Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: Subanalyses of a phase III trial

Jordi Bruix1,*, Jean-Luc Raoul1,†, Morris Sherman3,†, Vincenzo Mazzaferro4,†, Luigi Bolondi5,†, Antonio Craxi6,†, Peter R. Galle7,†, Armando Santoro8,†, Michel Beaugrand9,†, Angelo Sangiovanni10,†, Camillo Porta11,†, Guido Gerken12,†, Jorge A. Marrero13,†, Andrea Nadel14,†, Michael Shan14,†, Marius Moscovici15,†, Dimitris Voliotis14,†, Josep M. Llovet1,16,17,*,†

1Barcelona Clinic Liver Cancer (BCLC) Group, Liver Unit, CIBERehd, Institut d’Investigacions Biomèdiques, August Pi i Sunyer (IDIBAPS), Hospital Clinic Barcelona, Barcelona, Spain; 2Centre Eugène Marquis and Institut National de la Santé et de la Recherche Médicale (INSERM) U991, Rennes, France; 3Toronto General Hospital, Toronto, ON, Canada; 4National Cancer Institute, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Foundation, Milan, Italy; 5Azienda ospedaliero-universitaria Policlinico Sant’Orsola Malpighi, University of Bologna, Bologna, Italy; 6Cattedra ed Unità Operativa di Gastroenterologia, University of Palermo, Italy; 7Medical Department, University Medical Center, Mainz, Germany; 8Instituto Clinico Humanitas, Milan, Italy; 9Centre Hospitalier Universitaire (CHU) Hôpital Jean Verdier, Assistance Publique–Hôpitaux de Paris (AP-HP), Laboratoire de Cyrogénétique, Bondy, Paris, France; 10Fondazione Istituto Di Ricovero e Cura a Carattere Scientifico (IRCCS), Ca’ Granda Ospedale Maggiore Policlinico-Milano, Milan, Italy; 11IRCCS San Matteo University Foundation, Pavia, Italy; 12University Hospital Essen, Essen, Germany; 13Multidisciplinary Liver Tumor Clinic, University of Michigan, Ann Arbor, MI, USA; 14Bayer HealthCare Pharmaceuticals, Montville, NJ, USA; 15Bayer HealthCare Pharmaceuticals, Milan, Italy; 16Mount Sinai Liver Cancer Program, Mount Sinai School of Medicine, New York, NY, USA; 17Institució Catalana de Recerca i Estudis Avançats, Catalonia, Spain

Background & Aims: The Sorafenib Hepatocellular Carcinoma (HCC) Assessment Randomized Protocol (SHARP) trial demonstrated that sorafenib improves overall survival and is safe for patients with advanced HCC. In this trial, 602 patients with well-preserved liver function (>95% Child–Pugh A) were randomized to receive either sorafenib 400 mg or matching placebo orally b.i.d. on a continuous basis. Because HCC is a heterogeneous disease, baseline patient characteristics may affect individual responses to treatment. In a comprehensive series of exploratory subgroup analyses, data from the SHARP trial were analyzed to discern if baseline patient characteristics influenced the efficacy and safety of sorafenib.

Methods: Five subgroup domains were assessed: disease etiology, tumor burden, performance status, tumor stage, and prior therapy. Overall survival (OS), time to progression (TTP), disease control rate (DCR), and safety were assessed for subgroups within each domain.

Results: Subgroup analyses showed that sorafenib consistently improved median OS compared with placebo, as reflected by hazard ratios (HRs) of 0.50–0.85, similar to the complete cohort (HR = 0.69). Sorafenib also consistently improved median TTP (HR, 0.40–0.64), except in HBV-positive patients (HR, 1.03), and DCR. Results are limited by small patient numbers in some subgroups. The most common grade 3/4 adverse events included diarrhea, hand-foot skin reaction, and fatigue; the incidence of which did not differ appreciably among subgroups.

Conclusions: These exploratory subgroup analyses showed that sorafenib consistently improved median OS and DCR compared with placebo in patients with advanced HCC, irrespective of disease etiology, baseline tumor burden, performance status, tumor stage, and prior therapy.

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Introduction

Hepatocellular carcinoma (HCC) is often diagnosed at an advanced stage, when most potentially curative therapies, such as resection, transplantation, and percutaneous ablation, are of limited utility [1–3]. Only approximately 30–40% of patients are diagnosed at an early stage and can benefit from such curative...
therapies [1,2], and up to 70% of patients who undergo these procedures will have recurrent disease within 5 years and reach a more advanced tumor stage [4,5]. Patients diagnosed at an intermediate stage can benefit from transarterial chemoembolization (TACE) but after an initial therapeutic benefit, most patients progress to advanced stage.

Sorafenib is a multitargeted tyrosine kinase inhibitor that blocks the activity of Raf serine/threonine kinase isoforms, as well as the receptor tyrosine kinases vascular endothelial growth factor receptors (VEGFR)-2 and -3, platelet-derived growth factor receptor (PDGFR) β, c-KIT, FLT-3, and RET, to inhibit tumor angiogenesis and tumor cell proliferation [6–8]. Results from the multinational, randomized, placebo-controlled, phase III Sorafenib HCC Assessment Randomized Protocol (SHARP) trial demonstrated that sorafenib significantly improved overall survival (OS) in patients with advanced HCC and well-preserved liver function (>95% Child–Pugh A), and that drug-related adverse events (AEs) were manageable [9]. Median OS in the sorafenib and placebo groups was 10.7 and 7.9 months, respectively (hazard ratio [HR] 0.69, 95% confidence interval [95% CI] 0.55–0.87; \( p < 0.001 \)), median time to progression (TTP) was 5.5 and 2.8 months, respectively (HR 0.58, 95% CI 0.45–0.74; \( p < 0.001 \)), and disease control rate (DCR) was 43% and 32%, respectively (\( p = 0.002 \)) [9]. The positive impact of sorafenib in improving survival and delaying tumor progression was confirmed in the phase III Sorafenib Asia–Pacific trial, performed in China, South Korea, and Taiwan [10]. Together, these trials provided evidence for the effectiveness of sorafenib across a range of disease etiologies, leading to its approval as first-line systemic therapy for patients with advanced HCC [3,11–16].

Baseline characteristics may affect individual responses to treatment. To discern whether baseline patient characteristics influenced the efficacy and safety of sorafenib in patients with HCC, we performed a comprehensive series of exploratory subgroup analyses to evaluate whether patient and/or tumor characteristics at baseline affected response to sorafenib in the SHARP trial. Five subgroup domains were selected for analysis: HCC etiology (hepatitis C virus (HCV), hepatitis B virus (HBV) or alcohol-related), tumor burden (defined as macroscopic vascular invasion (MVI) and/or extrahepatic spread (EHS)), Eastern Cooperative Oncology Group performance status (ECOG PS), geographic region (North America; Central/South America; or Europe/Australia/New Zealand) and randomized to receive sorafenib or placebo in a double blinded fashion [9]. For the subset analyses, patients were subgrouped by tumor burden (MVI/EHS absent; MVI/EHS present) and ECOG PS (0, 1–2), and post hoc by etiology (HCV, HBV, alcohol); BCLC stage (B, C/D); and prior therapy (curative treatment, TACE).

Designation of alcohol as an etiologic factor was made by the investigator based on history. Laboratory screening for HBV or HCV antigen was performed at least 7 days prior to initial treatment. Any previous local therapy must have been completed at least 4 weeks prior to the baseline scan and any treatment-naive target lesion was identified for proper assessment of tumor progression.

**Statistical analysis**

The population for efficacy analysis in each subgroup was the intent-to-treat population (defined as all randomized patients). OS and TTP were estimated by Kaplan–Meier analysis. Because the SHARP study was not powered for subgroup analysis, the sorafenib and placebo subgroups were compared descriptively rather than statistically. Furthermore, as in any post hoc subgroup analysis, statistical strength decreases as sample size decreases, thereby obviating a formal assessment of statistical significance in cohorts with small sample sizes. We report HR and 95% CI only, calculated from a Cox regression with only treatment in the model.

The safety population included all patients who received at least one dose of study drug. AEs were summarized descriptively. The sorafenib and placebo groups were compared for the incidence of drug-related, treatment-emergent AEs, and serious AEs (SAEs).

**Results**

Baseline demographics, the major etiology of HCC, and disease characteristics of patients in the SHARP subgroups are shown in Table 1. Table 2 shows a summary of the efficacy results (OS, TTP, and DCR) of the subgroup analyses, as well as the results in the overall population.

The mean daily doses in the sorafenib and placebo groups were 710.5 ± 142.1 and 774.8 ± 65.4 mg, respectively, and the median daily doses were 797.2 and 800.0 mg, respectively. Overall, 227 (75.7%) and 284 (93.8%) patients in the sorafenib and placebo groups, respectively, received average daily doses >80%, and 204 (68.0%) and 269 (88.8%) patients, respectively, received average daily doses >90% of the planned daily dose.

**OS, TTP, and DCR by subgroups**

**Tumor etiology**

Three subsets were included in the analysis of etiology (Fig. 1): patients positive for anti-HCV antibody (n = 167), those positive for HBV surface antigen (HBsAg; n = 60), and those classified as presenting with alcohol-related HCC (n = 159). HCV-infected patients treated with sorafenib had superior median OS (14.0 vs. 7.4 months), TTP (7.6 vs. 2.8 months), and DCR (44.2% vs. 29.6%) than those who received placebo. Among HBV-positive patients, those treated with sorafenib had a longer median OS (9.7 vs. 6.1 months), but a shorter median TTP (2.7 vs. 4.2 months) and a similar DCR (34.4% vs. 32.1%) as those who received placebo. This subset, however, was much smaller than the other subsets and was not well balanced, in that 18 of 32 (56.3%) of those treated with sorafenib had an ECOG PS of 1 or 2, compared with 11 of 28 (39.3%) who received placebo (Table 1). Among patients with response of complete response (CR), partial response (PR), or stable disease (SD) for >4 weeks, based on independent radiologic review. Safety was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0. The 602 patients in the SHARP trial were stratified by tumor burden (presence or absence of MVI and/or EHS), ECOG PS (0 or 1–2), and geographic region (North America; Central/South America; or Europe/Australia/New Zealand) and randomized to receive sorafenib or placebo in a double blinded fashion [9]. For the subset analyses, patients were subgrouped by tumor burden (MVI/EHS absent; MVI/EHS present) and ECOG PS (0, 1–2); and post hoc by etiology (HCV, HBV, alcohol); BCLC stage (B, C/D); and prior therapy (curative treatment, TACE).
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*Includes Australia and New Zealand.
†One patient had BCLC stage D disease.
The sum in each column exceeded 100%, since some patients were infected with HBV + HCV and others were infected with either virus + alcohol.
HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; Sor, sorafenib; PI, placebo; ECOG PS, Eastern Cooperative Oncology Group performance status; BCLC, Barcelona Clinic Liver Cancer; MVI, macroscopic vascular invasion; EHS, extrahepatic spread.
EHS, sorafenib (n = 140) was associated with a longer median OS (14.1 vs. 7.9 months) and TTP (5.8 vs. 4.0 months) and a higher DCR (42.9% vs. 35.3%) than patients who received placebo (n = 153), and patients with EHS who were treated with sorafenib (n = 159) had a slightly longer median OS (8.9 vs. 8.3 months), a longer median TTP (5.3 vs. 2.7 months), and a higher DCR (44.0% vs. 28.0%) than those who received placebo (n = 150).

**ECOG PS**
Two subsets were included in the analysis of ECOG PS: patients with ECOG PS 0 (n = 325) and those with ECOG PS 1–2 (n = 277). Sorafenib treatment of patients with ECOG PS 0 (n = 161) resulted in a longer median OS (13.3 vs. 7.4 months) and TTP (5.5 vs. 2.9 months) and a higher DCR (46.6% vs. 36.0%) than placebo (n = 154). Similarly, sorafenib treatment of patients with ECOG PS 1–2 (n = 138) resulted in a longer median OS (8.9 vs. 5.6 months) and TTP (5.3 vs. 2.8 months) and a higher DCR (39.9% vs. 26.6%) than placebo (n = 139).

**BCLC stage**
Two subsets were included in the analysis of BCLC stage (Fig. 2): patients with BCLC B not suitable for or refractory to locoregional therapies (intermediate-stage; n = 105) and BCLC C (advanced-stage; n = 497). BCLC B patients treated with sorafenib (n = 54) had a longer median OS (14.5 vs. 11.4 months) and TTP (6.9 vs. 4.4 months) and a higher DCR (50.0% vs. 43.1%) than those who received placebo (n = 51). Similarly, sorafenib treatment of BCLC C patients (n = 245) resulted in a longer median OS (9.7 vs. 8.0 months) and a higher DCR (38.9% vs. 33.4%) than patients who received placebo (n = 219).

alcohol-related HCC, sorafenib was associated with a longer median OS (10.3 vs. 8.0 months) and TTP (5.5 vs. 3.9 months) and a higher DCR (54.4% vs. 38.8%) than placebo.

**Tumor burden**
Two subsets were included in the main analysis of tumor burden: patients with both MVI and EHS (MVI/EHS absent; n = 181) and those with MVI and/or EHS (MVI/EHS present; n = 421). We also separately analyzed patients with and without MVI, and those with and without EHS.

In each subset, sorafenib enhanced OS, TTP, and DCR compared with placebo. For example, patients with MVI/EHS absent who were treated with sorafenib (n = 90) had a longer median OS (14.5 vs. 10.2 months) and TTP (9.6 vs. 4.9 months) and a higher DCR (48.9% vs. 40.7%) than those who received placebo (n = 91). In the MVI/EHS–present subgroup, sorafenib (n = 209) was associated with a longer median OS (8.9 vs. 6.7 months) and TTP (4.1 vs. 2.7 months) and a higher DCR (41.2% vs. 28.0%) than placebo (n = 212). Similarly, patients without MVI treated with sorafenib (n = 190) had a longer median OS (14.1 vs. 10.2 months) and TTP (7.3 vs. 3.9 months) and a higher DCR (45.8% vs. 35.2%) than those who received placebo (n = 179); and patients with MVI who were treated with sorafenib (n = 108) had a longer median OS (8.1 vs. 4.9 months) and TTP (4.1 vs. 2.7 months), and a higher DCR (38.9% vs. 26.8%) than those who received placebo (n = 123). Among patients without EHS, sorafenib (n = 140) was associated with a longer median OS (14.1 vs. 7.9 months) and TTP (5.8 vs. 4.0 months) and a higher DCR (42.9% vs. 35.3%) than patients who received placebo (n = 153), and patients with EHS who were treated with sorafenib (n = 159) had a slightly longer median OS (8.9 vs. 8.3 months), a longer median TTP (5.3 vs. 2.7 months), and a higher DCR (44.0% vs. 28.0%) than those who received placebo (n = 150).

**Performance status**
ECOG PS 0 (n = 161) resulted in a longer median OS (14.0 vs. 7.4 months) and TTP (9.6 vs. 4.9 months) and a higher DCR (45.8% vs. 38.8%) than those who received placebo (n = 150). Similarly, sorafenib treatment of patients with ECOG PS 0 (n = 150) resulted in a longer median OS (9.7 vs. 6.7 months) and TTP (4.1 vs. 2.7 months) and a higher DCR (34.4% vs. 28.0%) than patients who received placebo (n = 141). In ECOG PS 1–2 (n = 282), sorafenib was associated with a longer median OS (11.4 vs. 8.8 months) and TTP (6.9 vs. 4.4 months) and a higher DCR (43.1% vs. 36.0%) than placebo (n = 260).
and TTP (5.8 vs. placebo (n = 77). Similarly, sorafenib treatment of patients with HCC due to (A) hepatitis C virus (HCV) infection, (C) hepatitis B virus (HBV) infection, and (E) chronic alcohol consumption. Time to progression (TTP) in patients with HCC due to (B) HCV infection, (D) HBV infection, and (F) chronic alcohol consumption.

7.0 months) and TTP (4.9 vs. 2.8 months) and a higher DCR (42.0% vs. 29.4%) than placebo (n = 252). We also identified 220 patients staged BCLC C because of MVI and/or EHS spread, but with an ECOG PS of 0; of these, the 107 who received sorafenib had a longer median OS (10.7 vs. 8.3 months) and TTP (4.9 vs. 2.8 months) than the 113 who received placebo (data not shown).

Previous treatment
The SHARP trial permitted the enrollment of patients previously treated for HCC, with 158 (26.2%) receiving prior curative treatments (e.g. partial hepatectomy, segmentectomy, wedge resection, radiofrequency ablation, or percutaneous ethanol injection) and 176 (29.2%) who had undergone TACE (Fig. 3). Sorafenib treatment of patients with prior curative treatment (n = 81) resulted in a longer median OS (11.9 vs. 8.8 months) and TTP (5.5 vs. 2.8 months) and a higher DCR (49.4% vs. 32.5%) than placebo (n = 77). Similarly, sorafenib treatment of patients with prior TACE (n = 86) resulted in a longer median OS (11.9 vs. 9.9 months) and TTP (5.8 vs. 4.0 months) and a higher DCR (44.2% vs. 34.4%) than placebo (n = 90).

Safety
The incidence of adverse events (AEs) was similar across all subgroups. The most frequently reported drug-related treatment-emergent AEs in patients receiving sorafenib were diarrhea, fatigue, anorexia, and hand-foot skin reaction (HFSR). The incidence of drug related AEs of any severity in the sorafenib and placebo subgroups were 71.9–84.9% and 43.2–60.7%, respectively, and the incidences of drug related SAEs were 9.4–14.6% and 5.0–25%, respectively.

Composite results of the exploratory subgroup analyses and the subgroup safety analysis are depicted schematically in Fig. 4.

Discussion
In a series of exploratory subgroup analyses, we evaluated the relative effects of baseline patient characteristics on the efficacy and safety of sorafenib in patients with advanced HCC who were enrolled in the SHARP trial. In general, sorafenib consistently improved OS, TTP, and DCR compared with placebo, irrespective of baseline health status, disease etiology, tumor burden, tumor stage, or prior therapy received.

Among the most frequent etiologic factors in patients with HCC are chronic HBV infection, chronic HCV infection, and alcohol [3,18–21]. Although the mechanisms by which chronic viral infection induces HCC may differ by specific virus and genotype, HCC typically emerges after cirrhosis has become completely established [21]. Similarly, chronic alcohol use induces oxidative damage and inflammation in the liver, with subsequent repair mechanisms causing cirrhosis and genetic aberrations [22]. It is presently unclear, however, whether these etiologically different

Fig. 1. Relationship between etiology of HCC and survival outcomes in patients enrolled in the SHARP trial. Overall survival (OS) in patients with HCC due to (A) hepatitis C virus (HCV) infection, (C) hepatitis B virus (HBV) infection, and (E) chronic alcohol consumption. Time to progression (TTP) in patients with HCC due to (B) HCV infection, (D) HBV infection, and (F) chronic alcohol consumption.

Fig. 2. Relationship between Barcelona Clinic Liver Cancer (BCLC) stage and survival outcomes in patients enrolled in the SHARP trial. Overall survival (OS) in patients with (A) BCLC B and (C) BCLC C stage. Time to progression (TTP) in patients with (B) BCLC B and (D) BCLC C stage.
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Fig. 3. Relationship between prior treatment and survival outcomes in patients enrolled in the SHARP trial. Overall survival (OS) in patients with (A) prior curative treatment (resection/local ablation, percutaneous ethanol injection, or radiofrequency ablation) and (C) prior transarterial chemoembolization (TACE). Time to progression (TTP) in patients with (B) prior curative treatment and (D) prior TACE.

Oncogenic mechanisms result in tumors that have different genetic, as opposed to etiologic, characteristics and therefore may respond differently to treatment with sorafenib. In addition, the incidence of these etiologies varies among different patient populations [23,24]. HCC is most frequently associated with chronic HBV infection in Africa and many Asian countries but with chronic HCV infection and chronic alcohol use in Western countries and Japan. Because the SHARP trial was performed in Western populations, HCC in most of the enrolled patients was associated with either HCV infection or chronic alcohol use [9]. Sorafenib improved OS, TTP, and DCR in patients with HCC due to either etiology.

The SHARP trial was not randomized relative to etiology (i.e. HBV vs. HCV vs. alcohol). Thus, the resulting subgroups were at risk of imbalance. This clearly occurred among patients with HBV-associated HCC, with the number of these patients being relatively small, likely because the SHARP trial included centers in Europe, North and South America and Australasia, areas in which HBV is non-endemic, but did not include centers in Asia, where HBV is endemic. Moreover, examination of the subset of patients with HBV-associated HCC showed that 56.3% of those treated with sorafenib, compared with 39.3% of those who received placebo, had an ECOG PS >0, indicating that the sorafenib group was at a more advanced clinical stage [25,26]. This imbalance may have confounded the results of our sub-analysis of patients with HBV-associated HCC, in that OS was greater, while TTP was lower, in sorafenib-treated patients. In the phase III Sorafenib Asia Pacific trial, which included centers in China, South Korea, and Taiwan, areas in which HBV infection is endemic, 165 of the 226 enrolled patients were infected with HBV; analysis showed that sorafenib enhanced both OS (5.9 vs. 4.1 months; HR 0.74, 95% CI 0.51–1.06) and TTP (2.8 vs. 1.4 months, HR 0.57, 95% CI 0.29–1.13), relative to placebo, in patients with HBV-associated HCC [10,27], further suggesting that the results observed in SHARP patients with HBV-associated HCC were due to patient imbalance and not to these patients responding differently to sorafenib. Moreover, a recent phase III trial reported that the

Fig. 4. Summary of efficacy and safety outcomes for subgroups of patients enrolled in the SHARP trial. (A) Overall survival, (B) time to progression, (C) disease control rate, and (D) frequency of grade 3/4 adverse events among subgroups of patients with advanced HCC randomized to sorafenib or placebo.

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median OS in 288 patients with HBV-associated HCC treated with sorafenib was 7.9 months [28].

Another possibility suggested by our sub-analysis was that patients with HCV-related HCC derive more clinical benefit from sorafenib treatment than do patients with HBV-related HCC. In addition, in vitro results in the human HuH7.5 liver cancer cell line have suggested that sorafenib inhibits HCV replication [29]. Recent results have shown, however, that sorafenib had little or no effect on HCV viral load in 18 patients with HCV-associated HCC [30]. Thus, the combined results of these trials suggest that sorafenib is effective for the treatment of advanced HCC irrespective of viral etiology.

Tumor burden has been defined as MVI and EHS, both of which have been shown to be independent factors affecting the mortality of patients with HCC [25], and both of which are therefore included in many staging systems [31–41]. The occurrence of MVI and/or EHS limits treatment options, in that curative treatments (such as partial heptatectomy, radiofrequency ablation, and percutaneous ethanol injection) and TACE are generally not recommended. We found that, among patients in the SHARP trial, sorafenib extended both OS and TTP in patients with and without MVI and/or EHS, compared with placebo. Moreover, sorafenib had the same safety profile, irrespective of the presence of MVI and/or EHS.

ECOG PS assesses the effect of a tumor on a patient’s daily living ability [42], making it an important measure of patient health and a strong indicator of prognosis [25,33,36]. ECOG PS is considered during treatment assignment and is included in staging systems, although patients with ECOG PS >2 are usually not treated because of the high probability of poor short-term survival. When we evaluated the OS, TTP, and DCR in patients with ECOG PS 0 and those with ECOG PS 1–2, we found that sorafenib was equally effective, relative to placebo, and was well tolerated, in both subsets.

The BCLC staging system, a widely used algorithm for the classification of HCC and the assignment of treatment that incorporates several prognostic factors, including tumor morphology, liver function, and general patient performance status [32], has been validated externally [40], and its components shown in a meta-analysis to be an independent predictor of 1- and 2-year survival rates [41]. BCLC B tumors are asymptomatic and without MVI or EHS, whereas BCLC C tumors have already affected patient performance status and/or are associated with MVI and/or EHS; in the latter, a safe and effective treatment option was lacking until the availability of sorafenib. Our subanalyses showed that sorafenib was more effective than placebo in patients with BCLC stages B and C tumors; however, the wide confidence interval for OS in the BCLC B subgroup did not allow a robust conclusion in these patients.

Curative treatments available for patients with early-stage HCC include organ transplantation and tumor removal by resection or percutaneous ablation [3]. TACE, which blocks the artery feeding the tumor and injects a concentrated dose of chemotherapeutic agent at the tumor site, is recommended for, and prolongs survival in, patients with intermediate-stage HCC who are not candidates for curative treatments. Our analysis of patients who had received prior curative therapies or TACE showed that sorafenib improved TTP and demonstrated a trend toward improved OS, irrespective of prior therapy.

Sorafenib has a favorable safety profile, with a low incidence of serious or life-threatening AEs in patients with HCC [9,10]. We found that the incidence of sorafenib-associated AEs was not affected by any of our subgroupings, suggesting that sorafenib is safe for use in a wide range of patients with HCC. The most common AEs were diarrhea, HFSR, fatigue, and rash/desquamation, all of which were considered medically manageable. Interestingly, we observed no differences in HFSR related to etiology (HBV vs. HCV).

Assessment of patient health and tumor stage influences the selection of treatment at all stages of HCC. Individualized treatment strategies are based on baseline characteristics. The parameters evaluated in this study are those usually evaluated during this clinical decision-making process, with treatment designed to optimize survival while maintaining quality of life. This is of key importance in patients with HCC, as clinical status is affected both by the tumor itself and by the impairment resulting from the underlying liver disease. The results shown here confirm that the BCLC stratification into intermediate and advanced stage is valid, as those patients without MVI or EHS and ECOG PS 0 had a 9–10 month OS with placebo; whereas those with an adverse predictor (e.g. MVI, EHS, or ECOG PS 1 or 2) had an OS of 5–6 months with placebo.

This study had several limitations. The SHARP study was not originally empowered to assess outcomes in patient subgroups. Therefore, we compared the sorafenib and placebo subgroups descriptively rather than statistically. In addition, the numbers of patients in some groups was small. Due to these limitations, formal statistical testing was not performed; instead, we reported HRs and 95% CIs, as calculated from a Cox regression analysis with only treatment in the model.

The results of our SHARP trial subgroup analyses suggest that the efficacy and safety of sorafenib, relative to placebo, in patients with advanced HCC and well-preserved liver function do not appear to be affected by baseline health status, disease etiology, tumor burden, tumor stage, or prior therapy.

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**Conflict of interest**

Jordi Bruix has received honoraria and research funding from Bayer HealthCare Pharmaceuticals and consulting fees from Bayer HealthCare Pharmaceuticals, Onyx Pharmaceuticals, Bio-compatibles, Bristol-Myers Squibb, Glaxo, Kowa, Novartis, and ArQule; Jean-Luc Raoul has received consulting fees from Bayer HealthCare Pharmaceuticals and Bio-compatibles and lecture fees from Bayer HealthCare Pharmaceuticals; Vincenzo Mazzaferro has received consulting fees from Bayer HealthCare Pharmaceuticals; Luigi Bolondi has received consulting and lecture fees from Bayer HealthCare Pharmaceuticals; Peter R. Galle has received...
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2012.06.014.

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