some long-term responders, residual small fibrotic hypovascular lesions were identified. The achievement of CR in this subgroup of patients was based on their fibrotic appearance together with the persistence and stability of such small lesions over time, rather than the simple assessment of lack of enhancement.

After securing the existence of CR, it is important to note that we had only one recurrence in patients kept under treatment, whereas recurrence was observed in five of the seven patients in whom the drug was interrupted. According to these observations, it seems sound to keep sorafenib in place until intolerance or adverse events promote its interruption.

In conclusion, our study reveals that around 1% of the patients with advanced HCC treated with sorafenib achieve a long-term CR as reflected by a complete disappearance of all tumor sites. This is probably mediated through immune reactivation mediated by the drug as reflected by the significant association with the development of dermatologic adverse events. These findings, together with the recent description of high risk of tumor recurrence after antiviral therapy,\textsuperscript{(35)} indicate the major role of immune surveillance in cancer control and thus, supports the ongoing investigation in this field in HCC patients.

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18) Supporting Information

Author names in bold designate shared co-first authorship.

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