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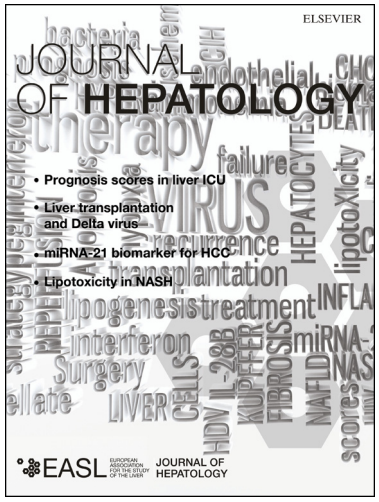

Early dermatologic adverse events predict better outcome in HCC patients treated with sorafenib

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Early dermatologic adverse events predict better outcome in HCC patients treated with sorafenib.

Maria Reig[1,3*], Ferran Torres[4*], Carlos Rodriguez-Lope[1,3], Alejandro Forner[1,3], Neus LLarch[1,3], Jordi Rimola[2,3], Anna Darnell[2], José Ríos[4], Carmen Ayuso[2,3], Jordi Bruix[1,3]

[1]Barcelona Clinic Liver Cancer (BCLC) Group, Liver Unit, Hospital Clínic Barcelona, IDIBAPS, University of Barcelona, Barcelona, Spain.

[2]Barcelona Clinic Liver Cancer (BCLC) Group, Radiology Department, Hospital Clínic Barcelona, IDIBAPS, University of Barcelona, Barcelona, Spain.

[3]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Spain.

[4]Biostatistics and Data Management Platform, IDIBAPS, Hospital Clínic; Biostatistics Unit, School of Medicine, Universitat Autònoma de Barcelona; Barcelona, Spain.

Corresponding author:

Jordi Bruix,

BCLC group, Liver Unit, Hospital Clínic,

C/Villarroel 170, Floor 4 Stair 11

08036 Barcelona, Spain.

Phone: 34 93 227 9803

FAX: 34 93 227 5792

jbruix@clinic.ub.es

*Both authors contributed equally to the study.

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Conflict of interest.

Jordi Bruix: consulting for Bayer Schering Pharma, Pharmexa, Eisai, Lilly, Biocompatibles, ArQule, BioAlliance, Novartis, ImClone, Schering-Plough, MedImmune, Roche, Abbott, BMS, Jennerex, OSI, Sanofi, GSK, AngioDynamics, Terumo, and Kowa. Research funding by Bayer Schering Pharma.

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Abstract:

Background and Aim: There are no clinical data/markers to predict improved survival in patients with hepatocellular carcinoma treated with sorafenib. Majority of sorafenib adverse events appear within the first 60 days of treatment and studies correlating them with outcome are needed.

Patients: We prospectively studied 147 hepatocellular carcinoma patients (97% cirrhotic, 82% Child-Pugh A, BCLC-B 77, BCLC-C 69) treated with sorafenib. Follow-up included monthly clinical and laboratory monitoring and tumor staging at week 4 and every 8 weeks.

Results: After a median follow up of 11.6 months (treatment duration 6.7 months), time to progression and overall survival were 5.1 and 12.7 months. All but one patient presented at least one adverse event (median time to appearance 56 days). Time dependent covariate analysis (HR [CI95%]) identified baseline performance status (2.86 [1.75 to 4.55], p<0.001), BCLC (1.69 [1.18 to 2.50], p=0.005) and dermatologic adverse event requiring dose adjustment within the first 60 days (0.58 [0.36 to 0.92], p=0.022) as independent predictors of better outcome. Other early adverse events did not have an impact in outcome. The predictive value of dermatologic adverse events for survival was confirmed by the landmark analysis (p= 0. 0270).

Conclusion: Development of dermatologic adverse events within 60 days of sorafenib initiation is associated with better survival. Therefore, this should not to be taken as a negative event and discourage treatment maintenance. Likewise, second line clinical trials should be designed and/or evaluated considering this information to avoid significant bias.

Keywords: Hepatocellular carcinoma, sorafenib, early adverse events, clinical marker, overall survival

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List of abbreviations in the order of appearance.

Overall survival (OS)

Hepatocellular carcinoma (HCC)

AE (adverse events)

Performance status (PS)

Barcelona Clinic Liver Cancer classification (BCLC)

Time to progression (TTP)

American association for the study of liver disease (AASLD)

AE with in the first 60 days (AE60)

Hepatitis virus C (HCV):

Hepatitis virus B (HVB)

Dermatologic AE60 (DAE60)

Arterial hypertension (AHT)

P25, P33, P66, P75: 25^{th}, 33^{th}, 66^{th} and 75^{th} percentiles, respectively

Background

Sorafenib improves the overall survival (OS) of patients with advanced hepatocellular carcinoma (HCC) with a good safety profile and it is the first molecular target treatment approved for HCC therapy [1]. It decreases the risk of death by 31% (Hazard Ratio. 0.69) and its impact in the OS of patients with HCC is maintained regardless of race, etiology and the baseline characteristics of patients [1, 2].

Despite the analysis of different biomarkers [3] and/or functional radiologic evaluation in this population, it has been unfeasible to identify those patients that benefit most from this treatment. Thus, there is no baseline or early marker (clinical, radiologic and/or biochemical) within the first 30-60 days after starting sorafenib that would inform patients and physicians about the higher or lower impact of treatment.

Previous retrospective studies have suggested a correlation between dermatologic AE (adverse events) and TTP (time to progression)/OS [4-6]. These dermatologic AEs have been proposed as a marker of enhanced efficacy of sorafenib treatment. However, this possibility has not yet been demonstrated in a prospective study using time dependent covariate analysis and taking into account all other factors related to the prognosis of HCC patients. Thus, our goal was to prospectively evaluate the impact of the recognition of a dermatologic adverse event within the first 60 days in the outcome of patients.

In that regard it is worth recalling that none of the phase III head to head trials challenging sorafenib in HCC patients has been positive [7, 8]. Interestingly enough, the frequency of hand foot skin reaction grade III in sorafenib arm of these trials was more prevalent than than in the sunitinib [7](21% vs.13%) or brivanib arm [8] (15% vs.2%). Hence, putting together the data from the phases III trials in first line [7, 8] and the retrospective studies [4-6], the potential link between dermatologic adverse events

and improved outcome could be reinforced. Confirmation of this association in a large cohort study would prove important to understand the prognosis of patients under molecular targeted therapies and modify the current design of treatment trials. Ultimately, the investigation of the mechanisms responsible for the emergence of dermatologic adverse events as a predictor of improved therapeutic response would permit a personalized treatment approach.

Patients and methods:

This prospective study considered all patients referred to our center between March 2008 and July 2011 for sorafenib treatment according to the BCLC strategy [9, 10].

Inclusion criteria were: 1) HCC diagnosed according to AASLD guidelines [9, 11] 2) presence of a naïve target lesion; 3) adequate liver function (albumin > 2.8g/dL; total bilirubin <3mg/dL; and alanine and aspartate aminotransferases <5 times the upper limit of the normal range), and Child-Pugh score ≤7 points; 4) performance status (PS) 0-1; 5) controlled arterial hypertension and stable peripheral vascular disease; 6) adequate hematologic profile (platelet count > $60x10^9$/L; haemoglobin >8.5g/dL; and prothrombin time >50%); 7) adequate renal function (serum creatinine <1.5 times the upper limit of the normal range).

Exclusion criteria were: 1) myocardial infarction in the past year or active ischemic heart disease; 2) acute variceal bleeding in the past month; 3) severe peripheral arterial disease; 4) cardiac arrhythmia under treatment with drugs other than beta-blockers or digoxin; 5) uncontrolled ascites; 6) encephalopathy; 7) unfeasibility to fulfil the follow-up schedule.

All the patients provided written informed consent before enrolment. The study was approved by the institutional review board and complied with the provisions of the Good Clinical Practice guidelines and the Declaration of Helsinki.

Outcomes and Assessments

Time to progression was defined as the time from the date of starting sorafenib to disease progression. Radiologic evaluation of response during follow-up was done by CT-scan according to the RECISTv1.1 [12] with the amendments that were implemented in the pivotal SHARP trial [1] that ultimately was reflected in the mRECIST proposal [13, 14] . Radiology assessment was blinded to the evolution and outcome of the patients. Those patients who died before the first imaging assessment were classified as progressors.

Overall survival was measured from the date of starting sorafenib until the date of death and survival post-definitive interruption was defined as the time from definitive sorafenib interruption to death occurred

Treatment

Sorafenib was initiated at full dose (400 bid), which was modified upon development of adverse events according to manufacturer's recommendations. Treatment was continued until symptomatic progression, unacceptable adverse events or death occurred.

Follow-up:

Clinical and laboratory assessments were done monthly and radiology tumour evaluation at week 4 and afterwards every 8 weeks. Unscheduled visits due to adverse events occurred according to patients needs.

Adverse events (AE) were graded according to version 3.0 of the CTCAE of the National Cancer Institute, during treatment and 30 days after the last dose. Despite the cause of the AE, we focused on the AE within the first 60 days (AE60) of treatment, which determined dose modification. Thus, the following results will be especially

focused on those kinds of patients: patients who developed AE60 (between day zero and day 60) and needed dose modification.

We divided the AE60 in 5 groups: dermatologic (*Hand-Foot reaction / Rash /Edema-erythema/ Foliculitis)* cardiovascular (arterial hypertension/rhythm alteration/ ischemic events), gastrointestinal, bleeding, infection and others.

Statistical analysis

Categorical variables are described as frequencies and percentages and continuous variables as median and percentiles 25 and 75 (P25-P75), or otherwise specified. Times to event data for survival are estimated by Kaplan-Meier for death or using the cumulative incidence curves of progression in a competing risks framework, with death without progression as competing event [15, 16]. The landmark approach [17] was used to rule-out time-dependent bias of dermatologic adverse events as a predictor for survival and to reinforce the findings by excluding patients with early events (i.e. before 60 days). To define the predictors of overall survival we used a time-dependent covariates survival approach including statistically significant clinical variables ($p<0.05$) from the univariate Cox analysis [18].

The Fisher's exact test was used to compare categorical variables and the Mann-Whitney method was used to compare ordinal and continuous variables.

The analysis was performed using SAS version 9.2 software (SAS Institute Inc., Cary, NC, USA), SPSS v18 (SPSS, Inc., Chicago IL) and, significance was established at the 0.05 level (two-sided).

Results:

Between March 2008 and July 2011, 229 patients were assessed for sorafenib treatment. Of the 229, 82 patients were excluded per study criteria and 147 were eventually enrolled in the study. The majority of exclusions were due to impaired PS and deteriorated liver function at screening.

At the time of database lock (May 2012), their median follow-up was 11.6 months (range: 0.4-51.8): 111 died, 28 out of 147 patients were still alive (with 7 continuing sorafenib) and 8 were lost to follow-up.

Baseline characteristics

Clinical and laboratory baseline characteristics are summarized in Table 1. All but 4 patients were cirrhotic. The most frequent etiology of cirrhosis was HCV (57.1%), followed by alcohol abuse (25.2%) and HBV (11.6%). The majority of the patients were asymptomatic (PS-0 83.6%) and 77 (52.3%) were BCLC B who failed or presented contraindication to loco-regional treatment. Fifty-one patients (34.7%) presented vascular invasion, 121 patients (82.3%) were Child–Pugh A class. Sixty-five patients had not received previous therapies and 82 (55.78%), had received prior locoregional therapy. None of the patients had received systemic therapy.

Overall survival and radiologic evaluation

The median OS was 12.7 months [(95% CI; 10.3 to 15.2), (percentiles 33th-66th, P33-P66: 8.2 - 16.1 months)](Figure. 1a in the Supplementary Appendix). The response rate was: stable disease (SD) in 36 patients (24.5%), partial response in 2 patients and complete response in 1 patient. Tumor progression occurred in 108 patients (73.5%). Median TTP was 5.1 months (95% CI; 3.7 to 6.4) (Figure.1b in the Supplementary Appendix).

Treatment, adverse events and dose modification

The median duration of treatment was 6.7 months (range: 0.26-35) (P33: 3.6, P66: 10.2 months)]. The median (percentile 25^{th} – 75^{th}) cumulative dose was 70,400 mg (29,200-15,4400) and the median daily dose was 546 mg (343-795).

All but one patient presented at least one adverse event (median time to appearance 56 days; this primed the use of 60 days as the cut-off to define early vs late AE), and all but 4 out of 147 needed at least one dose modification. Thirteen out of the 51 patients that had dose reduction had re-escalation to full dose. Sixty-one of those 92 that stopped restarted therapy. This refers to the first dose adjustment and not to the number of dose adjustments during follow-up.

Tables 2 shows all the adverse events presented in at least 5% of the patients during the whole treatment and table 1 in the supplementary appendix shows the main reasons for definitive interruption in the whole cohort. The overall discontinuation rate (95%CI) due to adverse events (drug related or not) was 43.6% (35.6%-51.8%), 61/140 patients.

Seventy-four patients presented definitive interruption due to PS deterioration. Sixty-one of these 74 patients presented radiologic progression at the same time. Moreover, simultaneous radiologic progression was also observed in 11/14 (79%) patients who developed ascites and in 7/8 (88%) patients who presented encephalopathy. Definitive discontinuation because of AEs deemed to be drug related was registered in 44/140 patients (30.5%). Such drug related AEs were observed at any time (early or late) during follow-up. There were no deaths related to treatment.

We observed that patients with at least one dermatologic or cardiovascular AE at some point during treatment presented better OS than patients without one of them. In addition, in patients who discontinued sorafenib due to hand foot reaction or cardiovascular events (peripheral vasculopathy, transient ischemic cerebrovascular

accident, acute myocardial infarction or unstable angina) the median survival post-definitive interruption was greater than 9 months (Table 1 in the Supplementary Appendix).

Adverse events

One hundred forty-four (98%) patients presented at least one AE during that time. The median number of AE for each patient was 3 (1-9). The majority of the events were dermatologic (37%), gastrointestinal (26%) or other AEs (27%). A non-negligible number of patients presented cardiovascular (10%) events due to arterial hypertension. Nevertheless, the majority of AE were mild (65 %) or moderate (26%). 9 % of the events were grade III and 0.7% grade IV. We did not have drug related deaths. One hundred and seven patients needed at least one dose modification during follow-up. The main reason for that modification within the first 60 days (107 out of 147 patients) is presented in table 3.

Assessment of prognostic predictors by time dependent analysis.

We included all baseline parameters described in Table 1 and the emergence of adverse events during the first 60 days of follow-up in the univariate analysis and in the time dependent multivariate analysis. We did three separate multivariate models. The first model included all significant variables at univariate analysis ($p<0.05$) forced in the model. The second model included all significant variables at univariate analysis ($p<0.05$) considered for a forward stepwise approach. The third model included all clinically statistically significant variables at univariate analysis ($p<0.05$) considered for a forward stepwise approach. The later was selected as the most informative and is shown in table 4. The results of model 1 and 2 are exposed in supplementary table 2.

The multivariate analysis consistently identified baseline PS and BCLC as well as the early dermatologic AE60 (DAE60) as independent predictors of OS (Table 4). AFP had no predictive power in this series. TTP was significantly different according to the presence of DAE60 (p=0.016): [8.1 months (CI95%:1.6-14.5) vs. 3.9 months (CI95%:2.08-5.7). We also observed a different OS when dividing the patients according to the presence or not of DAE60, 18.2 months (95% CI; 11.9 to 24.4) in patients with DAE60 vs. 10.1 months (CI 95%: 10.1-13.0) in patients without them (p= 0.009). Patients who die early may also have had a lower chance of having early dermatological events by other causes not related to the early death. However, survival results did not change when conducting a landmark analysis at 2 months discarding all patients with follow-up less than 2 months (p=0.0270)(Figure 2 of supplementary material.

The cumulative incidence of progression was also done with death as competitive risk using landmark approach. The Gray's test yielded a p=0.0757 including the 101 patients without death or progression within the first 60 days (Fig 3 of the supplementary material).

Moreover, we did not observe significant differences between patients with and without DAE60 in terms of baseline characteristics or in the treatment duration (Table 3 and table 4 in the Supplementary Appendix). The first dose modification (p=0.004) occurred earlier and the median time between dose modifications to re-start/full dose of sorafenib was shorter (p=0.0032) in patients with DAE60 than no-DAE60 and the median number of dose modification was higher in patients with DAE60 [3(1-7)] than without DAE60 [2(0-7)] p=0.006. (Table 4 in the Supplementary Appendix). The association between the development of DAE60 *(Hand-Foot reaction / Rash /Edema-erythema/ Foliculitis)* and better OS was maintained regardless of treatment duration.

In addition, we evaluated the OS according to the presence of hand foot reaction vs. other dermatologic AE in the 37 patients with DAE60 and we did not find any difference: 18.2 months (95% CI; 5.2 to 31.2) vs. 19.7 (95% CI; 10.7 to 28.8)(p=0.61).

Discussion:

Our study is a prospective validation of prior retrospective studies [4-6] that suggested the role of dermatologic adverse events as a predictor of OS in HCC patients under sorafenib treatment. Since AEs are evolutionary events that are inmeasurable at baseline, we used time dependent multivariate analysis to avoid a statistical flaw that is commonly disregarded. Furthermore, we also assessed the data by competitive risk assessment and by landmark analysis. All assessment were consistent in identifying DAE60 as a parameter significantly associated to better outcome. Thereby, we properly demonstrate for the first time the validity of DAE60 as an early predictor of better OS in clinical practice. Our data should not be taken as absence of DAE60 being a marker of absence of treatment efficacy with no impact in survival. To unequivocally assess this possibility, the study should have been randomized and include an untreated control arm. This approach is currently unfeasible for ethical reasons.

In our investigation the treatment duration was longer than other cohort studies with similar population [6, 19] and even within the SHARP trial (5.3 months)[1]. There are at least two explanations: our patients continued treatment until symptomatic progression and those patients who needed dose modification due to AE development continued with treatment regardless of the dose. In most settings, AEs are seen as a negative event and they are the main reason for definitive sorafenib interruption in a relevant number of patients. However, our results demonstrate that DAE60 development is not a negative event and should rather be taken as a surrogate of better OS. As a

consequence, a nihilistic view about sorafenib treatment because of the potential induction of dermatologic adverse events is not justified. This leads to the debate about the optimal sorafenib dose at the time of starting treatment. In the pivotal trials [1] the dose that was used was 800 mg/day, which was to be adjusted according to tolerance. Thus, this is the starting dose to be recommended according to scientific evidence. However, some authors [6, 19-21] suggest starting at half dose to avoid the development of AE. However, the low dose strategy to ramp up according to tolerance may not trigger the mechanism associated to the development of dermatologic adverse events with loss of the survival improvement associated with them. Obviously, appearance of DAE within the first 60 days explains that the patients who developed them needed more dose modification than those who did not present DAEs.

In conventional clinical practice it is mandatory to establish early close follow up after treatment initiation, and that patients should be given easy access to unscheduled visits and consultations to detect AEs manage them promptly and adjust dosage. This surely improves treatment compliance with optimal efficacy without unneeded treatment interruptions or cancellations. Accordingly, treatment duration in our study is due to the growing experience in the management of the drug and its side effects, but also to the decision to maintain treatment until symptomatic progression as was established in SHARP [1]. In other settings, the detection of adverse events or radiology progression may prompt treatment withdrawal. This might be due to the belief that radiology progression reflects treatment “failure” or “resistance” to it, or to the willingness to consider the patients for second line options, usually within research trials. This flaw in the clinical path of patients is not well reported but surely helps to understand some of the conflicting published data about treatment duration, time to progression and survival. In addition to key aspects for clinical practice, our results should influence the design and analysis of first and second line trials. Up to now, all the first[7, 8, 22, 23] and second line trials[24] after the pivotal SHARP study have been

negative. The design of most first line trials has similarities with SHARP trial [1] in terms of patients' characterization and stratification. However, in second line trials after sorafenib it will be key to take into account the development of DAEs while under this drug and either stratify patients prior to randomization to a trial in second line and/or include a preplanned analysis according to this feature. As mentioned, the frequency of hand foot skin reaction grade III in sorafenib arm of the first line trials that compared sorafenib with sunitinib [7] (21% vs.13%) or sorafenib vs. brivanib [8] (15% vs.2%) is higher in the sorafenib arm. This suggests that the research about the mechanisms leading to DAE60 may give some insight about the biological process that is responsible for the sorafenib benefits. The biological link between hypoxia (that could be enhanced by sorafenib), inflammation and cancer progression [25] deserves some attention. The same applies to the need to gather data about the bioavailability of sorafenib and its metabolites during treatment, the metabolic profiling capacity of the patients and other parameters linked to drug effectiveness[26-28]. Their future availability should help to optimize sorafenib treatment and move towards a personalized therapeutic approach where dosage and schedule of administration may be individualized.

Finally, cardiovascular events are another concern in clinical practice and previous authors [29] also suggest arterial hypertension (AHT) as a predictor of OS. We observed a better OS in patients with at least one cardiovascular event at some point during treatment but it was not a predictor of OS if detected early during follow-up. The other cardiovascular events (peripheral vasculopathy, transient ischemic cerebrovascular accident, acute myocardial infarction or unstable angina) appeared in patients with long-term treatment. Obviously, treatment at long-term will always correlate with long term survival and this analysis will always be flawed if a complex time dependent analysis is not done.

In conclusion, development of clinically significant dermatologic adverse events requiring dose adjustment within the first 60 days of sorafenib initiation is associated with better survival. Therefore, this should not be taken as a negative event and hence, discourage treatment maintenance.

References:

[1] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008 Jul 24;359(4):378-90.
[2] Bruix J, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. J Hepatol. 2012 Oct;57(4):821-9.
[3] Llovet JM, Pena CE, Lathia CD, Shan M, Meinhardt G, Bruix J. Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. Clin Cancer Res. 2012 Apr 15;18(8):2290-300.
[4] Vincenzi B, Santini D, Russo A, Addeo R, Giuliani F, Montella L, et al. Early skin toxicity as a predictive factor for tumor control in hepatocellular carcinoma patients treated with sorafenib. Oncologist. 2010;15(1):85-92.
[5] Otsuka T, Eguchi Y, Kawazoe S, Yanagita K, Ario K, Kitahara K, et al. Skin toxicities and survival in advanced hepatocellular carcinoma patients treated with sorafenib. Hepatol Res. 2012 Sep;42(9):879-86.
[6] Di Costanzo GG, Tortora R, Iodice L, Lanza AG, Lampasi F, Tartaglione MT, et al. Safety and effectiveness of sorafenib in patients with hepatocellular carcinoma in clinical practice. Dig Liver Dis. 2012 Sep;44(9):788-92.
[7] Cheng AL, Kang YK, Lin DY, Park JW, Kudo M, Qin S, et al. Sunitinib Versus Sorafenib in Advanced Hepatocellular Cancer: Results of a Randomized Phase III Trial. J Clin Oncol. 2013 Sep 30.
[8] Johnson PJ, Qin S, Park JW, Poon RT, Raoul JL, Philip PA, et al. Brivanib Versus Sorafenib As First-Line Therapy in Patients With Unresectable, Advanced Hepatocellular Carcinoma: Results From the Randomized Phase III BRISK-FL Study. J Clin Oncol. 2013 Aug 26.
[9] Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology. 2011 Mar;53(3):1020-2.
[10] Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet. 2012 Mar 31;379(9822):1245-55.
[11] Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology. 2005 Nov;42(5):1208-36.
[12] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.
[13] Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. 2008 May 21;100(10):698-711.
[14] Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010 Feb;30(1):52-60.
15 Fine J, Gray R. A Proportional Hazards Model for the Subdistribution of a Competing Risk. . Journal of the American Statistical Association 1999;94:496-509.
[16] Gray RA. Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. . The Annals of Statistics 1988;16:1141–54.
[17] Anderson J, Cain K, Gelber R. Analysis of survival by tumor response. J Clin Oncol. 1983;1 710 –9.
[18] Therneau T, Grambsch P. Modeling Survival Data: Extending the Cox Model (Statistics for Biology and Health). . Springer-Verlag New York Inc. 2000(Edición: 1st ed.).
[19] Iavarone M, Cabibbo G, Piscaglia F, Zavaglia C, Grieco A, Villa E, et al. Field-practice study of sorafenib therapy for hepatocellular carcinoma: a prospective multicenter study in Italy. Hepatology. 2011 Dec;54(6):2055-63.
[20] Finn RS. Drug therapy: sorafenib. Hepatology. 2010 May;51(5):1843-9.

[21] Camma C, Cabibbo G, Petta S, Enea M, Iavarone M, Grieco A, et al. Cost-effectiveness of sorafenib treatment in field practice for patients with hepatocellular carcinoma. Hepatology. 2013 Mar;57(3):1046-54.
[22] Zhu A, Rosmorduc O, Evans J, al. e. SEARCH: a phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with hepatocellular carcinoma (HCC). Ann Oncol 2012;23((Suppl 9):):Abstract LBA2.
[23] Calin C, Shukui Q, Wen-Tsung H, Ik-Joo C, Hongming Pan, Ying Cheng, et al. Phase III trial of linifanib versus sorafenib in patients with advanced hepatocellular carcinoma (HCC). J Clin Oncol 2013;30((suppl 34; abstr 249)).
[24] Llovet JM, Decaens T, Raoul JL, Boucher E, Kudo M, Chang C, et al. Brivanib in Patients With Advanced Hepatocellular Carcinoma Who Were Intolerant to Sorafenib or for Whom Sorafenib Failed: Results From the Randomized Phase III BRISK-PS Study. J Clin Oncol. 2013 Aug 26.
[25] Eltzschig HK, Carmeliet P. Hypoxia and inflammation. N Engl J Med. 2011 Feb 17;364(7):656-65.
[26] Lee JH, Chung YH, Kim JA, Shim JH, Lee D, Lee HC, et al. Genetic predisposition of hand-foot skin reaction after sorafenib therapy in patients with hepatocellular carcinoma. Cancer. 2013 Jan 1;119(1):136-42.
[27] Boudou-Rouquette P, Narjoz C, Golmard JL, Thomas-Schoemann A, Mir O, Taieb F, et al. Early sorafenib-induced toxicity is associated with drug exposure and UGTIA9 genetic polymorphism in patients with solid tumors: a preliminary study. PLoS One. 2012;7(8):e42875.
[28] Boudou-Rouquette P, Ropert S, Mir O, Coriat R, Billemont B, Tod M, et al. Variability of sorafenib toxicity and exposure over time: a pharmacokinetic/pharmacodynamic analysis. Oncologist. 2012;17(9):1204-12.
[29] Estfan B, Byrne M, Kim R. Sorafenib in Advanced Hepatocellular Carcinoma: Hypertension as a Potential Surrogate Marker for Efficacy. Am J Clin Oncol. 2012 Apr 27.

Table 1: Demographic and Baseline characteristics of the patients.

	Total cohort (n=147)
Age, median [IQR]	64.1 [35-80]
Male/Female, n	124/23
HCV/Ethanol/HVB/others, n	84/37/17/9
***Child-Pugh A/B/, n**	121/22
Vascular invasion yes/no, n	51/96
Extrahepatic spread, yes/no n	27/120
BCLC stage, B/C, n	77/70
Performance status, 0 /1, n	123/24
PT, median [IQR] (%)	83 [35-100]
Bilirubin, median [IQR] (mg/dL)	1 [0.3-4.5]
Albumin, median [IQR] (g/dL)	39 [26-49]
HB, median [IQR] (mg/dL)	13.5 [8.8-17.5]
ASAT, median [IQR] (UI/L)	68.0 [5-575]
ALAT, median [IQR] (UI/L)	62.0 [16-493]
AP, median [IQR] (UI/L)	292.0 [49-2256]
GGT ,median [IQR] (109/L)	149 [18-1673]
Platelets, median [IQR] (109/L)	130.0 [72-509]
Systolic arterial pressure, median [IQR] (mm Hg)	130.0 [90-169]
Diastolic arterial pressure, median [IQR] (mm Hg)	75.5 [50-95]

*IQR: InterQuartile Range [Percentile 25 – Percentile 75]; HCV: Hepatitis virus C; HVB: Hepatitis virus B; NA: not applicable; PS: Performance status; BCLC: Barcelona Clinic Liver Cancer classification; PT: prothrombin time; HB: hemoglobin; ASAT: aspartate aminotransferase; ALAT: alanine aminotransferase; AP: alkaline phosphatase; GGT: gamma-glutamyltranspeptidase.** 4 patients with non-cirrhotic liver

Table 2: All type adverse events according CTCAE v3.0 in at least 5% of patients while on treatment.

	Grade I	Grade II	Grade III	Grade IV	All
	n (%)	n (%)	n (%)	n (%)	n (%)
Dermatologic					
Hand-Foot reaction II	-	44(30)	-	-	44(30)
Hand-Foot reaction I	31 (21)	-	-	-	31(21)
Rash	18(12.3)	5(3.4)	3(2)	-	26(18)
Foliculitis	16(10.9)	5(3.4)	2(1.4)	-	23(15.7)
Hand-Food reaction III	-	-	18(12.3)	-	18(12.3)
Facial edema-eritema	8(5.4)	2(1.4)	2(1.4)	-	12(8.2)
Dry mouth	9(6.1)	-	-	-	9(6.1)
Gastrointestinal					
Diarrhea mild-moderate	35(23.8)	7(4.8)	2(1.4)	-	44(30)
Increased bowel movements	28(19)	1(0.7)	1(0.7)	-	30(20.4)
Abdominal pain	2(1.4)	16(10.9)	1(0.7)	-	19(13)
Constipation	15(12.2)	1(0.7)	1(0.7)	-	17(11.6)
Abdominal disconfort	12(8.2)	3(2)	1(0.7)	-	16(10.8)
Diarrhea (occassional)	13(8.8)	-	-	-	13(8.8)
Pancreatitis	4(2.7)	4(2.7)	-	-	8(5.4)
Severe diarrhea	-	4(2.7)	5(3.4)	-	9(6.1)
Vomiting	8(5.4)	1(0.7)	-	-	9(6.1)
Epigastric pain	9(6.1)	-	-	-	9(6.1)
Cardiovascular					
Arterial Hypertension	28(19)	15(12.2)	1(0.7)	1(0.7)	45(30.6)
Others					
Hiporexia	64(43.5)	10(6.8)	-	-	74(50.3)
PS deterioration	26(17.7)	40(27.2)	-	-	66(44.9)
Fatigue	29(19.8)	8(5.4)	-	-	37(25.2)
Ascites	13(8.8)	19(13)	2(1.4)	-	34(23.1)
Pain	12(8.2)	12(8.2)	2(1.4)	2(1.4)	28(19)
Itching	18(12.3)	2(1.4)	1(0.7)	-	21(14.3)
Encephalopathy	7(4.8)	10(6.8)	4(2.7)	-	21(14.3)
Ascitis and edemas	1(0.7)	20(13.6)	-	-	21(14.3)

Infection	5(3.4)	2(1.4)	6(4.2)	-	13(8.8)
Voice change	12(8.2)	-	-	-	12(8.2)
Fall from standing height	8(5.4)	1(0.7)	1(0.7)	-	10(6.8)
Cramps	8(5.4)	-	-	-	8(5.4)

Table 3: Patients with adverse events ≥ grade II within the first 60 days.

AE ≥ Grade II within first 60 days with sorafenib dose modification (n= 107)		
	Patients - n	**%**
Dermatologic (n=37)		
Hand-Foot reaction II	13	12.1
Rash	8	7,5
Hand-Foot reaction III*	9	8.4
Facial edema-erythema	5	4.7
Testicular erythema	1	0.9
Psoriasis outbreak	1	0.9
Cardiovascular (n=14)		
Arterial Hypertension *	11	10.3
Sinusal tachycardia	2	1.9
Intermittent claudication	1	0.9
Gastrointestinal (n=3)		
Diarrhea	3	2.8
Others (n=56)		
PS deterioration**	18	16.8
Encephalopathy	7	6.5
Ascites	6	5.6
Anemia	4	3.7
Infection	3	2.8
Pancreatitis	3	2.8
Gout	2	1.9
Hemoptysis	1	0.9
Hematuria	1	0.9
Variceal bleeding	1	0.9
Abdominal pain	1	0.9

Shiver	1	0.9
Protrombin alteration	1	0.9
Chest pain - non cardiovascular	1	0.9
Symptomatic tumor progression	1	0.9
Itching	1	0.9
Mucosistis	1	0.9
Liver function alteration	1	0.9
Renal colic	1	0.9
Other	1	0.9

*3 patients developed Arterial Hypertension and Hand-Foot reaction III within the first 60 days and they needed more than 1 dose modification.
** 6 patients presented radiology tumor progression within the first 60 days. In those patients the median treatment duration was 1.4 months and the median OS was 3 months (IC95%: 0.6-5.5).
The median treatment duration of the other 12 patients was 5.6 months and the median OS was 11.6 months ((IC95%: 6.6-16.5).

Table 4: Hazard Ratios 95%CI for univariate analysis and multivariate analysis with time-dependent covariates

	Univariate	Multivariate***
Age, per 10 years increase	0.88 [0.72 to 1.06] p=0.176	
Gender (reference: Male)	0.96 [0.58 to 1.60] p=0.885	
Etiology (reference: HCV)	**1 (reference p=0.047**	
Ethanol	0.76 [0.39 to 1.48]	
HVB	0.64 [0.41 to 1.02]	
Others	1.74 [0.89 to 3.40]	
*Child-Pugh A/B (Reference: A)	1.49 [0.89 to 2.50] p=0.131	
Vascular invasion	1.39 [0.94 to 2.04] p=0.097	
Extrahepatic spread	**1.78 [1.14 to 2.79] p=0.012**	
BCLC stage, (Reference: B)	**1.72 [1.19 to 2.50] p=0.004**	**1.69 [1.18 to 2.50] p=0.005**
Performance status (Reference:0)	**3.33 [2.08 to 5.56] p<0.001**	**2.86 [1.75 to 4.55] p<0.001**
PT per 1 % increase	0.99 [0.98 to 1.01] p=0.390	
Bilirubin per 1 mg/dL increase	1.28 [0.99 to 1.65] p=0.060	
Albumin per 1 g/dL increase	**0.94 [0.91 to 0.98] p=0.004**	
HB per 1 mg/dL increase	**0.80 [0.72 to 0.89] p<0.001**	
ASAT, per 10 UI/L increase	1.02 [1.00 to 1.05] p=0.072	
ALAT, per 10 UI/L increase	1.02 [1.00 to 1.05] p=0.066	
AP, per 10 UI/L increase	**1.02 [1.01 to 1.02] p<0.001**	
AFP (Reference :≤200 ng/dl)	1.26 [0.87 to 1.82] p=0.216	
GGT, per 10 109/L)	**1.01 [1.00 to 1.02] p=0.012**	
Platelets, per 10 109/L increase	1.00 [0.98 to 1.02] p=0.932	
SBP, per 10 mmHg increase	0.96 [0.87 to 1.07] p=0.476	
DBP, per 10 mmHg increase	0.86 [0.72 to 1.03] p=0.108	
AE ≥ grade 2 within 60days**		
Dermatologic	**0.54 [0.34 to 0.87] p=0.010**	**0.58 [0.36 to 0.92] p=0.022**
Cardiovascular	0.98 [0.51 to 1.92] p=0.958	
Gastrointestinal	0.79 [0.41 to 1.52] p=0.461	
Bleeding	2.22 [0.70 to 7.14] p=0.174	
Infection	0.99 [0.31 to 3.13] p=0.983	
Other	1.59 [0.77 to 3.33] p=0.211	

HCV: Hepatitis virus C; HVB: Hepatitis virus B; NA: not applicable; PS: Performance status; BCLC: Barcelona
Clinic Liver Cancer classification; PT: prothrombin time; HB: hemoglobin; ASAT: aspartate aminotransferase;
ALAT: alanine aminotransferase; AP: alkaline phosphatase; GGT: gamma-glutamyltranspeptidase.
SBP: Systolic Blood Pressure.DSP: Diastolic Blood Pressure
*4 patients with non-cirrhotic
**AE ≥ grade 2 within 60days:Adverse Events (which determine doses modification)
***Multivariate 3: clinical significant variables at univariate analysis considered for a forward stepwise approach.