

## ORIGINAL ARTICLE

# Sorafenib in Advanced Hepatocellular Carcinoma

Josep M. Llovet, M.D., Sergio Ricci, M.D., Vincenzo Mazzaferro, M.D., Philip Hilgard, M.D., Edward Gane, M.D., Jean-Frédéric Blanc, M.D., Andre Cosme de Oliveira, M.D., Armando Santoro, M.D., Jean-Luc Raoul, M.D., Alejandro Forner, M.D., Myron Schwartz, M.D., Camillo Porta, M.D., Stefan Zeuzem, M.D., Luigi Bolondi, M.D., Tim F. Greten, M.D., Peter R. Galle, M.D., Jean-François Seitz, M.D., Ivan Borbath, M.D., Dieter Häussinger, M.D., Tom Giannaris, B.Sc., Minghua Shan, Ph.D., Marius Moscovici, M.D., Dimitris Voliotis, M.D., and Jordi Bruix, M.D., for the SHARP Investigators Study Group\*

## ABSTRACT

**BACKGROUND**

No effective systemic therapy exists for patients with advanced hepatocellular carcinoma. A preliminary study suggested that sorafenib, an oral multikinase inhibitor of the vascular endothelial growth factor receptor, the platelet-derived growth factor receptor, and Raf may be effective in hepatocellular carcinoma.

**METHODS**

In this multicenter, phase 3, double-blind, placebo-controlled trial, we randomly assigned 602 patients with advanced hepatocellular carcinoma who had not received previous systemic treatment to receive either sorafenib (at a dose of 400 mg twice daily) or placebo. Primary outcomes were overall survival and the time to symptomatic progression. Secondary outcomes included the time to radiologic progression and safety.

**RESULTS**

At the second planned interim analysis, 321 deaths had occurred, and the study was stopped. Median overall survival was 10.7 months in the sorafenib group and 7.9 months in the placebo group (hazard ratio in the sorafenib group, 0.69; 95% confidence interval, 0.55 to 0.87;  $P < 0.001$ ). There was no significant difference between the two groups in the median time to symptomatic progression (4.1 months vs. 4.9 months, respectively,  $P = 0.77$ ). The median time to radiologic progression was 5.5 months in the sorafenib group and 2.8 months in the placebo group ( $P < 0.001$ ). Seven patients in the sorafenib group (2%) and two patients in the placebo group (1%) had a partial response; no patients had a complete response. Diarrhea, weight loss, hand-foot skin reaction, and hypophosphatemia were more frequent in the sorafenib group.

**CONCLUSIONS**

In patients with advanced hepatocellular carcinoma, median survival and the time to radiologic progression were nearly 3 months longer for patients treated with sorafenib than for those given placebo. (ClinicalTrials.gov number, NCT00105443.)

\*The affiliations of the authors and the names of the investigators in the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) Investigators Study Group are listed in the Appendix. Address reprint requests to Dr. Llovet or Dr. Bruix at the Barcelona Clinic Liver Cancer Group, Liver Unit, Hospital Clinic, Villarroel 170, 08036 Barcelona, Spain, or at [jmllovet@clinic.ub.es](mailto:jmllovet@clinic.ub.es) or [jbruix@clinic.ub.es](mailto:jbruix@clinic.ub.es).

N Engl J Med 2008;359:378-90.  
Copyright © 2008 Massachusetts Medical Society.

**H**EPATOCELLULAR CARCINOMA IS A MAJOR health problem, accounting for more than 626,000 new cases per year worldwide.<sup>1</sup> The incidence of hepatocellular carcinoma is increasing in the United States and Europe, and it is the third highest cause of cancer-related death globally, behind only lung and stomach cancers.<sup>1</sup> In the West, the disease is diagnosed in 30 to 40% of all patients at early stages and is amenable to potentially curative treatments, such as surgical therapies (resection and liver transplantation) and locoregional procedures (radiofrequency ablation).<sup>2</sup> Five-year survival rates of up to 60 to 70% can be achieved in well-selected patients.<sup>2</sup> However, disease that is diagnosed at an advanced stage or with progression after locoregional therapy has a dismal prognosis, owing to the underlying liver disease and lack of effective treatment options.<sup>2-4</sup> No systemic therapy has improved survival in patients with advanced hepatocellular carcinoma.<sup>5,6</sup>

Sorafenib (Nexavar, Bayer HealthCare Pharmaceuticals—Onyx Pharmaceuticals) is a small molecule that inhibits tumor-cell proliferation and tumor angiogenesis and increases the rate of apoptosis in a wide range of tumor models.<sup>7,8</sup> It acts by inhibiting the serine–threonine kinases Raf-1 and B-Raf and the receptor tyrosine kinase activity of vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3 and platelet-derived growth factor receptor  $\beta$  (PDGFR- $\beta$ ).<sup>7,8</sup> Cellular signaling that is mediated by the Raf-1 and vascular endothelial growth factor (VEGF) pathways has been implicated in the molecular pathogenesis of hepatocellular carcinoma,<sup>9-12</sup> providing a rationale for investigating sorafenib for this indication. In pre-clinical experiments, sorafenib had antiproliferative activity in liver-cancer cell lines, and it reduced tumor angiogenesis and tumor-cell signaling and increased tumor-cell apoptosis in a mouse xenograft model of human hepatocellular carcinoma.<sup>13</sup>

Results of an uncontrolled phase 2 study involving 137 patients with advanced hepatocellular carcinoma and Child–Pugh class A or B status indicated that single-agent sorafenib might have a beneficial therapeutic effect. Sorafenib treatment resulted in a median overall survival of 9.2 months and a median time to progression of 5.5 months (as assessed by independent radiologic evaluation).<sup>14</sup> On the basis of these data, we conducted a large phase 3, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma.

## METHODS

### PATIENTS

The study population consisted of patients with advanced-stage hepatocellular carcinoma, as confirmed by pathological analysis. None of the patients had received previous systemic therapy. Patients were classified as having advanced disease if they were not eligible for or had disease progression after surgical or locoregional therapies. The eligibility criteria also included an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less (Table A1 in the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org)),<sup>15</sup> Child–Pugh liver function class A (Table A2 in the Supplementary Appendix),<sup>16,17</sup> a life expectancy of 12 weeks or more, adequate hematologic function (platelet count,  $\geq 60 \times 10^9$  per liter; hemoglobin,  $\geq 8.5$  g per deciliter; and prothrombin time international normalized ratio,  $\leq 2.3$ ; or prothrombin time,  $\leq 6$  seconds above control), adequate hepatic function (albumin,  $\geq 2.8$  g per deciliter; total bilirubin,  $\leq 3$  mg per deciliter [ $51.3 \mu\text{mol}$  per liter]; and alanine aminotransferase and aspartate aminotransferase,  $\leq 5$  times the upper limit of the normal range), and adequate renal function (serum creatinine,  $\leq 1.5$  times the upper limit of the normal range).

Patients were required to have at least one untreated target lesion that could be measured in one dimension, according to the Response Evaluation Criteria in Solid Tumors (RECIST) (Table A3 in the Supplementary Appendix).<sup>18</sup> Concomitant antiviral systemic therapy was allowed. Patients were excluded if they had previously received molecularly targeted therapies or any other systemic treatment.

All patients provided written informed consent before enrollment in the study. The study was approved by the institutional review board or ethics committee at each center and complied with the provisions of the Good Clinical Practice guidelines and the Declaration of Helsinki and local laws.

### STUDY DESIGN

This multicenter, randomized, double-blind, placebo-controlled, phase 3 trial was conducted at 121 centers in 21 countries in Europe, North America, South America, and Australasia. All eligible patients were randomly assigned in a 1:1 ratio to receive continuous oral treatment with either 400 mg of sorafenib (consisting of two 200-mg tablets) twice daily or matching placebo (both sup-

plied by Bayer HealthCare Pharmaceuticals). Study randomization was centralized, and assignment to study groups was conducted by computer to achieve a balance between the two groups, with stratification before randomization according to region, ECOG performance status (a score of 0 vs. a score of 1 or 2), and the presence or absence of macroscopic vascular invasion (portal vein or branches) or extrahepatic spread.

Treatment interruptions and up to two dose reductions (first to 400 mg once daily and then to 400 mg every 2 days) were permitted for drug-related adverse effects (see Tables B1 and B2 in the Supplementary Appendix). If further dose reductions were required, patients were withdrawn from the study.

Treatment continued until the occurrence of both radiologic progression, as defined by RECIST,<sup>18</sup> and symptomatic progression, as defined by the Functional Assessment of Cancer Therapy–Hepatobiliary Symptom Index 8 (FHSI8) questionnaire (Table A4 in the Supplementary Appendix),<sup>19</sup> or the occurrence of either unacceptable adverse events or death. Crossover of patients in the placebo group to the sorafenib group was not permitted before the definitive overall analysis of survival.

The study was designed by Bayer HealthCare Pharmaceuticals in conjunction with the principal academic investigators. Data collection was performed by Covance. Axio Research performed the statistical analysis for the data and safety monitoring committee. Data were managed in parallel by the sponsor and the principal investigators. The academic investigators were responsible for the decision to publish the results of the study, had unrestricted access to the final data, and vouch for the completeness and accuracy of the data and data analyses.

#### OUTCOMES AND ASSESSMENTS

The primary outcomes of the study were overall survival and the time to symptomatic progression. Overall survival was measured from the date of randomization until the date of death from any cause. The time to symptomatic progression was measured from the date of randomization until the first documented event of symptomatic progression. Symptomatic progression was defined as either a decrease of 4 or more points from the baseline score on patients' responses to the FHSI8 questionnaire, a change that was confirmed 3 weeks

later (Table A4 in the Supplementary Appendix<sup>19</sup>), a deterioration in ECOG performance status to 4, or death.

Secondary outcomes included the time to radiologic progression, the disease-control rate, and safety. The time to radiologic progression was defined as the time from randomization to disease progression (according to RECIST) on the basis of independent radiologic review. Data from patients who died without tumor progression were censored. The disease-control rate was defined as the percentage of patients who had a best-response rating of complete response, partial response, or stable disease (according to RECIST) that was maintained for at least 28 days after the first demonstration of that rating on the basis of independent radiologic review. Safety was assessed in all patients receiving at least one dose of a study drug, with the use of version 3.0 of the National Cancer Institute's Common Terminology Criteria for adverse events.

Although treatment was administered in a continuous manner, for the purpose of data recording, the treatment period was divided into 6-week cycles. Tumor measurements were performed at screening, every 6 weeks during treatment (within 10 days before the end of each cycle), and at the end of treatment by computed tomography or magnetic resonance imaging. Patients visited the clinic every 3 weeks and at the end of treatment for assessment of compliance, safety, and determination of side effects. Compliance was assessed on the basis of pill counts and diary entries of patients. Safety assessments included documentation of adverse events, clinical laboratory tests (hematologic and biochemical analyses), physical examination, and measurement of vital signs. An end-of-treatment visit was made 21 to 35 days after the last dose of the study drug. The time to symptomatic progression was assessed at baseline, every 3 weeks during treatment, and at the end-of-treatment visit for patients who discontinued the study drug for reasons other than symptomatic progression.

#### STATISTICAL ANALYSIS

The primary outcomes were assessed according to the intention-to-treat principle. For the primary analysis of overall survival and the time to symptomatic progression, we compared the two study groups using a one-sided overall alpha level of 0.02 or 0.005, respectively, thus maintaining the

overall type I error rate for the trial at a one-sided alpha level of 0.025. These analyses were performed with the use of log-rank tests, stratified according to region, ECOG performance status (a score of 0 vs. a score of 1 or 2), and the presence or absence of macroscopic vascular invasion (portal vein or branches) or extrahepatic spread. Two formal interim analyses after approximately 170 and 300 deaths had occurred and one final analysis were planned for the survival outcome. A single final analysis was planned for the outcome of the time to symptomatic progression. The O'Brien–Fleming spending function<sup>20</sup> was specified prospectively to ensure that the one-sided false positive rate was 0.02 or less for overall survival. A Cox proportional-hazards model was used to evaluate the interaction between baseline characteristics and the effect of sorafenib on overall survival.

We calculated the number of patients needed for the study on the basis of the primary outcome of overall survival, taking into account two interim analyses and one final analysis. Assuming a one-sided type I error of 0.02, a randomization ratio of 1:1 between the sorafenib group and the placebo group, and a median overall survival of 7 months in the placebo group, we estimated that with 424 deaths in the two groups combined, the study would have a power of 90% to detect a 40% increase in overall survival in the sorafenib group. On the basis of these calculations, we estimated we needed to enroll approximately 560 patients.

Formal analysis of the time to radiologic progression with the use of a stratified log-rank test was planned when approximately 227 progression events had occurred on the basis of RECIST. The required number of progression events was projected to occur by a prespecified cutoff date of May 12, 2006. Independent radiologic assessment was not continued after this date. We compared disease-control rates in the two study groups using the Cochran–Mantel–Haenszel test with a two-sided alpha level of 0.05. Adverse events were compared with the use of Fisher's exact test. All reported P values are two-sided.

## RESULTS

### PATIENTS

From March 10, 2005, to April 11, 2006, we screened 902 patients. Of these patients, 602 met the eligibility criteria and underwent randomization, with 299 patients assigned to the sorafenib group and

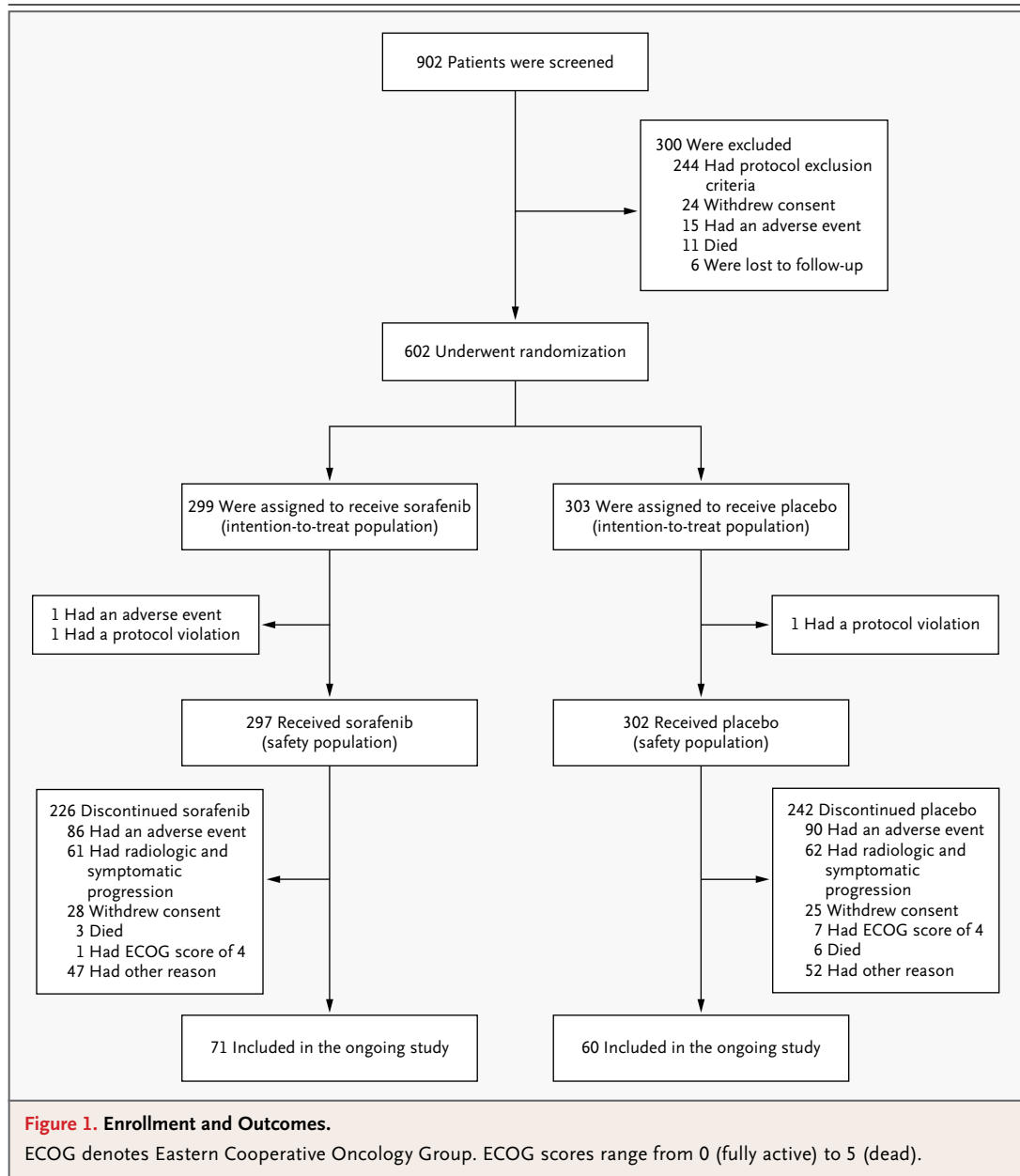
303 patients assigned to the placebo group. These patients were all included in the intention-to-treat analysis (Fig. 1). The remaining patients were excluded from the study during the screening period because they did not meet inclusion or exclusion criteria, withdrew their consent, had an adverse event, were lost to follow-up, or died. Among the 602 randomized patients, 297 received at least one dose of sorafenib and 302 received at least one dose of placebo; these 599 patients were included in the safety analysis.

There were no relevant differences between the two study groups with respect to demographic characteristics, the cause or severity of liver disease, previous antitumor therapy for hepatocellular carcinoma, prognostic characteristics, ECOG performance status, and tumor-staging criteria, according to the Barcelona Clinic Liver Cancer (BCLC) staging system (Table 1, and Table A5 in the Supplementary Appendix).<sup>2,3</sup> Most patients were recruited in Europe. Chronic hepatitis C virus infection was the predominant cause of liver disease, followed by alcohol consumption and chronic hepatitis B virus infection. The disease in 581 patients (97%) was rated as Child–Pugh class A at baseline, reflecting well-preserved liver function. No significant differences were observed between the sorafenib group and the placebo group with respect to mean baseline plasma levels of albumin, alkaline phosphatase, and total bilirubin. At baseline, 231 patients (38%) had macroscopic vascular invasion, and 309 (51%) had extrahepatic spread, with the most common extrahepatic sites being lymph nodes and lung. Approximately half the patients (305) presented with tumors that had not been previously treated, and locoregional therapy had failed in the remaining 297 patients.

### EFFICACY

#### *Overall Survival*

We conducted the second planned interim analysis using a cutoff date of October 17, 2006, when 321 deaths had occurred (143 in the sorafenib group and 178 in the placebo group). Overall median survival was significantly longer in the sorafenib group than in the placebo group (10.7 months vs. 7.9 months; hazard ratio in the sorafenib group, 0.69; 95% confidence interval [CI], 0.55 to 0.87;  $P < 0.001$ ) (Table 2 and Fig. 2A). Survival rates at 1 year were 44% in the sorafenib group and 33% in the placebo group. This significant survival benefit represented a 31% relative



reduction in the risk of death. On the basis of these data and guided by the prespecified O'Brien–Fleming spending function<sup>20</sup> (which stipulates a one-sided nominal alpha level of 0.0077 for this interim analysis), the independent data and safety monitoring committee recommended that the trial be stopped in February 2007. The results reported here are considered final.

An exploratory multivariate analysis with the use of a Cox proportional-hazards model identified eight baseline characteristics that were prognostic

indicators for overall survival: ECOG performance status, presence or absence of macroscopic vascular invasion, extent of tumor burden (defined as presence or absence of vascular invasion, extrahepatic spread, or both), Child–Pugh status, and median baseline levels of alpha-fetoprotein, albumin, alkaline phosphatase, and total bilirubin. After adjustment for these prognostic factors, the effect of sorafenib on overall survival remained significant (hazard ratio, 0.73; 95% CI, 0.58 to 0.92;  $P=0.004$ ). A prespecified subgroup analysis

showed a survival benefit for sorafenib over placebo in most of the subgroups analyzed (Fig. 3).

#### TIME TO SYMPTOMATIC PROGRESSION

The median time to symptomatic progression (which was defined as either a decrease of 4 or more points from the baseline score on the FHSI8 questionnaire or an ECOG status of 4 or death, whichever occurred first) did not differ significantly between the sorafenib group and the placebo group (4.1 and 4.9 months, respectively; hazard ratio, 1.08; 95% CI, 0.88 to 1.31;  $P=0.77$ ) (Fig. 2B).

#### TIME TO RADIOLOGIC PROGRESSION

By the cutoff date of May 12, 2006, radiologic progression had occurred in 263 patients (107 in the sorafenib group and 156 in the placebo group). On the basis of an independent review of radiologic data, the median time to progression was significantly longer in the sorafenib group than in the placebo group (5.5 vs. 2.8 months; hazard ratio, 0.58; 95% CI, 0.45 to 0.74;  $P<0.001$ ) (Table 2 and Fig. 2C). The estimated rate of progression-free survival at 4 months was 62% in the sorafenib group and 42% in the placebo group.

#### RESPONSE RATES AND DISEASE-CONTROL RATE

In the sorafenib group, 7 patients (2%) had a partial response and 211 (71%) had stable disease (according to RECIST), whereas in the placebo group, 2 patients (1%) had a partial response and 204 (67%) had stable disease (Table 2). There were no complete responses in either group. The disease-control rate was significantly higher in the sorafenib group than in the placebo group (43% vs. 32%,  $P=0.002$ ) (Table 2).

#### TREATMENT COMPLIANCE

At the October 17, 2006, cutoff date, 468 patients had discontinued treatment (226 in the sorafenib group and 242 in the placebo group) (Fig. 1). The most common reasons for discontinuation in both groups were adverse events (176 patients) and radiologic and symptomatic progression (123 patients). The median duration of treatment was 5.3 months (range, 0.2 to 16.1) in the sorafenib group and 4.3 months (range, 0.1 to 16.6) in the placebo group. Overall, 227 patients in the sorafenib group (76%) and 284 in the placebo group (94%) received more than 80% of the planned daily dose of the study drug.

#### SAFETY

The overall incidence of treatment-related adverse events was 80% in the sorafenib group and 52% in the placebo group (Table 3). Adverse events that were reported for patients receiving sorafenib were predominantly grade 1 or 2 in severity and gastrointestinal, constitutional, or dermatologic in nature. Diarrhea, weight loss, hand-foot skin reaction, alopecia, anorexia, and voice changes occurred at a higher frequency in the sorafenib group than in the placebo group ( $P<0.001$ ). Grade 3 drug-related adverse events included diarrhea (8% in the sorafenib group vs. 2% in the placebo group,  $P<0.001$ ), hand-foot skin reaction (8% vs. <1%,  $P<0.001$ ), hypertension (2% vs. <1%,  $P=0.28$ ), and abdominal pain (2% vs. 1%,  $P=0.17$ ); there were no grade 4 drug-related adverse events in any of these categories in either study group (Table 3). Grade 3 or 4 laboratory abnormalities occurred at similar frequencies in the two study groups, with the exception of grade 3 hypophosphatemia (11% in the sorafenib group vs. 2% in the placebo group,  $P<0.001$ ) and grade 3 or 4 thrombocytopenia (4% in the sorafenib group vs. <1% in the placebo group,  $P=0.006$ ).

The rate of discontinuation of the study drug due to adverse events was similar in the two study groups (38% vs. 37%). The most frequent adverse events leading to discontinuation of sorafenib treatment were gastrointestinal events (6%), fatigue (5%), and liver dysfunction (5%). Dose reductions due to adverse events occurred in 26% of the patients in the sorafenib group and 7% of those in the placebo group, whereas dose interruptions due to adverse events occurred in 44% and 30% of the patients, respectively. The most frequent adverse events leading to dose reductions in the sorafenib group were diarrhea (8%), hand-foot skin reaction (5%), and rash or desquamation (3%). Drug-related adverse events leading to permanent treatment discontinuation occurred in 34 patients in the sorafenib group (11%) and 15 patients in the placebo group (5%).

The overall incidence of serious adverse events from any cause was similar in the two study groups: 52% (153 patients) in the sorafenib group and 54% (164 patients) in the placebo group. (In the Supplementary Appendix, adverse events and serious adverse events during treatment are described in Table C1 and Table C2, respectively.)

In the sorafenib group and the placebo group, the incidences of serious hepatobiliary adverse

**Table 1. Demographic and Baseline Characteristics of the Patients (Intention-to-Treat Population).\***

Variable	Sorafenib (N = 299)	Placebo (N = 303)
Age — yr	64.9±11.2	66.3±10.2
Sex — no. (%)		
Male	260 (87)	264 (87)
Female	39 (13)	39 (13)
Region — no. (%)		
Europe and Australasia	263 (88)	263 (87)
North America	27 (9)	29 (10)
Central and South America	9 (3)	11 (4)
Cause of disease — no. (%)		
Hepatitis C only	87 (29)	82 (27)
Alcohol only	79 (26)	80 (26)
Hepatitis B only	56 (19)	55 (18)
Unknown	49 (16)	56 (19)
Other	28 (9)	29 (10)
ECOG performance status — no. (%)†		
0	161 (54)	164 (54)
1	114 (38)	117 (39)
2	24 (8)	22 (7)
BCLC stage — no. (%)‡		
B (intermediate)	54 (18)	51 (17)
C (advanced)	244 (82)§	252 (83)
Macroscopic vascular invasion — no. (%)	108 (36)	123 (41)
Extrahepatic spread — no. (%)	159 (53)	150 (50)
Lymph nodes	89 (30)	65 (21)
Lung	67 (22)	58 (19)
Macroscopic vascular invasion, extrahepatic spread, or both — no. (%)		
Absent	90 (30)	91 (30)
Present	209 (70)	212 (70)
Child–Pugh class — no. (%)¶		
A	284 (95)	297 (98)
B	14 (5)	6 (2)
Biochemical analysis		
Albumin — g/dl		
Median	3.9	4.0
Range	2.7–5.3	2.5–5.1
Total bilirubin — mg/dl		
Median	0.7	0.7
Range	0.1–16.4	0.2–6.1
Alpha-fetoprotein — ng/ml		
Median	44.3	99.0
Range	0–208×10 <sup>4</sup>	0–5×10 <sup>5</sup>

Table 1. (Continued.)

Variable	Sorafenib (N=299)	Placebo (N=303)
Previous therapy — no. (%)		
Surgical resection	57 (19)	62 (20)
Locoregional therapy		
Transarterial chemoembolization	86 (29)	90 (30)
Percutaneous ethanol injection	28 (9)	20 (7)
Radiofrequency ablation	17 (6)	12 (4)
Radiotherapy**	13 (4)	15 (5)
Systemic anticancer therapy		
Hormonal therapy	7 (2)	8 (3)
Cytotoxic chemotherapy	1 (<1)	1 (<1)
Concomitant systemic antiviral therapy — no. (%)	6 (2)	2 (1)

\* Plus-minus values are means  $\pm$ SD. None of the differences between the two study groups were significant ( $P \geq 0.05$ ). To convert the values for bilirubin to micromoles per liter, multiply by 17.1. BCLC denotes Barcelona Clinic Liver Cancer staging system, and ECOG Eastern Cooperative Oncology Group.

† The ECOG performance status assesses the daily living abilities of the patient, on a scale ranging from 0 (fully active) to 5 (dead).<sup>15</sup>

‡ The BCLC system ranks hepatocellular carcinoma in five stages, ranging from 0 (very early stage) to D (terminal stage).<sup>3</sup>

§ One patient in the sorafenib group had a BCLC score of D and a Child–Pugh class of C.

¶ The Child–Pugh system evaluates the severity of liver disease, with patients divided into classes from A to C, with class C representing the worst prognosis.<sup>16,17</sup>

|| Patients may have received more than one type of therapy. There was no significant difference between groups in the number of patients who had received previous palliative or curative therapy or previous adjuvant or neoadjuvant therapy ( $P \geq 0.05$ ).

\*\* Radiotherapy was applied to extrahepatic metastatic lesions in all patients except five in the sorafenib group and three in the placebo group.

events (11% and 9%, respectively), serious hemorrhagic events (9% and 13%), variceal bleeding (2% and 4%), renal failure (<1% and 3%), and cardiac ischemia or infarction (3% and 1%) were similar; the most common serious adverse events of any cause (aside from death) were liver dysfunction (7% and 5%, respectively), diarrhea (5% and 2%), and ascites (5% and 4%) (Table C2 in the Supplementary Appendix). Within 30 days after the final dose of the study drug, there were 13 deaths in the sorafenib group and 29 deaths in the placebo group that were not attributed to disease progression.

## DISCUSSION

In this trial, patients with advanced hepatocellular carcinoma who received sorafenib treatment had nearly a 3-month median survival benefit, as compared with those who received placebo. At the time the study was stopped, after the second prespecified interim analysis (conducted when 321

patients had died), patients in the sorafenib group had a median survival of 10.7 months, as compared with 7.9 months in the placebo group. The effect of sorafenib on overall survival remained significant after adjustment for baseline prognostic factors that were found to influence survival, thus supporting the primary analysis. The benefit of sorafenib was also consistent among all prespecified stratification groups, including patients with the worst prognosis, such as those with an ECOG performance status of 1 or 2 or with macroscopic vascular invasion or extrahepatic spread.

This study was designed to capture the benefits of a potentially efficacious drug while avoiding the confounding effect of deaths unrelated to cancer progression. Since hepatocellular carcinoma develops mainly in patients with cirrhosis, it was critical to select patients with well-preserved liver function (Child–Pugh class A).<sup>16,17</sup> If the trial had included patients with more advanced liver failure (Child–Pugh class B or C), deaths related to advanced liver disease might have masked any



**Table 2. Summary of Efficacy Measures.\***

Outcome	Sorafenib (N=299)	Placebo (N=303)	Hazard Ratio (95% CI)	P Value
Overall survival (mo)			0.69 (0.55–0.87)	<0.001
Median	10.7	7.9		
95% CI	9.4–13.3	6.8–9.1		
1-yr survival rate (%)	44	33		0.009
Time to symptomatic progression (mo)†			1.08 (0.88–1.31)	0.77
Median	4.1	4.9		
95% CI	3.5–4.8	4.2–6.3		
Time to radiologic progression (mo)			0.58 (0.45–0.74)	<0.001
Median	5.5	2.8		
95% CI	4.1–6.9	2.7–3.9		
Level of response (%)‡				
Complete	0	0		NA
Partial	2	1		0.05
Stable disease	71	67		0.17
Disease-control rate (%)§	43	32		0.002

\* NA denotes not applicable.

† Symptomatic progression was defined as a decrease of 4 or more points from the baseline score on the Functional Assessment of Cancer Therapy–Hepatobiliary Symptom Index 8 (FHSI8) questionnaire, deterioration to a score of 4 in Eastern Cooperative Oncology Group performance status, or death, whichever occurred first.<sup>19</sup> The scores were confirmed 3 weeks later at the next scheduled assessment.

‡ The level of response was measured according to RECIST (Response Evaluation Criteria in Solid Tumors)<sup>18</sup> by independent radiologic review.

§ The disease-control rate was the percentage of patients who had a best-response rating of complete or partial response or stable disease (according to RECIST) that was maintained for at least 28 days after the first demonstration of that rating on independent radiologic review.

significant activity of sorafenib. Further data will be needed to confirm the safety and survival benefit of sorafenib in patients with poorer liver function. In addition, the choice of survival as a primary outcome was important, since other potential surrogate outcomes that are often used in oncology, such as progression-free survival, are considered to be suboptimal for the clinical evaluation of this cancer because of the confounding effect of the underlying cirrhosis. The absence of overlap in the confidence intervals between the groups that was observed for overall survival and the time to progression suggests that most of the patients receiving sorafenib had a delay in the progression of the disease that might have resulted in the prolongation of survival.

The second primary outcome, the time to symptomatic progression, did not differ significantly between the two groups. The FHSI8 questionnaire is a patient-oriented outcome instrument that might have been influenced by both the pres-

ence of symptoms related to the toxic effects of the drug and the effect of the response to tumor-related symptoms.<sup>19</sup> The lack of a significant difference in responses to the FHSI8 questionnaire might reflect the effect of the reporting of sorafenib's toxic effects by patients. In addition, the quality of life of these patients might have been affected by symptoms related to liver failure, which continued, regardless of whether the tumor stabilized or regressed.

Sorafenib simultaneously inhibits molecular components of the Raf–MEK–ERK signaling pathway, abrogating tumor growth and VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR- $\beta$ , thus inhibiting neoangiogenesis.<sup>7</sup> By targeting two key pathways that are reported to play an important role in the pathogenesis of hepatocellular carcinoma,<sup>9–12</sup> sorafenib is likely to delay disease progression; this might explain the observed survival benefit despite the low incidence of objective responses. Nonetheless, pharmacogenomic studies are under

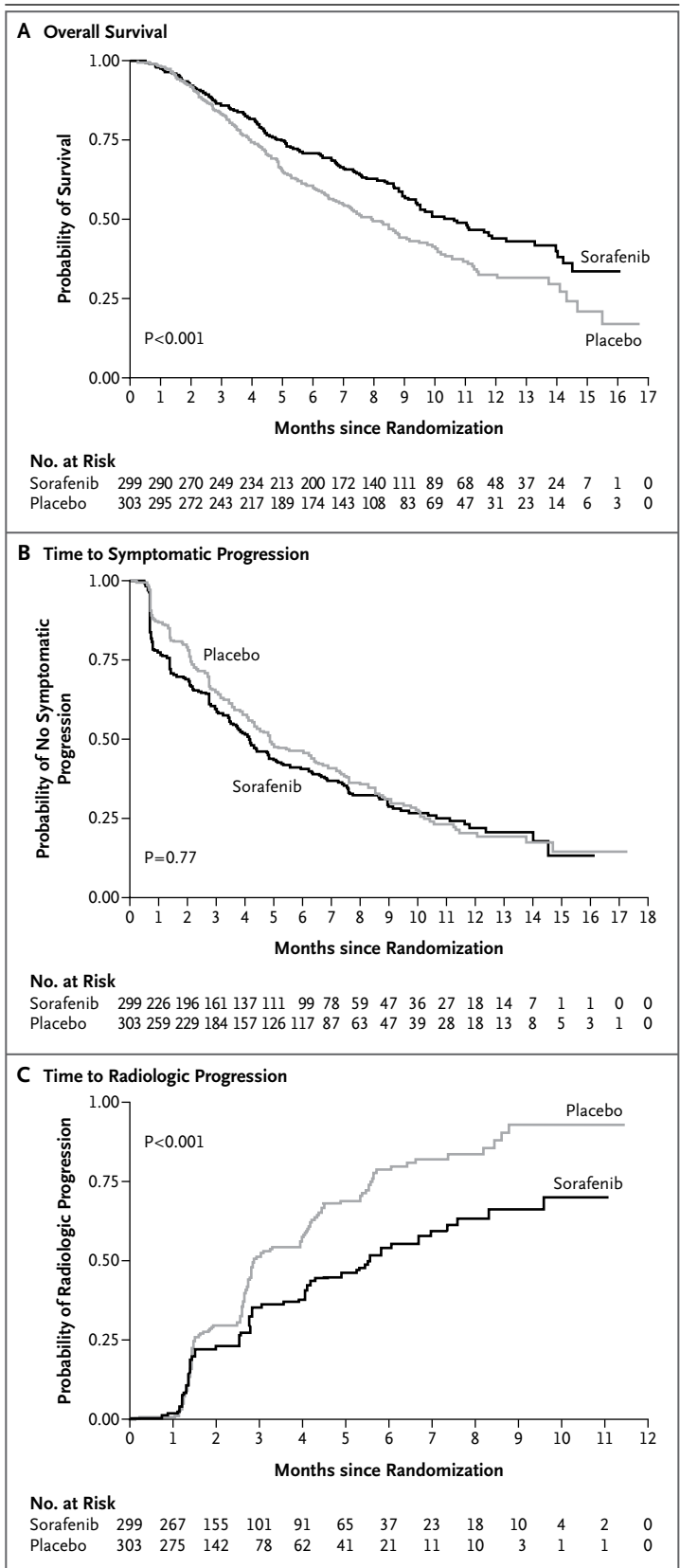
**Figure 2. Kaplan–Meier Analysis of Overall Survival, the Time to Symptomatic Progression, and the Time to Radiologic Progression.**

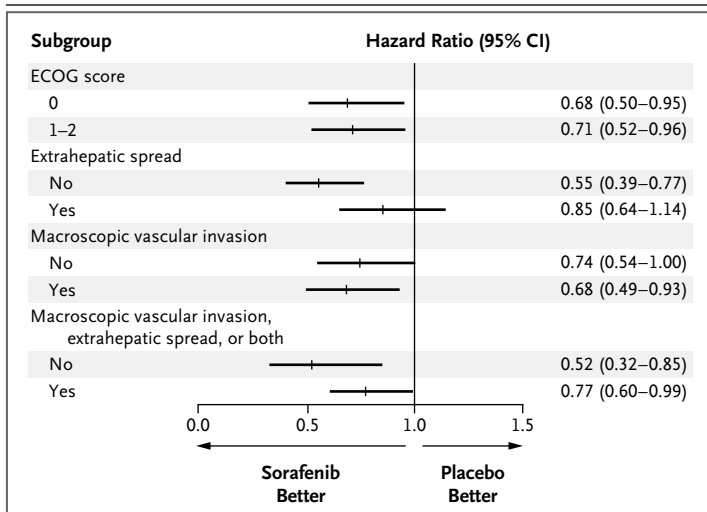
Among 602 patients (of whom 299 received sorafenib and 303 received placebo), the median overall survival was 10.7 months in the sorafenib group, as compared with 7.9 months in the placebo group (hazard ratio for death in the sorafenib group, 0.69; 95% CI, 0.55 to 0.87) (Panel A). The median time to symptomatic progression was 4.1 months in the sorafenib group, as compared with 4.9 months in the placebo group (hazard ratio for progression in the sorafenib group, 1.08; 95% CI, 0.88 to 1.31) (Panel B). The median time to radiologic progression was 5.5 months in the sorafenib group, as compared with 2.8 months in the placebo group (hazard ratio for progression in the sorafenib group, 0.58; 95% CI, 0.45 to 0.74) (Panel C).

way to gain a further understanding of the drug's molecular mechanisms of action. In addition, the safety profile compares well with those of previously reported systemic therapies, such as the PIAF regimen (cisplatin, interferon, doxorubicin, and fluorouracil), which was associated with more severe complications than those observed with sorafenib.<sup>21</sup>

This trial shows that sorafenib improves overall survival by nearly 3 months in patients with advanced hepatocellular carcinoma. This finding is important, given the increasing incidence of the disease around the world<sup>22</sup> and the lack of efficacious therapeutic options in this setting.<sup>2-6</sup> Furthermore, no consistent survival benefits for anticancer agents in hepatocellular carcinoma have been recorded in approximately 100 randomized studies reported during the past 30 years,<sup>2-6</sup> including systemic and intraarterial chemotherapy (predominantly doxorubicin-based or platinum-based), various hormonal therapies (tamoxifen and antiandrogens), and immunotherapy (usually interferon alfa).<sup>5,6,21</sup> In some instances, such as studies of tamoxifen, encouraging data from underpowered initial studies<sup>23,24</sup> were not confirmed by subsequent large, well-designed, randomized studies.<sup>3,6</sup> Thus, scientific guidelines and regulatory agencies have not recommended or approved any drug for advanced hepatocellular carcinoma, representing a unique situation in the treatment of solid tumors and clearly an unmet medical need.<sup>3,4</sup>

Our finding that sorafenib, a multikinase inhibitor, has activity in hepatocellular carcinoma shows the potential of molecularly targeted therapies in this neoplasm. Other targeted agents that





**Figure 3. Overall Survival of Selected Subgroups, According to Baseline Prognostic Factors.**

ECOG denotes Eastern Cooperative Oncology Group. ECOG scores range from 0 (fully active) to 5 (dead).

have been evaluated in phase 2 clinical trials for the treatment of hepatocellular carcinoma include tyrosine kinase inhibitors of the epidermal growth factor receptor (erlotinib<sup>25,26</sup> and gefitinib<sup>27</sup>), a humanized monoclonal antibody against antivascular endothelial growth factor (bevacizumab<sup>26,28,29</sup>), and a multitargeted tyrosine kinase inhibitor (sunitinib<sup>30,31</sup>). Future studies should assess the benefits of combined molecular therapy, as compared with sorafenib alone.

The most frequent adverse events in this study were consistent with those observed in a previous phase 2 study involving patients with hepatocellular carcinoma<sup>14</sup> and in clinical trials of sorafenib in patients with advanced renal-cell carcinoma.<sup>32,33</sup> The adverse events that were more common in the sorafenib group (e.g., diarrhea, weight loss, and hand-foot skin reaction) were mainly mild to moderate in severity.<sup>34</sup> The two most relevant grade 3 drug-related adverse events were diarrhea and hand-foot skin reaction (both

**Table 3. Incidence of Drug-Related Adverse Events (Safety Population).\***

Adverse Event	Sorafenib (N = 297)			Placebo (N = 302)			P Value	
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3 or 4
Overall incidence	80			52				
Constitutional symptoms								
Fatigue	22	3	1	16	3	<1	0.07	1.00
Weight loss	9	2	0	1	0	0	<0.001	0.03
Dermatologic events								
Alopecia	14	0	0	2	0	0	<0.001	NA
Dry skin	8	0	0	4	0	0	0.04	NA
Hand-foot skin reaction	21	8	0	3	<1	0	<0.001	<0.001
Pruritus	8	0	0	7	<1	0	0.65	1.0
Rash or desquamation	16	1	0	11	0	0	0.12	0.12
Other	5	1	0	1	0	0	<0.001	0.12
Gastrointestinal events								
Anorexia	14	<1	0	3	1	0	<0.001	1.00
Diarrhea	39	8	0	11	2	0	<0.001	<0.001
Nausea	11	<1	0	8	1	0	0.16	0.62
Vomiting	5	1	0	3	1	0	0.14	0.68
Voice changes	6	0	0	1	0	0	<0.001	NA
Hypertension	5	2	0	2	1	0	0.05	0.28
Liver dysfunction	<1	<1	0	0	0	0	0.50	0.50
Abdominal pain not otherwise specified	8	2	0	3	1	0	0.007	0.17
Bleeding	7	1	0	4	1	<1	0.07	1.00

\* Listed are adverse events, as defined by the National Cancer Institute Common Terminology Criteria (version 3.0), that occurred in at least 5% of patients in either study group. NA denotes not applicable.

of which occurred in 8% of patients in the sorafenib group). As has been previously observed in the treatment of renal-cell carcinoma,<sup>33</sup> sorafenib-associated adverse events led to dose reductions and interruptions in a subgroup of patients. Previous studies have raised caution about the risk of hemorrhagic and cardiac events in patients treated with sorafenib and other tyrosine kinase inhibitors.<sup>12,34</sup> This study did not identify an overall increase in the risk of bleeding, and the rates of variceal hemorrhage were similar in the two study groups, although the study may not have been large enough to accurately establish the incidence of uncommon adverse events.

In summary, this study showed that sorafenib prolonged median survival and the time to progression by nearly 3 months in patients with advanced hepatocellular carcinoma. Future studies are warranted to evaluate sorafenib as an adjuvant therapy after curative or locoregional therapies. Also needed are studies evaluating sorafenib in combination with other molecular targeted therapies and as a standard comparator, conducted according to recent guidelines for the design of clinical trials in hepatocellular carcinoma.<sup>35</sup>

Supported by Bayer HealthCare Pharmaceuticals—Onyx Pharmaceuticals.

Presented in part in abstract form at the annual meeting of the American Society of Clinical Oncology, Chicago, June 1–5, 2007.

Dr. Llovet reports receiving consulting and lecture fees and research grants from Bayer HealthCare Pharmaceuticals, research grants from Exelixis, and consulting fees from Biocompatibles International and MDS Nordion; Drs. Mazzaferro, Santoro, and Schwartz, consulting fees from Bayer HealthCare Pharmaceuticals; Dr. Hilgard, lecture fees from Bayer HealthCare Pharmaceuticals and MDS Nordion; Dr. Gane, lecture fees from Novartis and GlaxoSmithKline; Dr. Raoul, consulting fees from Bayer HealthCare Pharmaceuticals and Biocompatibles and lecture fees from Bayer HealthCare Pharmaceuticals; Dr. Forner, lecture fees from Bayer HealthCare Pharmaceuticals; Dr. Porta, consulting and lecture fees and research grants from Bayer HealthCare Pharmaceuticals; Drs. Zeuzem, Bolondi, and Galle, consulting and lecture fees from Bayer HealthCare Pharmaceuticals; Dr. Greten, consulting and lecture fees from Bayer HealthCare Pharmaceuticals and lecture fees from Roche and Pfizer; Dr. Seitz, consulting fees from Sanofi-Aventis and Bayer HealthCare Pharmaceuticals; Dr. Borbath, consulting fees from Bayer HealthCare Pharmaceuticals and lecture fees from Novartis and Ipsen; Dr. Häussinger, lecture fees from Falk Foundation, Merz Pharma, and Roche; Mr. Giannaris and Drs. Shan, Moscovici, and Voliotis, being employees of Bayer HealthCare Pharmaceuticals; and Dr. Bruix, receiving consulting and lecture fees and research grants from Bayer HealthCare Pharmaceuticals, consulting and lecture fees from Biocompatibles, consulting fees and research grants from Eisai, consulting fees from Bristol-Myers Squibb, AstraZeneca, and Pharmexa, and lecture fees from Bracco. No other potential conflict of interest relevant to this article was reported.

We thank the patients who participated in the study and their families, the members of the independent data and safety monitoring committee, Andrea Nadel of Bayer HealthCare Pharmaceuticals for data analysis, Noel Curtis of GeoMed for medical writing support, and Lila Adnane of Bayer HealthCare Pharmaceuticals for critical review of the manuscript.

#### APPENDIX

The affiliations of the authors are as follows: Barcelona Clinic Liver Cancer Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Centro de Investigaciones en Red de Enfermedades Hepáticas y Digestivas Hospital Clínic Barcelona, Barcelona (J.M.L., A.F., J.B.); Mount Sinai School of Medicine, New York (J.M.L., M. Schwartz); St. Chiara University Hospital, Pisa, Italy (S.R.); National Cancer Institute, Milan (V.M.); University Hospital of Essen, Essen, Germany (P.H.); Auckland City Hospital, Auckland, New Zealand (E.G.); Centre Hospitalier Universitaire Hôpital Saint André, Bordeaux, France (J.-F.B.); Hospital das Clínicas de São Paulo, São Paulo (A.C.O.); Instituto Clinico Humanitas, Milan (A.S.); Institut de Cancérologie de Rennes, European University in Brittany, Rennes, France (J.-L.R.); IRCCS San Matteo University Hospital, Pavia, Italy (C.P.); J.W. Goethe University Hospital, Frankfurt, Germany (S.Z.); University of Bologna, Bologna, Italy (L.B.); Medizinische Hochschule Hannover, Hannover, Germany (T.F.G.); Mainz University, Mainz, Germany (P.R.G.); Hôpital Timone, Université de la Méditerranée, Marseille, France (J.-F.S.); Cliniques Universitaires Saint-Luc, Brussels (L.B.); Universitätsklinikum Düsseldorf, Düsseldorf, Germany (D.H.); Bayer HealthCare Pharmaceuticals, Toronto (T.G.) and West Haven, CT (M. Shan); and Bayer Schering Pharma, Milan (M.M.) and Wuppertal, Germany (D.V.).

The following principal investigators enrolled patients in the SHARP trial: **Argentina:** M.G. Pallota, J.J. Zarba; **Australia:** M. Boyer, S. Riordan, A. Strickland, N. Tebbutt, B. Thomson; **Belgium:** I. Borbath, J. De Greve, J.-L. Van Laethem, W. Van Steenberghe, H. Van Vlierberghe; **Brazil:** C. Barrios, A. Cosme de Oliveira; **Bulgaria:** I. Kotzev, D. Takov, K. Tchernev; **Canada:** K. Burak, M. Ma, P. Metrakos, C. Olweny, M. Sherman; **Chile:** C. Gamargo Garate, J. Martinez-Castillo; **France:** M. Beaugrand, J. Bennouna, J.-F. Blanc, J.-P. Bronowicki, F. Degos, S. Dominguez, J.-D. Grange, P. Hillon, J.-L. Raoul, J.-F. Seitz; **Germany:** H. Blum, P. Buggisch, W. Caspary, M. Dollinger, P.R. Galle, G. Gerken, B. Göke, M. Gregor, T. Greten, D. Häussinger, J. Scherübl, M. Scheulen, R. Schmid, U. Spengler, R. Wiest, S. Zeuzem; **Greece:** C. Arvanitakis, G. Germanidis, I. Katsos; **Israel:** A. Figer, S. Stemmer; **Italy:** D. Amadori, L. Bolondi, F. Cognetti, A. Craxi, F. Farinati, C. Gridelli, A. Martoni, V. Mazzaferro, C. Porta, S. Ricci, A. Sangiovanni, A. Santoro, F. Trevisani; **Mexico:** L.E. Cisneros Garza; **New Zealand:** E. Gane, A. O'Donnell; **Peru:** J. Leon, A. Lozano; **Poland:** J. Jassem, G. Rydzewska, A. Szawłowski, P. Tomczak; **Romania:** F. Badulescu, L. Miron; **Russia:** V. Kubyshekin; **Spain:** J. Bruix, A. Forner, J. Bustamante Schneider, M. Diago, J.L. Montero Alvarez, S. Pascual, L. Ruiz del Arbol, B. Sangro, R. Solá, J. Tabernero; **Switzerland:** B. Muellhaupt, A. Roth; **United Kingdom:** T.R. Jeffrey Evans, S. Falk, T. Meyer, H. Reeves, P. Ross; **United States:** A. Befeler, T. Boyer, C. Britten, T. Byrne, G. Garcia-Tsao, P. Gold, A. Goldenberg, D. Heuman, P. Kennedy, A. Koch, J.M. Llovet, J. Marrero, M. Schilsky, J. Schwartz, M. Schwartz.

## REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74-108.
2. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003;362:1907-17.
3. Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005;42:1208-36.
4. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma: conclusions of the Barcelona-2000 EASL Conference. *J Hepatol* 2001;35:421-30.
5. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology* 2003;37:429-42.
6. Lopez PM, Villanueva A, Llovet JM. Systematic review: evidence-based management of hepatocellular carcinoma — an updated analysis of randomized controlled trials. *Aliment Pharmacol Ther* 2006;23:1535-47.
7. Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res* 2004;64:7099-109.
8. Chang YS, Adnane J, Trail PA, et al. Sorafenib (BAY 43-9006) inhibits tumor growth and vascularization and induces tumor apoptosis and hypoxia in RCC xenograft models. *Cancer Chemother Pharmacol* 2007;59:561-74.
9. Ito Y, Sasaki Y, Horimoto M, et al. Activation of mitogen-activated protein kinases/extracellular signal-regulated kinases in human hepatocellular carcinoma. *Hepatology* 1998;27:951-8.
10. Villanueva A, Newell P, Chiang DY, Friedman SL, Llovet JM. Genomics and signaling pathways in hepatocellular carcinoma. *Semin Liver Dis* 2007;27:55-76.
11. Calvisi DF, Ladu S, Gorden A, et al. Ubiquitous activation of Ras and Jak/Stat pathways in human HCC. *Gastroenterology* 2006;130:1117-28.
12. Semela D, Dufour JF. Angiogenesis and hepatocellular carcinoma. *J Hepatol* 2004;41:864-80.
13. Liu L, Cao Y, Chen C, et al. Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. *Cancer Res* 2006;66:11851-8.
14. Abou-Alfa GK, Schwartz L, Ricci S, et al. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2006;24:4293-300.
15. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649-55.
16. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973;60:646-9.
17. Child CG III, ed. The liver and portal hypertension. Vol. 1 of Major problems in clinical surgery. Philadelphia: W.B. Saunders, 1964:50-64.
18. Therasse P, Arbusk SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000;92:205-16.
19. Yount S, Cella D, Webster K, et al. Assessment of patient-reported clinical outcome in pancreatic and other hepatobiliary cancers: the FACT Hepatobiliary Symptom Index. *J Pain Symptom Manage* 2002;24:32-44.
20. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549-56.
21. Yeo W, Mok TS, Zee B, et al. A randomized phase III study of doxorubicin versus cisplatin/interferon alpha-2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. *J Natl Cancer Inst* 2005;97:1532-8.
22. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 1999;340:745-50.
23. Martínez Cerezo FJ, Tomás A, Donoso L, et al. Controlled trial of tamoxifen in patients with advanced hepatocellular carcinoma. *J Hepatol* 1994;20:702-6.
24. Lai CL, Lau JY, Wu PC, et al. Recombinant interferon-alpha in inoperable hepatocellular carcinoma: a randomized controlled trial. *Hepatology* 1993;17:389-94.
25. Philip PA, Mahoney MR, Allmer C, et al. Phase II study of erlotinib (OSI-774) in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2005;23:6657-63.
26. Thomas MB, Chadha R, Iwasaki M, Glover K, Abbruzzese JL. The combination of bevacizumab (B) and erlotinib (E) shows significant biological activity in patients with advanced hepatocellular carcinoma (HCC). *J Clin Oncol* 2007;25:Suppl:214s. abstract.
27. O'Dwyer PJ, Giantonio BJ, Levy DE, Kauh JS, Fitzgerald DB, Benson AB III. Gefitinib in advanced unresectable hepatocellular carcinoma: results from the Eastern Cooperative Oncology Group's Study E1203. *J Clin Oncol* 2006;24:Suppl:213s. abstract.
28. Schwartz JD, Schwartz M, Lehrner D, et al. Bevacizumab in unresectable hepatocellular carcinoma (HCC) for patients without metastasis and without invasion of the portal vein. *J Clin Oncol* 2006;24:Suppl:213s. abstract.
29. Zhu AX, Blaszkowsky LS, Ryan DP, et al. Phase II study of gemcitabine and oxaliplatin in combination with bevacizumab in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2006;24:1898-903.
30. Faivre SJ, Raymond E, Douillard J, et al. Assessment of safety and drug-induced tumor necrosis with sunitinib in patients (pts) with unresectable hepatocellular carcinoma (HCC). *J Clin Oncol* 2007;25:Suppl:149s. abstract.
31. Zhu AX, Sahani DV, di Tomaso E, et al. A phase II study of sunitinib in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2007;25:Suppl:231s. abstract.
32. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007;356:125-34. [Erratum, *N Engl J Med* 2007;357:203.]
33. Ratain MJ, Eisen T, Stadler WM, et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2006;24:2505-12.
34. Wood LS. Managing the side effects of sorafenib and sunitinib. *Community Oncol* 2006;3:558-62.
35. Llovet JM, DiBisceglie A, Bruix J, et al. Design and end-points of clinical trials in hepatocellular carcinoma. *J Natl Cancer Inst* 2008;100:698-711.

Copyright © 2008 Massachusetts Medical Society.