Predictors of survival of patients with advanced hepatocellular carcinoma who permanently discontinued sorafenib.

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FOOTNOTE PAGE

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Abbreviation:

Adverse effects (AE)

Alpha-fetoprotein (AFP)

Barcelona Clinic Liver Cancer (BCLC)

Confidence interval (CI)

Contrast-enhanced computed tomography (CT-scan)

Eastern Cooperative Oncology Group (ECOG)

Extrahepatic growth (EHG)

Hazard ratio (HR)

Hepatitis B virus (HBV)

Hepatitis C virus (HCV)

Hepatocellular carcinoma (HCC)

Intrahepatic growth (IHG)

Magnetic resonance imaging (MRI)

New extrahepatic lesion and/or vascular invasion (NEH)

New intrahepatic lesion (NIH)

Post progression survival (PPS)

Performance status (PS)

Post-sorafenib survival (PSS)

Response Evaluation Criteria in Solid Tumors (RECIST)

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ABSTRACT

Background and aims: Treatment with sorafenib of patients with advanced hepatocellular carcinoma (HCC) is challenged by anticipated discontinuation due to tumor progression, liver decompensation or adverse effects (AE). While post-progression survival is clearly determined by the pattern of tumor progression, understanding the factors that drive prognosis in patients who discontinued sorafenib for any reason may help to improve patient management and second line trial design. Methods: Patients consecutively admitted to 3 referral centers who were receiving best supportive care following permanent discontinuation of sorafenib for any reason, were included. Post-sorafenib survival (PSS) was calculated from the last day of treatment to death or last visit available. Results: Two-hundred and sixty patients were included in this prospective study, 67 year old, 60% hepatitis C, 51% Child-Pugh A, 83% Performance Status (PS) ≥1, 41% macroscopic vascular invasion and 38% extrahepatic tumor spread. Overall, median PSS was 4.1 (3.3-4.9) months, resulting from 4.6 (3.3-5.7) months for 123 progressors, 7.3 (6.0-10.0) months in 77 with AE and 1.8 (1.6-2.4) months in 60 decompensated patients ($p<0.001$). PSS was independently predicted by PS, prothrombin time, extrahepatic tumor spread and macrovascular invasion and reason for discontinuation. Two hundred patients potentially eligible to second line therapy, had a PSS of 5.3 (4.6-7.1) months, which was dependent on reasons of discontinuation ($p=0.004$), PS ($p<0.001$), macrovascular invasion ($p<0.001$) and extrahepatic metastases ($p<0.002$). Conclusion: discontinuation due to AE in the absence of macrovascular invasion, extrahepatic metastases and deteriorated PS, predicts the best PSS in compensated patients, thereby setting the stage for both improved patient counseling and selection second line therapy.

INTRODUCTION

Sorafenib is the standard of care for treatment of patients with advanced hepatocellular carcinoma (HCC), following a registration and a confirmatory study that proved efficacy of this regimen in extending survival of the affected patients, with a satisfactory record of tolerability and safety (1-4). While the patients populations enrolled in the two trials showed significant differences in treatment duration (5 months for western vs 3 months for eastern), likely reflecting nuances in the severity of the background liver disease associated to liver cancer, in both cohorts treatment outcome was inexorably challenged by high rates of anticipated discontinuation caused by tumor progression, liver decompensation and adverse effects (AE) (3,4). This was also the *leitmotiv* of several field practice studies, where the median duration of treatment with sorafenib barely exceeded 7 months in the context of a median survival (OS) of approximately 13 months, suggesting a 6 month gain of survival after stopping anti-cancer therapy, on average (5,6). In a strive of optimizing sorafenib therapy in patients with HCC, the database of pragmatic studies carried out in different geographical regions have extensively been scrutinized with the aim to identify serum bio-markers or clinical features predictive of a response which might help sparing unnecessary treatment-related morbidity and costs in refractory patients (5-8). This, in fact, is not a trivial point as it might help optimizing treatment schedules on one side and, on the other hand, identifying patients to be enrolled in second line treatment on the basis of the reasons for treatment interruption. This is in fact the message of a recent study in Spain describing how survival of patients with tumor progression during sorafenib therapy strictly depended on the pattern of tumor progression, meaning a worse prognosis for patients with de-novo extrahepatic tumor lesions or neoplastic vascular invasion compared to patients with an expansion of pre-existing nodules or new intra-hepatic lesions, only (5). However, owing to the fact that in addition to the pattern of tumor progression, other factors may drive prognosis in patients who discontinued sorafenib for any reason, we prospectively aimed to identify such predictors of survival in this specific set of HCC patients. A subsidiary aim of the study was to identify and classify by survival predictors patients

who were potential candidates to a second line therapy, with the hope of powering future registration trials.

METHODS

Study design

This is a prospective multicenter, investigator driven, observational study that in July 2008 started enrolling patients from three referral centers in Italy and ended in March 2013. The primary end point was patient survival after permanent discontinuation of sorafenib (PPS); the secondary end points were a) identification of predictors of survival after sorafenib discontinuation and b) identification of survival predictors of patients who were potentially eligible to second line therapy.

Patients' selection

Included were patients in Barcelona Clinic Liver Cancer (BCLC) -C and patients in BCLC-B stage who received sorafenib because were unfit to or failed locoablative treatments. Excluded were patients with a performance status (PS) score >2 and clinical decompensation (6,9). In a kick-off meeting between the participating centers, standardized criteria for treatment compliance, type/degree of AE, treatment interruption and dose reduction, were established All the three participating centers at the present study were involved in the previous reports of the SOFIA study (6,8). Included were all patients who permanently discontinued sorafenib for any reason and were subsequently receiving best supportive care. The enrollment was consecutive and independent on Child-Pugh score and BCLC stage. Excluded were patients with a liver transplant, those previously enrolled in first-line registration trials and those included in second-line trials after sorafenib discontinuation. Tumor progression was defined either radiologically by modified response evaluation criteria in solid tumors (mRECIST) criteria or clinically in terms of worsening of PS or onset of symptoms unrelated to liver failure. By the same token, all deaths following clinical decompensation with jaundice, haemorrhage or encephalopathy in the absence of radiological signs of cancer progression, were attributed to liver failure (10,11). Radiological evaluation by mRECIST was employed to assess a response to both locoregional and systemic therapy when the SOFIA (6) study was designed. Another reason for treatment discontinuation was unacceptable treatment toxicity, i.e. grade 2-4 AEs not responding to dose reductions and/or temporary interruption of

treatment as suggested by the manufacturer (13). In patients who interrupted treatment for both tumor progression and AE, the former was considered the leading cause for interruption (6). Liver decompensation was defined by one of the following events: jaundice, ascites, gastrointestinal hemorrhage, encephalopathy in absence of radiologic signs of tumor progression, although it could be difficult to exclude unequivocally underlying tumor progression when liver function deteriorates (6). Therefore, whenever both tumor progression and liver decompensation occurred, the former was considered the leading cause for discontinuation (6). A written informed consent was obtained from each patient according to the ethics committee and the ethical guidelines of the 1975 Declaration of Helsinki, as updated in 2004.

Follow-up and measures

The primary end point of PSS was the time lag between the last day of treatment to death or last visit available. Clinical and laboratory exams were performed within 5 days after sorafenib discontinuation to be repeated monthly or at closer intervals if clinically indicated. Blood cell count, serum chemistries, and serum alfa-fetoprotein (AFP) levels were measured by standard laboratory procedures. PS was graded according to the Eastern Cooperative Oncology Group (ECOG) (11). A radiological response to therapy was evaluated by Contrast-enhanced computed tomography (CT-scan) or Magnetic Resonance Imaging (MRI) according to mRECIST at the end of treatment, independently of the reason for discontinuation. Imaging studies were repeated every 2 months during post-sorafenib follow-up, whenever allowed by the general conditions of the patient (11). The other objectives of the study were: patients potentially eligible to a second line treatment because of preserved liver function and secondly, survival evaluation according to patients stratification by the pattern of tumor progression according to Reig et al (5). In that study, survival was efficiently stratified by intrahepatic growth (IHG) or extrahepatic growth (EHG), i.e. a >20% increase in tumor size against a known baseline lesion, onset of a new intrahepatic lesion (NIH), or new extrahepatic lesions and/or vascular invasion (NEH) (5). In patients with concomitant IHG/EHG and NIH/NEH, the latter was considered dominant in terms of progression pattern.

Lastly, we modeled the probability of survival in three hypothetical compensated patients according to predictors identified by the Cox model.

Statistical Analysis

Data were collected by experienced medical personnel involved in the study using a common electronic database. Continuous variables were expressed as mean ± standard deviation, while categorical variables were analyzed as frequency and percentages. The following baseline features were considered for univariate analysis: age, gender, ECOG Performance Status (PS), etiology of liver disease, platelet count, albumin level, bilirubin level, alkaline phosphatase, creatinine levels, international normalized ratio (INR), AFP level, macrovascular invasion, extrahepatic spread, tumor size, number of neoplastic lesions, presence of ascites, presence of encephalopathy, and reasons for end of sorafenib therapy. Patient characteristic considered for analysis are those identified at the time of sorafenib interruption. Survival was analyzed by a Kaplan-Meier test, and differences in the survival rates were assessed by the log-rank test. Variables with a p value <0.10 at univariate analysis were included in the final multivariate model. Cox's proportional-hazard model was used to identify prognostic factors for mortality in a multiple regression analysis. To avoid the effect of co-linearity with single variables, BCLC and Child-Pugh score were not included in the same multivariate model. For all analyses, $p \leq 0.05$ was considered statistically significant. All analyses and graphics were performed using the R Statistical Computing Environment (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

We identify 312 patients attending the three centers who permanently discontinued sorafenib. Excluded were 8 patients treated by liver transplantation, 4 treated with sorafenib in a first line clinical trial and 40 enrolled in second-line trials. Ultimately, 260 (83%) patients were enrolled, and at the time of database lock (November 2013) 225 patients died, 31 were still alive and 4 were lost to follow-up.

Patients at sorafenib discontinuation

Clinical and laboratory characteristics of the patients when sorafenib was permanently discontinued are summarized in Table 1. All patients had cirrhosis (60% HCV, 16% HBV, 51% Child-Pugh A, 42% Child-Pugh B and 7% Child Pugh C). The majority (83%) of the patients had PS >1, 41% had macroscopic vascular invasion and 38% had extrahepatic tumor spread. Twenty-one patients (8%) had remained in the BCLC B, 193 (74%) either migrated to or maintained BCLC C and 46 (18%) migrated to BCLC D. Reasons for permanent treatment discontinuation were liver decompensation in 60 (23%) patients, AE in 77 (30%) and tumor progression in 123 (47%). The dominant cause of treatment discontinuation among the 77 patients who permanently discontinued sorafenib following AE was fatigue, either alone or associated to another AE (Table 2).

Post-sorafenib survival

While median overall PSS was 4.1 (95% CI 3.3-4.9) months (Figure 1), the median PSS according to the BCLC B, BCLC C and BCLC D status was 9.3 (95%CI 7.4–14.6) months, 4.6 (95%CI 3.7–5.6) months and 1.6 months (95% CI 1.3-2.8) respectively ($p<0.001$). The median PSS who permanently interrupted sorafenib in patients with tumor progression, AE and liver decompensation was 4.6 (95% CI 3.3–5.7), 7.3 (95% CI 6.0–10.0) and 1.8 (95% CI 1.6–2.4) months, respectively ($p<0.001$; Figure 2).

By univariate analysis, 11 variables of PSS were identified (Table 3). By multivariate Cox analysis, PS [HR 2.4 (1.6-3.5)], prothrombin time [HR 2.9 (1.7-4.9)], macrovascular invasion [HR 1.8 (1.3-2.4)], extrahepatic spread [HR 1.6 (1.2-2.1)], AFP [HR 1.4 (1.01-1.9)], reason for sorafenib

discontinuation [liver decompensation vs AEs HR 2.6 (1.8–3.7) and tumor progression vs AEs [HR 1.5 (1.1–2.1)], were the independent predictors of shorten survival (Table 3).

Estimated survival of potentially candidates to 2nd line trials

Two hundred compensated patients (77%) with compensated disease were considered potentially eligible to a second-line treatment, whereas 60 patients who permanently interrupted sorafenib for liver decompensation, were excluded. These patients had a Child-Pugh score up to B7, if ascites controlled by diuretics was present, only one between bilirubin 2-3 mg/dL and serum albumin 2.8-3.5 g/dL, was accepted. In these patients the median PSS was 5.3 (95% CI 4.6-7.1) months, being 7.3 (95% CI 6.0-10.0) months for those patients who discontinued for AE compared to 4.6 (95% CI 3.3-5.7) months in those who discontinued for tumor progression (p=0.005). In this subset of selected patients, the independent predictors of mortality by multivariate Cox analysis were: PS, reason for sorafenib discontinuation, macrovascular invasion and extrahepatic spread (Table 4). The estimated probability of PSS in three hypothetical compensated patients with advanced HCC, according to the predictors of mortality by the Cox model (ECOG PS, vascular invasion, extrahepatic spread and reasons of discontinuation) is shown in Figure 3. The 1-year probability of overall survival for a patient who discontinued for AE, with ECOG PS 0, without macrovascular invasion and without extrahepatic metastases is 73%, compared to 0.6% for a patient who discontinued for tumor progression with ECOG PS 1, macrovascular invasion and extrahepatic metastases.

Validation of BCLC upon progression

The median PSS in patients with radiologic tumor progression due to >20% increase in tumor size (IHG, n 20; EHG, n 10), NIH (n 30), or NEH (n 58) was 7.5, 3.2, 5.4, and 3.1 months, respectively. Progression due to NEH was associated to a significantly worse PSS compared to other patterns of progression [3.1 (95%CI 2.25-3.36) vs 5.7 (95%CI 3.50-8.04) months, p=0.02]. Using the new proposed classification of "BCLC upon progression", 7 patients were found to be BCLCp-B [PSS 4.7 (1.7-11.5) months] at the time of sorafenib discontinuation for tumor progression, while 37

patients were BCLCp-C1 and 58 were BCLCp-C2 [5.7 (0.6-27.7) vs 3.0 (0.6-25.5) months, p=0.001].

DISCUSSION

Sorafenib therapy in HCC patients is frequently challenged by the onset of unfavorable events, mainly represented by AE, cancer progression and liver failure, all leading a majority of patients to prematurely interrupt treatment and lose significant therapeutic benefits (3-7). The different reasons for premature interruption of sorafenib therapy in such a difficult to treat population may have different implications on prognosis and patient access to a second-line salvage therapy. Survival after sorafenib discontinuation could be predicted in previous studies including the registration trial SHARP, however the present is the first study specifically designed to investigate the course and survival predictors of these patients with an adequate sample size and follow-up. In the context of this study, we modelled three categories of patients who following sorafenib discontinuation had different expected survival times and different expected benefits by second line drugs/management. Finally, the study allowed to identify those prognostic factors during post sorafenib course which in the future may help tailoring management of patients.

While our cohort of patients enrolled in the registration trial achieved similar survival benefits after sorafenib discontinuation, yet the two study cohorts consistently differed by the reasons for treatment interruption. Not surprisingly, the best survival benefits were seen in patients who discontinued sorafenib for AEs and in those who maintained PS and BCLC stage unchanged, compared to patients in whom either liver disease or cancer progressed. Our findings of a favorable prognostic relevance of AEs in patients under sorafenib, lend indirect support to the observations of Reig and co-workers who recently associated early onset of dermatologic AEs with better outcomes of sorafenib therapy in HCC patients (13). Dermatological AE were seen in a minority (25/77) of our 77 patients who discontinued sorafenib for any AE, whereas the only 4 patients who permanently discontinued treatment for dermatological reason, achieved an extended survival after survival discontinuation. Incidentally, one major difference between our study and the sorafenib registration trial SHARP and the study by Reig and co-workers, was the use as co-primary end-points of overall survival and time to symptomatic progression, thereby allowing symptomless

patients to maintain sorafenib therapy even after radiological progression of HCC as determined by RECIST.

Our observations are not unprecedented since similar conclusions were drawn by a small study that however, described 36 patients treated with sorafenib, most receiving different second line regimens and a minority BSC only (14).

Not unexpectedly, while BCLC stage system retained its prognostic power even in patients with advanced cancer disease who discontinued sorafenib, at the same time, our study validates the prognostic value of "*BCLC staging system upon progression*" as proposed by Reig et al., who firstly established a correlation between progression pattern and PPS, and demonstrated differences in survival of BCLC C patients after radiological progression based on the absence or presence of NEH (5). In that study, BCLC stage at the time of radiologic progression was crucial to properly predict the prognosis of patients who were still eligible to second-line therapies because of preserved liver function (Child-Pugh A) and PS (0-1). We acknowledge that our study might to some extent be biased by a time-fixed analysis of the outcomes compared to the study of Reig and coworkers relying on a more complex time-dependent scrutiny of the findings. However, at variance with dr Reig's investigation covering the period of time of sorafenib therapy, our study focused on HCC course after permanent discontinuation of sorafenib, only, thereby lacking any interaction with external time-dependant covariates (15). Moreover, our study further highlights the complexity of prognosis in HCC which depends on an interaction between the degree of liver dysfunction, constitutional symptoms and tumor burden, the modeling of three patient categories having different survival probabilities and characteristics in terms of tumor burden and liver function at the time of sorafenib interruption, might help designing more sensitive second line treatment studies based on the enrolment of appropriate target populations. Not unexpectedly, patients who withdrew sorafenib due to deterioration of liver function were those with the shortest survival time of 1.8 months on average who were unfit to tumor targeted therapies compared to those who discontinued for tumor progression or AE. While the latter patients could benefit from

potentially effective second line anti-cancer regimens, patients with tumor progression should be offered to keep on with sorafenib therapy on the assumption that HCC is notwithstanding responding to treatment, whereas add on therapy with another systemic drug targeting a different tumor pathway than sorafenib, needs validation in controlled trials. Data are cumulating demonstrating how patients with advanced HCC can tolerate continuous treatment with sorafenib even after radiological tumor progression was demonstrated. On the other hand, we must acknowledge that the course of HCC may accelerate upon sorafenib withdrawal (16,17).

Our finding of longer survival of compensated patients, potentially eligible to a second line treatment, suggests that in previous trials enrolling unselected populations of non-responders to sorafenib, evaluation of experimental treatments could have been inaccurate due to such a releant selection bias. In BCLC-C patients, three large randomized phase III trials evaluating brivanib, everolimus and ramucirumab as second-line therapies, failed to reach the predefined end points of increased survival with respect to placebo treated patients (18-20). Such a discrepancy with the outcome of phase II trials where these agents showed signals of anti-cancer activity, makes wondering whether failures with newer molecules was the consequence of an unbalanced stratification of patients leading to study enrichment with patients with less aggressive tumors like those who discontinued sorafenib for AE. As a matter of fact in the second-line Brisk-PS study of brivanib the survival times of patients on active treatment were not significantly longer than those in the placebo group (18). Reassessment of survival figures of the placebo arm of numerous RCTs disclosed a significant heterogeneity of survival (21-23), likely reflecting inclusion of patients at different stages of tumor disease and with different molecular and biological profile of their tumors, a variable that is not incorporated in any tumor staging system, as already demonstrated in previous meta-analysis (22,23). This make even more compelling to standardized assessment of survival in treated patients with respect to sorafenib interruption with the aim to: 1) evaluate the natural history and validate the predictive power of biological or radiological surrogate markers, 2) control for confounding factors in observational studies, 3) calculate the sample size and stratify subjects in

phase II and III RCTs, and 4) assess treatment effect size to formulate therapeutic strategies. Interestingly, our model based on predictors of shortened survival was able to efficiently separate candidates to second line therapy into those with a 75% probability of one-year survival who had the most favorable off-treatment predictors from those with unfavorable predictors but still were eligible to a second line trial. While this model may assist clinicians in counseling and decision-making, our finding of PSS being dependent on the cause of treatment interruption provides a practical means to better separate sorafenib-tolerant who should continue treatment despite tumor progression from intolerant ones who might benefit from inclusion into registration trials of second line therapy, only. Indeed, while waiting for well-grounded evidence for the existence of second-line options for HCC progressors, sorafenib could still be offered beyond radiological, but not symptomatic progression, a choice that represents a reasonable alternative to no treatment at all. In our opinion, as in other tumor types, this controversial approach, need to be investigated in future large trials.

LEGENDS TO FIGURES

1. Kaplan-Meier survival estimation after sorafenib discontinuation in the whole cohort. Among 260 patients, the median PSS was 4.1 (95% CI 3.3-4.9) months.
2. Kaplan-Meier survival estimation after sorafenib discontinuation according to the reason why sorafenib was discontinued.
3. Estimated probability of survival after sorafenib discontinuation for three hypothetical compensated patients with advanced HCC after sorafenib discontinuation, according to predictors of mortality identified by the Cox model. (A) Patient who discontinued for AE, with ECOG PS 0, without both macrovascular invasion and extrahepatic metastases; (B) patient who discontinued for tumor progression with ECOG PS 0 without macrovascular invasion but with extrahepatic metastases; (C) patient who discontinued for tumor progression with ECOG PS 1 with both macrovascular invasion and extrahepatic metastases.

REFERENCES

1. European Association For The Study Of The Liver; European Organization For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908-943.

2. Bruix J, Sherman M. American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020-1022.

3. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–390.

4. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34.

5. Reig M, Rimola J, Torres F, Darnell A, Rodriguez-Lope C, Forner A et al. Post-progression survival of patients with advanced hepatocellular carcinoma. Rationale for second line trial design. Hepatology 2013;58:2023-2031.

6. Iavarone M, Cabibbo G, Piscaglia F, Zavaglia C, Grieco A, Villa E, et al; SOFIA (SOraFenib Italian Assessment) study group. Field-practice study of sorafenib therapy for hepatocellular carcinoma: a prospective multicenter study in Italy. Hepatology 2011;54:2055-2263.

7. Personeni N, Bozzarelli S, Pressiani T, Rimassa L, Tronconi MC, Sclafani F, et al. Usefulness of alpha-fetoprotein response in patients treated with sorafenib for advanced hepatocellular carcinoma. J Hepatol 2012;57:101-107.

8. Cammà C, Cabibbo G, Petta S, Enea M, Iavarone M, Grieco A, et al; WEF study group; SOFIA study group. Cost-effectiveness of sorafenib treatment in field practice for patients with hepatocellular carcinoma. Hepatology 2013;57:1046-1054.

9. Agenzia Italiana del Farmaco. Registro farmaci oncologici sottoposti a monitoraggio. http://antineoplastici.agenziafarmaco.it/normativa_registro_trast.htm. Last access January 2014.

10. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30:52-60.

11. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

12. EU summary of Product Characteristics for Nexavar, November 2010, Bayer Schering Pharma AG, Berlin Germany.

13. Reig M, Torres F, Rodriguez-Lope C, Forner A, LLarch N, Rimola J, et al. Early dermatologic adverse events predict better outcome in HCC patients treated with sorafenib. J Hepatol 2014;61:318-324.

14. Shao YY, Wu CH, Lu LC, Chan SY, Ma YY, Yen FC, et al. Prognosis of patients with advanced hepatocellular carcinoma who failed first-line systemic therapy. J Hepatol 2014;60:313-318.

15. Fisher LD, Lin DY. Time-dependent covariates in the Cox proportional-hazards regression model. Annu Rev Public Health1999;20:145-157.

16. Oxnard GR, Morris MJ, Hodi FS, Baker LH, Kris MG, Venook AP, et al. When progressive disease does not mean treatment failure: reconsidering the criteria for progression. J Natl Cancer Inst 2012;104:1534-1541.

17. Miyahara K, Nouso K, Morimoto Y, Takeuchi Y, Hagihara H, Kuwaki K, et al; Okayama Liver Cancer Group. Efficacy of sorafenib beyond first progression in patients with metastatic hepatocellular carcinoma. Hepatol Res 2014;44:296-301.

18. 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;31:3509-3516.

19. Available at: http://www.novartis.com/newsroom/media-releases/en/2013/1721562.shtml [cited August 2013].

20. Available at: http://files.shareholder.com/downloads/LLY/3291466134x0x761362/32cec437-a8bc-4cfd-b19a-619a00af44b3/LLY_News_2014_6_11_Product.pdf [cited June 2014].

21. Bolos D, Finn RS. Systemic therapy in HCC: Lessons from brivanib. J Hepatol 2014;61:947-950.

22. Cabibbo G, Enea M, Attanasio M, Bruix J, Craxì A, Cammà C. A Meta-Analysis of Survival Rates of Untreated Patients in Randomized Clinical Trials of Hepatocellular Carcinoma. Hepatology 2010;51:1274-1283.

23. Combescure C1, Foucher Y, Jackson D. Meta-analysis of single-arm survival studies: a distribution-free approach for estimating summary survival curves with random effects. Stat Med 2014;33:2521-2537.

Table 1. Demography and baseline characteristics of the 260 patients enrolled in the study.

Patients – No.	260
Age – yrs*	67±9
Male – No. (%)	208 (80)
Etiology – No. (%)	
HCV only	156 (60)
HBV only	41 (16)
alcohol abuse only	19 (7)
multiple	19 (7)
other	25 (9)
ECOG PS – No. (%)	
0	43 (17)
1-2	180 (69)
3-4	37 (14)
Albumin – g/dL*	3.4±0.5
Total Bilirubin – mg/dL*	2.0±2.9
Ascites – No. (%)	110 (42)
Hepatic Encephalopathy, No. (%)	19 (7)
AFP ≥200 ng/dL – No. (%)	115 (44)
Disease burden – No. (%)	
macroscopic vascular invasion	107 (41)
extrahepatic spread	99 (38)
Reason for sorafenib interruption– No. (%)	
Tumor progression	123 (47)
Adverse events	77 (30)
Liver decompensation	60 (23)

*mean ± standard deviation; HCV: Hepatitis virus C; HVB: Hepatitis virus B; ECOG PS: Eastern Cooperative Oncology Group Performance Status; AFP alpha-fetoprotein.

Table 2. Causes of definitive interruption in 77 patients who discontinued for adverse effects.

Causes of definitive interruption	Frequency N (%)	Treatment duration Months, median (min-max)	Survival post-definitive interruption Months, median (min-max)
Fatigue alone	20 (26.0)	1.9 (0.5-17.9)	9.1 (0.9-38.4)
Acute upper gastrointestinal bleeding	7 (9.0)	2.9 (0.6-8.7)	11.5 (1.9-32.4)
Heart failure	6 (7.8)	2.7 (0.7-22.2)	5.6 (0.6-14.9)
Diarrhea	5 (6.5)	6.3 (0.7-9.5)	7.9 (1.2-23.7)
Fatigue and diarrhea	4 (5.2)	2.2 (0.8-5.3)	16.7 (10.2-24.2)
Hand-foot reaction	4 (5.2)	2.6 (0.5-5.6)	24.7 (7.4-39.5)
Anemia without apparent bleeding	3 (3.9)	1.2 (0.7-24.5)	13.4 (7.0-21.2)
Fatigue and arterial hypertension	3 (3.9)	3.7 (1.5-4.3)	16.3 (4.1-32.4)
Arterial hypertension	2 (2.6)	5.6 (5.0-6.2)	4.6 (2.0-7.1)
Cholangitis/cholecystitis	2 (2.6)	1.4 (0.7-2.1)	5.6 (1.2-10)
Fatigue and weight loss	2 (2.6)	1.1 (0.4-1.4)	5.7(5.4-6.0)
Anorectal abscess and sepsis	2 (2.6)	6.6 (6.3-7.0)	6.9 (6.5-7.3)
Rash	2 (2.6)	0.5 (0.3-0.7)	4.1 (1.0-7.1)
Pancytopenia	2 (2.6)	8.0 (1.6-14.5)	7.2 (5.1-9.3)
Thrombocytopenia	2 (2.6)	3.8 (1.8-5.8)	5.5 (1.9-9.0)
Hepatic abscess and sepsis	1 (1.3)	11.5	1.2
Acute myocardial infarction	1 (1.3)	0.7	4.6
Femoral fracture	1 (1.3)	2.7	3.8
Peripheral neuropathy	1 (1.3)	6.7	9.0
Duodenal ulcer	1 (1.3)	3.5	3.6
Acute kidney injury	1 (1.3)	46.9	8.9
Pulmonary embolism	1 (1.3)	8.4	3.0
Rectal bleeding	1 (1.3)	6.3	6.2
Erysipelas	1 (1.3)	2.3	1.4
Ventricular intracavitary thrombus	1 (1.3)	3.6	14.8
Fatigue and hand-foot reaction	1 (1.3)	4.0	15.3

Table 3. Univariate and multivariate Cox analysis of factors associated with mortality after sorafenib discontinuation in 260 HCC patients.

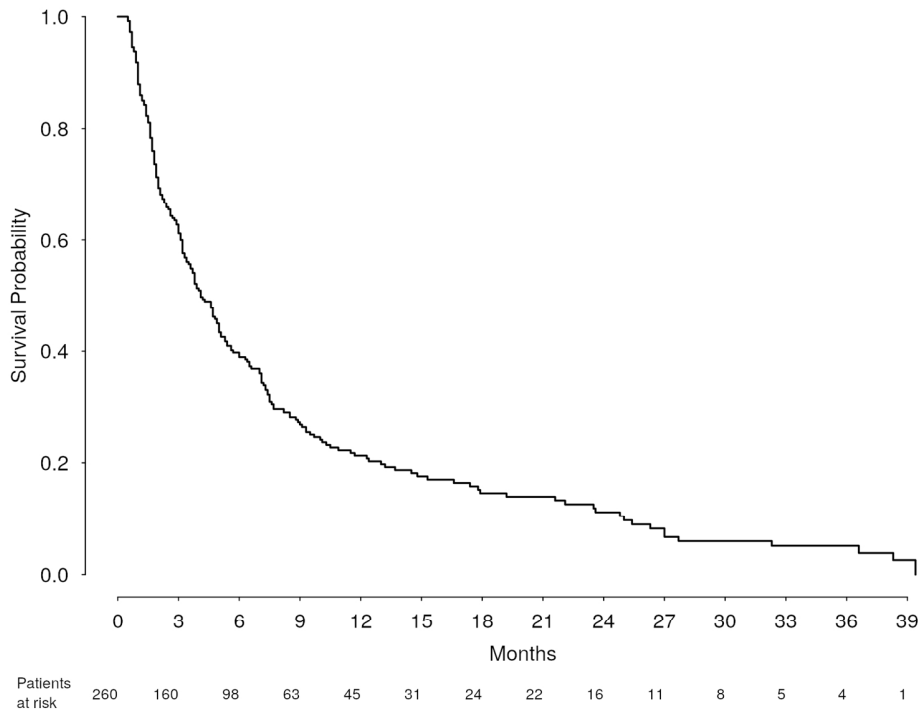
	Univariate		Multivariate	
Predictors	HR (95% CI)	p-value	HR (95% CI)	p-value
ECOG PS (>0 vs 0)	2.4 (1.6-3.5)	<0.001	2.4 (1.6-3.5)	<0.001
Prothrombin time (continue)	3.1 (2.0-4.8)	<0.001	2.9 (1.7-4.9)	<0.001
Macrovascular invasion (yes/no)	1.9 (1.5-2.5)	<0.001	1.8 (1.3-2.4)	<0.001
Reason for sorafenib discontinuation				
Tumor progression vs AE	1.6 (1.1-2.2)	<0.001	1.5 (1.1-2.1)	0.010
Clinical decompensation vs AE	3.0 (2.1-4.4)	<0.001	2.6 (1.8-3.7)	<0.001
Extrahepatic tumor spread (yes/no)	1.5 (1.2-4.7)	<0.002	1.6 (1.2-2.1)	0.001
AFP (≥400 vs <400 ng/mL)	1.6 (1.2-2.0)	<0.001	1.4 (1.0-1.9)	0.026
Ascites (yes/no)	1.7 (1.3-2.2)	<0.001	-	-
Bilirubin – mg/dL (continue)	1.03 (1.0-1.1)	0.0038	-	-
Sex (male vs female)	1.4 (1.0-2.0)	0.047	-	-
Albumin – g/dL (continue)	0.7 (0.6-0.9)	0.024	-	-

HR hazard ratio; CI confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; AE adverse effects; AFP alpha-fetoprotein.

Table 4. Multivariate Cox analysis of factors associated with mortality after sorafenib discontinuation in 200 compensated HCC patients.

	Multivariate analysis	
Predictors	HR (95% CI)	p-value
ECOG PS (1 vs 0)	2.6 (1.7-4.0)	<0.001
Reason for sorafenib discontinuation		
Tumor progression vs AE	1.6 (1.2-2.2)	0.004
Macrovascular invasion (yes vs no)	2.1 (1.6-3.0)	<0.001
Extra-hepatic spread (yes vs no)	1.8 (1.3-2.5)	0.001

HR hazard ratio; CI confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; AE adverse effects.



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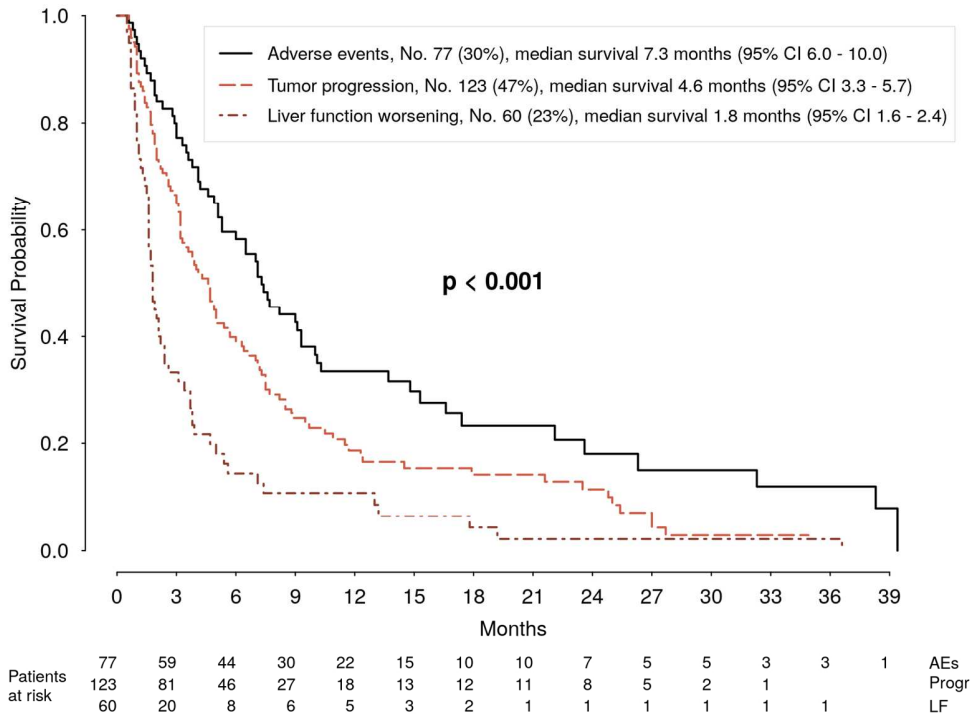

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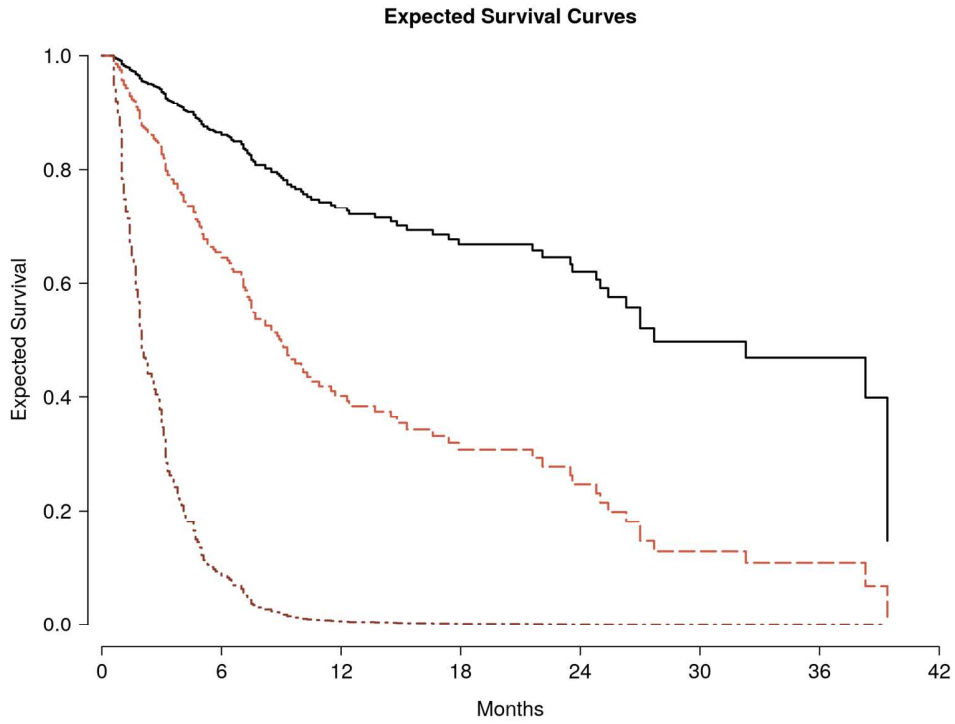

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