Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial

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Summary

Background There is no standard of care for adjuvant therapy for patients with hepatocellular carcinoma. This trial was designed to assess the efficacy and safety of sorafenib versus placebo as adjuvant therapy in patients with hepatocellular carcinoma after surgical resection or local ablation.

Methods We undertook this phase 3, double-blind, placebo-controlled study of patients with hepatocellular carcinoma with a complete radiological response after surgical resection (n=900) or local ablation (n=214) in 202 sites (hospitals and research centres) in 28 countries. Patients were randomly assigned (1:1) to receive 400 mg oral sorafenib or placebo twice a day, for a maximum of 4 years, according to a block randomisation scheme (block size of four) using an interactive voice-response system. Patients were stratified by curative treatment, geography, Child-Pugh status, and recurrence risk. The primary outcome was recurrence-free survival assessed after database cut-off on Nov 29, 2013. We analysed efficacy in the intention-to-treat population and safety in randomly assigned patients receiving at least one study dose. The final analysis is reported. This study is registered with ClinicalTrials.gov, number NCT00692770.

Findings We screened 1602 patients between Aug 15, 2008, and Nov 17, 2010, and randomly assigned 1114 patients. Of 556 patients in the sorafenib group, 553 (>99%) received the study treatment and 471 (85%) terminated treatment. Of 558 patients in the placebo group, 554 (99%) received the study treatment and 447 (80%) terminated treatment. Median duration of treatment and mean daily dose were 12·5 months (IQR 2·6–35·8) and 577 mg per day (SD 212·8) for sorafenib, compared with 22·2 months (8·1–38·8) and 778·0 mg per day (79·8) for placebo. Dose modification was reported for 497 (89%) of 559 patients in the sorafenib group and 206 (38%) of 548 patients in the placebo group. At final analysis, 464 recurrence-free survival events had occurred (270 in the placebo group and 194 in the sorafenib group). Median follow-up for recurrence-free survival was 8·5 months (IQR 2·9–19·5) in the sorafenib group and 8·4 months (2·9–19·8) in the placebo group. We noted no difference in median recurrence-free survival between the two groups (33·3 months in the sorafenib group *vs* 33·7 months in the placebo group; hazard ratio [HR] 0·940; 95% CI 0·780–1·134; one-sided p=0·26). The most common grade 3 or 4 adverse events were hand-foot skin reaction (154 [28%] of 559 patients in the sorafenib group *vs* four [<1%] of 548 patients in the placebo group) and diarrhoea (36 [6%] *vs* five [<1%] in the placebo group). Sorafenib-related serious adverse events included hand-foot skin reaction (ten [2%]), abnormal hepatic function (four [<1%]), and fatigue (three [<1%]). There were four (<1%) drug-related deaths in the sorafenib group and two (<1%) in the placebo group.

Interpretation Our data indicate that sorafenib is not an effective intervention in the adjuvant setting for hepatocellular carcinoma following resection or ablation.

Funding Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals.

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death globally, and the global incidence is rising, with roughly 700 000 cases diagnosed worldwide in 2012 alone.[1,2] HCC usually occurs in the setting of liver cirrhosis, because of chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infections, alcohol consumption, non-alcoholic steatohepatitis, or diabetes.[3–5]

In carefully selected patients diagnosed at an early disease stage, surgical resection, liver transplantation, and local ablation are potentially curative and are associated with 5-year survival rates of 60–80% (resection) and 40–70% (ablation).[3,4,6] However, tumour recurrence is common and jeopardises overall survival in these patients. Surgical resection and ablation are associated with tumour recurrence rates of 50% at 3 years and 70% at 5 years.[3,4,6–9] Thus, the long-term prognosis after resection or ablation remains unsatisfactory, and prevention of recurrence via adjuvant treatments is an important unmet medical need in patients with HCC.

Adjuvant therapy in HCC represents a considerable challenge, in particular because of the underlying liver

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Research in context

Evidence before this study
We searched PubMed using combinations of the search terms "hepatocellular carcinoma", "HCC", "systemic", "adjuvant", and "sorafenib", with no time restriction. We also assessed major clinical practice guidelines for hepatocellular carcinoma (HCC) and associated references. Sorafenib is the established standard of care in patients with advanced HCC and the only systemic agent approved for HCC. To the best of our knowledge, before this study, no study of sorafenib in the adjuvant setting after resection or ablation had been done. However, more recently, two studies of sorafenib as an adjuvant therapy for HCC were published. One, a pilot study of 31 patients, reported a significantly longer time to recurrence in the sorafenib group,

whereas the other, a retrospective study of 78 patients, noted that sorafenib prolonged overall survival, but not recurrence-free survival.

Added value of this study
Herein, we report the first, large-scale, randomised controlled trial assessing sorafenib as an adjuvant therapy for patients with HCC after resection or ablation.

Implications of all the available evidence
Although sorafenib has shown to be effective in the advanced setting, our findings, in combination with the additional evidence available, suggest that the drug is not an effective intervention in the adjuvant setting for HCC after resection or ablation.

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disease present in almost all patients. Currently, there is no standard of care for adjuvant therapy because no treatment has a proven benefit in randomised studies in patients with HCC after potentially curative treatment.[3,4,10–13] Although interferon is the most widely studied treatment in this setting, evidence is conflicting based on studies with small sample sizes, heterogeneous patient populations, and differing types and length of treatment.[13] Studies of other potential adjuvant treatment options, such as vitamin K2, retinoids, and systemic chemotherapy, have also been inconclusive in terms of efficacy and safety,[7,13–15] and a phase 3 trial (NCT00568308) of the heparanase inhibitor PI-88, which showed promise in phase 2,[16] was terminated.[17]

The oral multikinase inhibitor sorafenib is approved in patients with unresectable HCC based on two phase 3 randomised trials,[18,19] and is the recommended treatment in patients with advanced HCC.[3,4,10–12]

Tumour recurrence can be caused by unrecognised microscopic metastases, or de-novo development of primary tumours because of the underlying liver disease.[6,20] Thus, based on the mechanism of action of sorafenib (namely, inhibition of tumour cell proliferation and angiogenesis[21]), in addition to its proven efficacy in advanced HCC, there is rationale for the study of sorafenib as an adjuvant therapy in HCC. The STORM trial was thus designed to assess the efficacy and safety of sorafenib versus placebo as an adjuvant therapy in patients with HCC with a complete radiological response after curative treatment by surgical resection (R0 on pathological report) or local ablation (complete response by imaging techniques).

Methods

Study design and participants

The STORM trial was a randomised, double-blind, placebo-controlled, phase 3 study undertaken throughout the Americas, Asia-Pacific, and Europe across 202 sites (hospitals and research centres) in 28 countries (appendix). Site distribution was as follows: Argentina

(three centres), Australia (five centres), Austria (three centres), Belgium (four centres), Brazil (five centres), Bulgaria (two centres), Canada (five centres), Chile (two centres), China (27 centres), France (14 centres), Germany (15 centres), Greece (one centre), Hong Kong (three centres), Italy (14 centres), Japan (17 centres), Korea (ten centres), Mexico (three centres), New Zealand (one centre), Portugal (one centre), Romania (three centres), Russia (four centres), Singapore (two centres), Spain (11 centres), Sweden (two centres), Switzerland (two centres), Taiwan (seven centres), the UK (seven centres), and the USA (29 centres).

Eligible patients were men and women aged 18 years or older with a confirmed first diagnosis of HCC suitable for curative treatment (resection or local ablation) according to clinical guidelines.[3,4] An initial staging scan (CT or MRI of chest, abdomen, and pelvis), done before curative treatment, was used for patient stratification. Patients were required to have an eligibility scan (CT or MRI of chest, abdomen, and pelvis) confirming complete radiological response by masked central independent review based on validated imaging criteria[3,4,22] between 3 and 7 weeks after either complete tumour removal after surgical resection or the last local ablation treatment (only radiofrequency ablation or percutaneous ethanol injection). Although patients who underwent ablation were not required to have histological confirmation at the time of ablation, if this was not available, they needed to have met the imaging criteria. No more than 4 months must have passed between the initial staging scan and completion of curative treatment.

Patients eligible for enrolment had a maximum tumour load before curative therapy comprising one lesion of any size for resection, or a single lesion 5 cm or smaller or two or three lesions each 3 cm or smaller in size for ablation. Other eligibility criteria included a Child-Pugh score of 5–7 (Child-Pugh score 7 allowed only in the absence of ascites), Eastern Cooperative Oncology Group performance status of 0, and alpha fetoprotein concentration lower than 400 ng/mL. Patients were also

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required to have adequate bone marrow, liver, and renal function as assessed by laboratory tests done with samples taken within 14 days before randomisation, including haemoglobin, bilirubin, platelet count, neutrophil count, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and serum creatinine.

We assessed risk of recurrence for resection based on tumour characteristics as established by the pathology report, and included only patients with an intermediate or high risk of recurrence. Patients undergoing surgical resection were defined as having a high risk of recurrence if they had one tumour of any size plus microvascular invasion, satellite tumours, or poorly differentiated microscopic appearance, or two or three tumours each 3 cm or smaller in size. An intermediate risk was defined as a single tumour of 2 cm or larger with well-differentiated or moderately differentiated microscopic appearance, and the absence of microvascular invasion or satellite tumours. Patients with single tumours smaller than 2 cm without vascular invasion or satellites

were deemed low risk and thus not included in our study. Patients undergoing local ablation were stratified based on imaging and defined as having a high risk of recurrence if they had a tumour 3–5 cm in size or two or three tumours each 3 cm or smaller; intermediate risk was defined as a single tumour 2–3 cm in size. We deemed patients with single tumours smaller than 2 cm as low risk and did not include them in the study. These criteria for recurrence risk, although based on the scientific literature and reflecting the Barcelona Clinic Liver Cancer staging system,[4,23,24] were designed specifically for the STORM study to exclude patients with a low or extremely high risk of recurrence.

Exclusion criteria included: recurrent HCC; macrovascular invasion; a history of cardiovascular disease (myocardial infarction >6 months before study entry was allowed); infection with HIV or other clinically serious infections; seizure disorder requiring drugs; and previous anticancer treatment for HCC, including sorafenib. Antiviral treatment for chronic HBV or HCV was allowed in accordance with local practice guidelines.

All patients provided signed, informed consent. The trial was undertaken in accordance with the Declaration of Helsinki and the International Conference on Harmonisation guideline E6: Good Clinical Practice. The conduct of the study met all local legal and regulatory requirements, and documented approval from appropriate ethics committees and institutional review boards was obtained. Documented protocol approval from appropriate ethics committees and institutional review boards was obtained for all participating centres before the start of the study.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to receive 400 mg twice a day of oral sorafenib or placebo for a maximum treatment period of 4 years (204 weeks ± 1) or until disease recurrence. The treatment period of 4 years was chosen based on the expected length of the study. At randomisation, patients were stratified according to curative treatment (surgical resection vs local ablation), geographical region (Americas vs Europe vs Asia-Pacific), Child-Pugh status (Child-Pugh A5 or A6 vs Child-Pugh B7), and risk of tumour recurrence (high vs intermediate).Reporting of the STORM trial is in keeping with the CONSORT statements.[25] Patients were randomly assigned between 6 and 12 weeks after curative treatment. The study was double-blinded. Sorafenib and placebo tablets were identical in appearance to ensure treatment was masked. Randomisation was done in a parallel, stratified fashion using permuted blocks (block size of four) via a computer-generated system. Sequences were generated by an internal randomisation group and the list loaded into an interactive voice-response system (IVRS). The study investigators enrolled patients and then entered them into the IVRS to obtain the randomisation
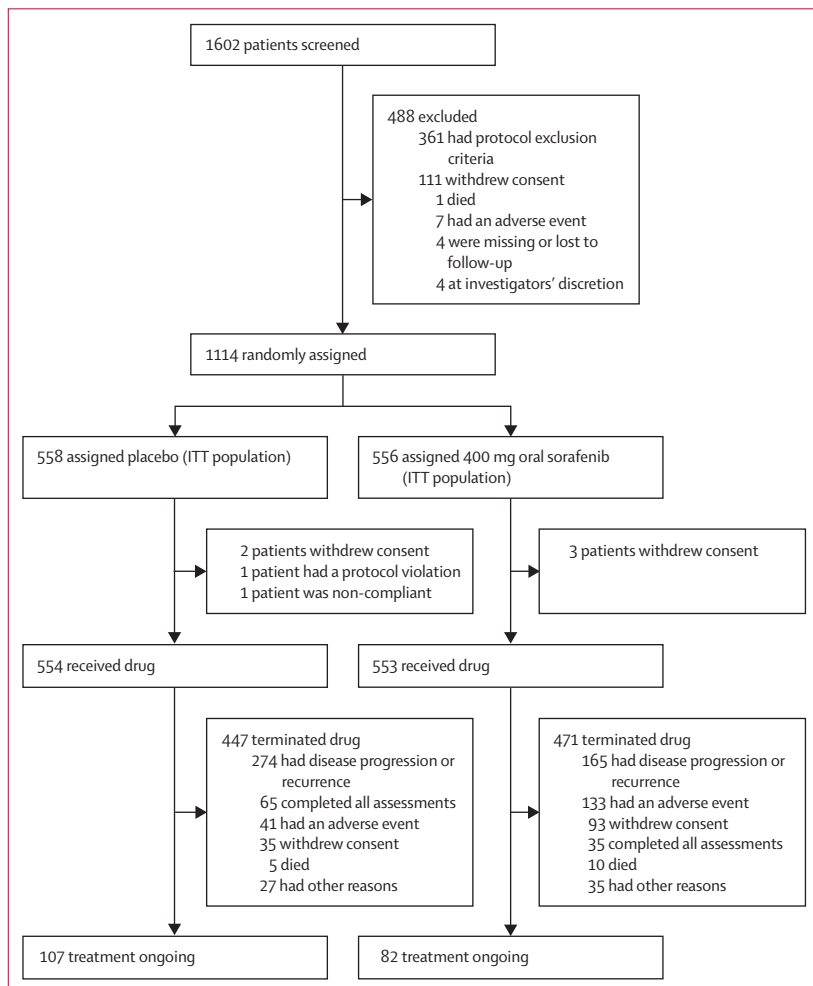
Figure 1: Trial profile
ITT=intention-to-treat.

	Sorafenib group (n=556)	Placebo group (n=558)
Age (years)	58 (24–85)	60 (19–83)
Age ≥65 years	173 (31%)	197 (35%)
Sex		
Female	105 (19%)	97 (17%)
Male	451 (81%)	461 (83%)
Ethnic origin		
Asian	348 (63%)	342 (61%)
White	186 (33%)	190 (34%)
Other or not reported	22 (4%)	26 (5%)
Region		
Americas (North, South)	60 (11%)	60 (11%)
Asia-Pacific (including Australia, New Zealand)	330 (59%)	330 (59%)
Europe	166 (30%)	168 (30%)
ECOG performance status		
0	551 (99%)	555 (100%)
1*	5 (<1%)	3 (<1%)
Curative treatment		
Local ablation	106 (19%)	108 (19%)
Surgical resection	450 (81%)	450 (81%)
Risk of recurrence†		
Intermediate	298 (54%)	308 (55%)
High	258 (46%)	250 (45%)
Child-Pugh score		
5	429 (77%)	432 (77%)
6	112 (20%)	106 (19%)
7	15 (3%)	16 (3%)
8*	0	4 (<1%)
Months from diagnosis to randomisation	2·6 (1·5–8·6)	2·6 (1·5–6·5)
	(Table 1 continues in next column)	

	Sorafenib group (n=556)	Placebo group (n=558)
(Continued from previous coloumn)		
Cause of underlying disease		
Alcohol use only	47 (9%)	45 (8%)
Hepatitis B only	282 (51%)	264 (47%)
Hepatitis C only	119 (21%)	151 (27%)
Unknown	67 (12%)	62 (11%)
Other	41 (7%)	36 (6%)
Alpha fetoprotein (ng/mL)‡	6·0 (1·1–348·4)	5·6 (1·0–532·8)
Bilirubin (mg/dL)‡	0·6 (0·2–2·0)	0·6 (0·2–2·6)
Albumin (g/dL)‡	3·9 (2·2–5·1)	4·0 (2·3–5·1)
Liver cirrhosis present	357 (64%)	344 (62%)
Number of lesions		
1	506 (91%)	521 (93%)
2	44 (8%)	33 (6%)
≥3	6 (1%)	4 (<1%)
Maximum tumour size (mm)	35 (10–200)	35 (10–190)
Tumour satellites§		
No	408 (91%)	411 (91%)
Yes	42 (9%)	39 (9%)
Microscopic vascular invasion§		
No	304 (68%)	303 (67%)
Yes	146 (32%)	147 (33%)

Data are n (%) or median (range). ECOG=Eastern Cooperative Oncology Group. *Protocol deviation. †Two patients with a low recurrence risk were included in the intermediate-risk group for the analysis. ‡Placebo (n=548). §Assessed only in the 450 patients in each group who underwent resection.

Table 1: Baseline patient demographics and disease characteristics by treatment group

number. Allocation of treatment was by an IVRS, which assigned each patient a treatment based on a unique bottle or drug number.

Procedures

Full patient assessment, including tumour assessment, complete blood count, and chemistry panel, was done at the initial visit, 4 weeks and 12 weeks after the initial visit, and every 12 weeks thereafter. After treatment initiation, an independent data safety monitoring committee assessed safety and treatment adherence at 1 month, 3 months, and every 6 months thereafter.

Treatment interruptions and up to two levels of dose reductions (first to 400 mg once a day and then to 400 mg every other day) were allowed if drug-related adverse events were recorded. If further dose reductions were needed, treatment was to be discontinued. For non-haematological adverse events other than skin toxicity, treatment interruption was indicated for any grade 3 adverse event, with a subsequent dose reduction by one level. For skin toxicity, treatment interruption

was indicated for any grade 2 or grade 3 adverse event, with a decreased dose frequency or level to be subsequently considered. Dose re-escalation was permitted at the physician's discretion if the adverse event resolved.

Outcomes

The primary endpoint of the study was recurrence-free survival (RFS), defined as the time from randomisation to the first documented disease recurrence by independent radiological assessment or death by any cause, whichever happened first. Secondary endpoints were time to recurrence, defined as the time from randomisation to the first documented disease recurrence by independent radiological assessment, and overall survival, defined as the time from randomisation to death by any cause.

Intrahepatic recurrence was defined as the appearance of one or more intrahepatic lesions with a longest diameter of at least 10 mm and a typical vascular pattern of HCC on dynamic imaging (ie, hypervascularisation in the arterial phase with washout in the portal venous or late venous phase). Lesions larger than 10 mm that did not show a typical vascular pattern could be diagnosed as HCC by

evidence of a growth interval of at least 1 cm in subsequent scans. Extrahepatic recurrence was defined as per Response Evaluation Criteria in Solid Tumors. Patients were allowed to withdraw from study treatment if they had ascites or pleural effusion deemed to be malignant.

Figure 2: Kaplan-Meier analysis of RFS based on independent assessment (A) and subgroup analysis of RFS by Cox regression based on independent assessment (B)

RFS=recurrence-free survival. HR=hazard ratio. ITT=intention to treat. NE=not evaluable.

Statistical analysis

The planned sample size for the study was 1100 patients and was calculated based on the primary endpoint. Initially, the study required 611 events based on 90% power to detect a 30% increase in RFS. Because of a higher than expected number of patients discontinuing treatment without recurrence of HCC, this was amended during the study to 457 events to achieve 80% power, assuming a 1:1 randomisation ratio and one-sided alpha of 0·025. The assumed RFS in the placebo group was 21 months, and the expected median overall survival was 60 months based on the scientific literature and taking into account the population to be enrolled in this study.[4,7]

Efficacy endpoints were analysed in the intention-to-treat population, defined as all randomly assigned patients. This represents the planned final analysis of RFS and the planned first interim analysis of overall survival. We used an O'Brien-Fleming spending function to work out the early stopping boundary for analysis of overall survival so that the overall alpha was less than or equal to 0·025 (one-sided). The amount of alpha spent at this analysis was 0·000449 (one-sided).

For each endpoint, the efficacy of sorafenib versus placebo was analysed with a log-rank test stratified by the same factors implemented at randomisation (one-sided alpha 0·025). Kaplan-Meier estimates, time to event curves, hazard ratios (HRs), and 95% confidence intervals (CIs) were also calculated for RFS, time to recurrence, and overall survival.

Safety analyses were descriptive and were done in the safety population, defined as all randomly assigned patients who received at least one dose of study drug. We used SAS version 9.2 for statistical analyses. The study is registered with ClinicalTrials.gov (NCT00692770) and the EU Clinical Trials Register (EudraCT number 2008-001087-36).

Role of the funding source

The funder was responsible for the study design and data collection and analysed and interpreted data, in collaboration with all authors. The funder also had input into the writing of the manuscript. JB and JML had full access to all of the study data, and all authors had access upon request. The corresponding author had access to the study data and had the final responsibility to submit the manuscript for publication.

Results

We recruited patients between Aug 15, 2008, and Nov 17, 2010. Of 1602 patients screened, 1114 met eligibility criteria and were randomly assigned: 556 to the sorafenib group and 558 to the placebo group (figure 1). 553 patients in the sorafenib group and 554 in the placebo group received treatment as initially assigned. Six patients assigned to placebo received one or more dose of sorafenib, and hence the safety analysis population
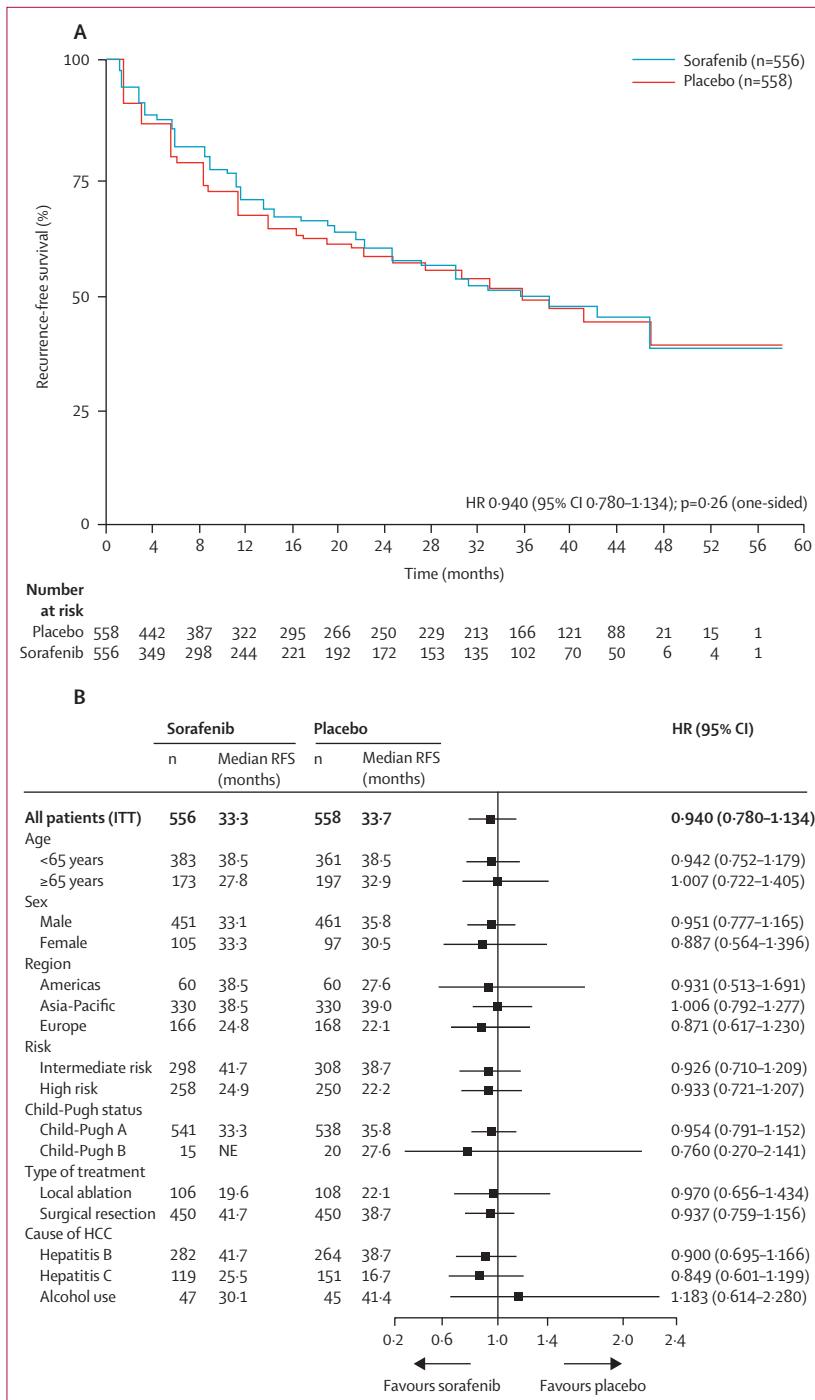
consisted of 559 patients in the sorafenib group and 548 in the placebo group.

Table 1 shows baseline characteristics. The median age was 59 years and most patients were male. Most patients were recruited from Asia-Pacific, then Europe and the Americas. Most patients had undergone surgical resection as curative therapy, and about half of patients were classified as having an intermediate risk of recurrence. Overall, HBV infection was the main cause of HCC in both the sorafenib group and the placebo group. Most patients had preserved liver function with Child Pugh status A.

Regionally, more patients in Europe had undergone ablation (110/344 [33%]) compared with patients in the Americas (18/120 [15%]) or Asia-Pacific (86/660 [13%]; appendix). HCV was the most common cause in the Americas (39/120 [33%]) and Europe (129/334 [39%]), whereas HBV was most common in Asia-Pacific (460/660 [70%]; appendix). Alcohol use as the underlying cause was most common in Europe (61/334 [18%]) compared with the other regions (appendix).

Median follow-up for RFS was 8·5 months (IQR 2·9–19·5) in the sorafenib group and 8·4 months (2·9–19·8) in the placebo group. At the analysis cut-off date of Nov 29, 2013, 464 actual RFS events (270 in the placebo group and 194 in the sorafenib group) and 217 deaths (113 in the placebo group and 104 in the sorafenib group) had occurred. We recorded no significant treatment effect of sorafenib on RFS according to the independent radiological assessment (HR 0·940; 95% CI 0·780–1·134; one-sided p=0·26; figure 2A). Median RFS was 33·3 months (95% CI 27·6–44·0) in the sorafenib group and 33·7 months (27·6–39·0) in the placebo group (figure 2A). Analysis of RFS according to independent assessment, in subgroups defined by baseline stratification factors (region, risk of recurrence, Child-Pugh status, primary treatment) as well as age, sex, and cause of underlying liver disease, showed no significant treatment effect of sorafenib across subgroups (figure 2B). Results were similar for RFS according to the investigators' assessments (HR 0·900; 95% CI 0·749–1·082; one-sided p=0·13; appendix). Median RFS was 35·9 months (95% CI 30·5–42·0) for sorafenib compared with 33·7 months (25·6–38·7) for placebo (appendix).

Time to recurrence according to independent assessment was not significantly different in the sorafenib group compared with the placebo group (HR 0·891; 95% CI 0·735–1·081; one-sided p=0·12; figure 3). Median time to recurrence was 38·5 months (95% CI 30·4–not estimable) for sorafenib compared with 35·8 months (30·3–41·4) for placebo (figure 3). According to the investigators' assessments, there was a suggestion of longer time to recurrence in the sorafenib group than in the placebo group, although this was not statistically significant (median 41·4 months, 95% CI 33·2–51·6) versus the placebo group (34·0, 27·9–39·0; HR 0·849; 95% CI 0·702–1·027; p=0·045; appendix).
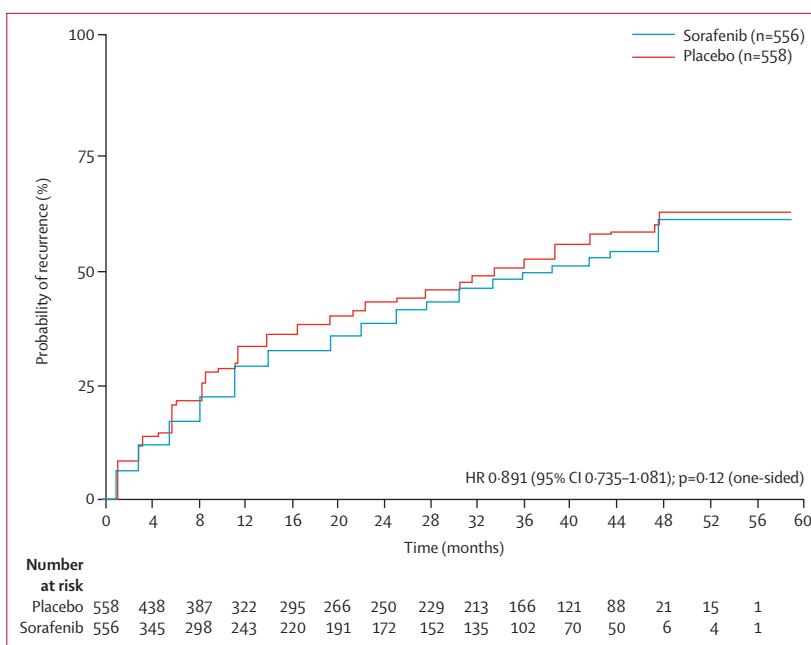
Figure 3: **Kaplan-Meier analysis of time to recurrence based on independent assessment**
HR=hazard ratio.
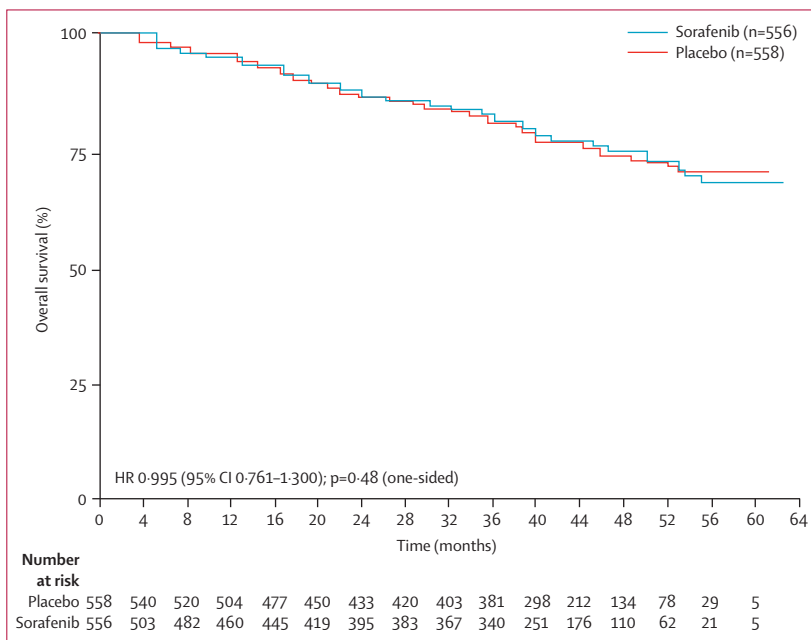
Figure 4: **Kaplan-Meier analysis of overall survival**
HR=hazard ratio.

Analysis of predefined subgroups suggested there were no notable treatment-group differences with respect to median time to recurrence based on Child-Pugh status, previous curative treatment, or risk of recurrence (appendix). We noted a suggestion of longer time to recurrence for patients given sorafenib who had HCV compared with those receiving placebo (median

	Sorafenib group (n=559)	Placebo group (n=548)
Duration of treatment (months)		
Mean	17·9 (16·5)	23·7 (16·5)
Median	12·5 (2·6–35·8)	22·2 (8·1–38·8)
Actual daily dose (mg/day)		
Mean	577·7 (212·8)	778·0 (79·8)
Median	600·0 (407·4–800·0)	800·0 (800·0–800·0)
Percent of planned dose (%)		
Mean	65·2 (29·0)	96·5 (10·7)
Median	58·3 (40·7–100·0)	100·0 (99·8–100·0)
Dose modification	497 (89%)	206 (38%)
Dose interruption	468 (84%)	185 (34%)
Dose reduction	372 (67%)	78 (14%)

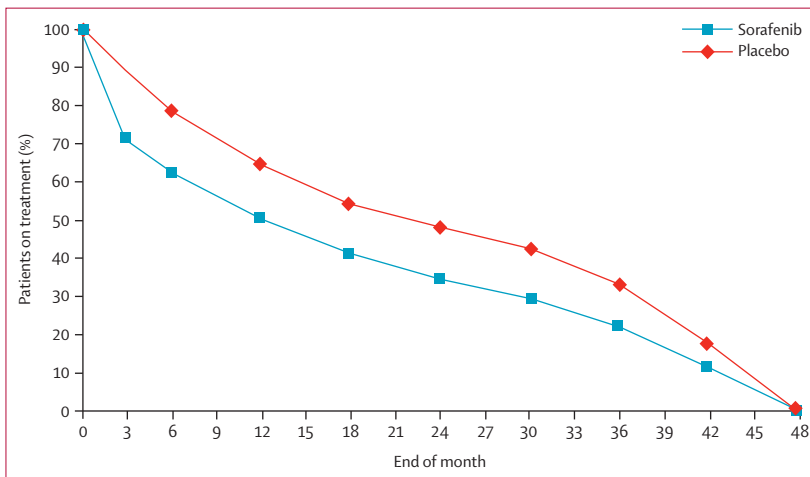Data are n (%), mean (SD), median (IQR).

Table 2: Study drug exposure

Figure 5: **Patients remaining on treatment over time**

	Sorafenib group (n=556)	Placebo group (n=558)
Terminated study drug	471 (85%)	447 (80%)
Main reason		
Disease recurrence	165 (30%)	274 (49%)
Adverse event	133 (24%)	41 (7%)
Consent withdrawn	93 (17%)	35 (6%)
Completed all planned assessments	35 (6%)	65 (12%)
Death	10 (2%)	5 (<1%)
Clinical progression*	10 (2%)	11 (2%)
Lost to follow-up	7 (1%)	3 (<1%)
Other	18 (3%)	13 (2%)

Data are n (%). *Radiological and clinical progression or progression based on clinical judgment.

Table 3: Reasons for discontinuation

27·8 months, 95% CI 19·0–not estimable) vs 16·8 months (13·6–33·1), although this difference was not significant (HR 0·785 [95% CI 0·546–1·129]) and the median time to recurrence in both treatment groups was shorter than in the other subgroups (appendix).

The median follow-up for overall survival was 23·0 months (IQR 12·7–36·0) in the sorafenib group and 22·0 months (IQR 14·4–35·5) in the placebo group. No significant treatment effect of sorafenib on overall survival was shown (HR 0·995; 95% CI 0·761–1·300; one-sided p=0·48; figure 4). Median overall survival was not reached in either treatment group.

Median duration of treatment was shorter with sorafenib than with placebo (table 2 and figure 5). Median duration of both sorafenib and placebo therapy was shorter in the Americas (3·6 months [IQR 1·5–21·4] vs 16·4 months [0·4–28·8]) and Europe (8·1 months [1·6–21·9] vs 21·2 months [8·8–37·4]) than in Asia-Pacific (16·9 months [4·6–38·4] vs 28·2 months [8·2–41·4]; appendix). Actual mean daily doses are shown in table 2. Overall, 497 (89%) patients given sorafenib and 206 (38%) patients given placebo required dose modifications (table 2).

The 1-year discontinuation rate was 49% (275/556) for sorafenib and 35% (195/558) for placebo (figure 5). The most common reason for treatment discontinuation in both treatment groups was disease recurrence, which was less frequent with sorafenib (165 [30%] of 556 patients) than with placebo (274 [49%] of 558 patients). Conversely, adverse events were a more frequent reason for discontinuation in the sorafenib group (133 [24%]) than in the placebo group (41 [7%]), as was withdrawal of consent (93 [17%] in the sorafenib group vs 35 [6%] in the placebo group; table 3 and appendix).

Overall, 545 (97%) of 559 patients who received sorafenib and 491 (90%) of 548 patients who received placebo had an adverse event. The overall incidence of drug-related adverse events was higher in the sorafenib group than in the placebo group (526 [94%] vs 254 [46%]). In the sorafenib group, adverse events were mainly grade 1 or grade 2 in severity, and were gastrointestinal, constitutional, or dermatological in nature (table 4). The most commonly reported drug-related adverse events in patients given sorafenib were hand-foot skin reaction, diarrhoea, and alopecia. Grade 3 adverse events in patients given sorafenib included hand-foot skin reaction, diarrhoea, and hypertension (table 4). Adverse events leading to a dose modification were recorded in 439 (79%) patients in the sorafenib group and 111 (20%) patients in the placebo group. The number of reported serious adverse events, of any attribution, was similar between the groups (225 [40%] in the sorafenib group vs 228 [42%] in the placebo group). Of note, patients who were admitted to hospital within 30 days of the last dose of study drug because of any procedure related to HCC recurrence

	Sorafenib group (n=559)						Placebo group (n=548)					
	Adverse events			Drug-related adverse events			Adverse events			Drug-related adverse events		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Any adverse event	545 (97%)	324 (58%)	60 (11%)	526 (94%)	280 (50%)	13 (2%)	491 (90%)	201 (37%)	57 (10%)	254 (46%)	48 (9%)	3 (<1%)
Constitutional symptoms												
Fatigue	85 (15%)	9 (2%)	1 (<1%)	73 (13%)	8 (1%)	1 (<1%)	66 (12%)	2 (<1%)	0	40 (7%)	2 (<1%)	0
Weight loss	60 (11%)	8 (1%)	..	41 (7%)	5 (<1%)	..	13 (2%)	0	..	2 (<1%)	0	..
Weight gain	14 (3%)	1 (<1%)	..	1 (<1%)	0	..	42 (8%)	3 (<1%)	..	1 (<1%)	0	..
Decreased appetite	40 (7%)	2 (<1%)	0	33 (6%)	2 (<1%)	0	18 (3%)	0	0	3 (<1%)	0	0
Arthralgia	34 (6%)	0	0	10 (2%)	0	0	30 (5%)	1 (<1%)	0	3 (<1%)	0	0
Back pain	41 (7%)	0	1 (<1%)	9 (2%)	0	0	38 (7%)	1 (<1%)	1 (<1%)	1 (<1%)	0	0
Headache	41 (7%)	3 (<1%)	0	22 (4%)	1 (<1%)	0	33 (6%)	1 (<1%)	0	10 (2%)	0	0
Pyrexia	33 (6%)	0	0	8 (1%)	0	0	24 (4%)	0	0	3 (<1%)	0	0
Insomnia	24 (4%)	1 (<1%)	0	5 (<1%)	0	0	31 (6%)	0	0	6 (1%)	0	0
Dermatological events												
Alopecia	187 (33%)	..	..	179 (32%)	..	..	18 (3%)	..	..	17 (3%)	..	..
Hand-foot skin reaction	393 (70%)	154 (28%)	..	389 (70%)	154 (28%)	..	28 (5%)	4 (<1%)	..	28 (5%)	4 (<1%)	..
Rash or desquamation	97 (17%)	15 (3%)	1 (<1%)	91 (16%)	15 (3%)	1 (<1%)	45 (8%)	1 (<1%)	0	27 (5%)	0	0
Pruritus	46 (8%)	3 (<1%)	..	43 (8%)	3 (<1%)	..	57 (10%)	1 (<1%)	..	33 (6%)	1 (<1%)	..
Gastrointestinal symptoms												
Diarrhoea	242 (43%)	36 (6%)	0	215 (38%)	34 (6%)	0	64 (12%)	5 (<1%)	0	40 (7%)	2 (<1%)	0
Nausea	50 (9%)	1 (<1%)	0	34 (6%)	1 (<1%)	0	24 (4%)	2 (<1%)	0	8 (1%)	0	0
Abdominal pain	57 (10%)	6 (1%)	..	29 (5%)	6 (1%)	..	46 (8%)	0	..	12 (2%)	0	..
Constipation	40 (7%)	0	0	14 (3%)	0	0	35 (6%)	0	0	8 (1%)	0	0
Ascites	38 (7%)	4 (<1%)	0	6 (1%)	1 (<1%)	0	19 (3%)	1 (<1%)	0	3 (<1%)	0	0
Dyspepsia	20 (4%)	1 (<1%)	..	10 (2%)	1 (<1%)	..	28 (5%)	0	..	3 (<1%)	0	..
Vascular disorders												
Hypertension	142 (25%)	34 (6%)	0	108 (19%)	24 (4%)	0	64 (12%)	9 (2%)	0	35 (6%)	6 (1%)	0
Laboratory investigations												
Decreased platelets	48 (9%)	15 (3%)	1 (<1%)	32 (6%)	8 (1%)	1 (<1%)	26 (5%)	5 (<1%)	0	13 (2%)	1 (<1%)	0
Increased ALT	52 (9%)	26 (5%)	1 (<1%)	28 (5%)	11 (2%)	1 (<1%)	37 (7%)	19 (3%)	0	15 (3%)	5 (<1%)	0
Increased AST	49 (9%)	23 (4%)	3 (<1%)	25 (5%)	10 (2%)	2 (<1%)	35 (6%)	13 (2%)	1 (<1%)	13 (2%)	6 (1%)	0
Respiratory												
Dysphonia	41 (7%)	1 (<1%)	0	32 (6%)	1 (<1%)	0	3 (<1%)	0	0	1 (<1%)	0	0
Cough	30 (5%)	2 (<1%)	..	6 (1%)	2 (<1%)	..	43 (8%)	1 (<1%)	..	2 (<1%)	0	..
Nasopharyngitis	30 (5%)	0	0	3 (<1%)	0	0	35 (6%)	0	0	0	0	0

Data are n (%). Adverse events are listed according to Medical Dictionary for Regulatory Activities terminology and graded according to Common Terminology Criteria for Adverse Events version 3.0. An adverse event is defined as any event arising or worsening after the start of study drug administration until 30 days after the last dose of study medication. Grade 5 events (n=1 unless otherwise stated) reported in the sorafenib group were renal failure, renal disorder, cerebral haemorrhage, peritonitis, hepatic failure or dysfunction (n=4), multi-organ failure (n=3), drowning, myocardial infarction, and atrioventricular block. Grade 5 events (n=1 unless otherwise stated) reported in the placebo group were peripheral embolism, cerebral haemorrhage, neoplasms (n=3), hepatitis B virus infection (n=2), death, and myocardial ischaemia. ALT=alanine aminotransferase; AST=aspartate aminotransferase.

Table 4: Adverse events and drug-related adverse events occurring in ≥5% of patients

(eg, resection) were categorised as having a serious adverse event, thereby somewhat confounding this result. Drug-related serious adverse events were noted in 52 (9%) patients in the sorafenib group and 14 (3%) in the placebo group. In the sorafenib group the most commonly reported drug-related serious adverse events were hand-foot skin reaction, abnormal hepatic function, and fatigue (table 4).

24 patients died during the study because of grade 5 adverse events, 15 (3%) in the sorafenib group and nine (2%) in the placebo group. The investigators considered four of these in the sorafenib group (three with abnormal hepatic function and one cerebral haemorrhage) and two in the placebo group (one myocardial ischaemia and one undetermined cause) to be drug-related.

Discussion

In this phase 3 randomised study of sorafenib as adjuvant therapy for early HCC after image-proven, successful surgical resection or local ablation, the primary objective of a significant improvement in RFS with sorafenib was not met. Similarly, we noted no significant treatment

effect on the secondary endpoints of time to recurrence and overall survival.

Adjuvant therapy in HCC represents an area of high unmet medical need, and, up to now, attempts to address this need have proved largely unsuccessful. Therefore, current guidelines do not endorse any particular adjuvant therapy but recommend that larger trials with lower risk of systematic error be undertaken. More generally, advances in the treatment of HBV and HCV have implications for HCC, including potentially in the adjuvant setting. Antiviral therapy with nucleotide analogues has shown promise for reducing the recurrence of HBV-related HCC, and further investigation is warranted.[7] Moreover, interferon-free regimens for HCV involving direct antiviral agents have substantially increased viral clearance rates, although the longer-term effect of this on HCC recurrence is yet to be established.[26,27]

The adverse events reported were consistent with the known safety profile of sorafenib, and no new tolerability concerns were raised. However, the rate of discontinuation of sorafenib (50% at 1 year) was higher than we anticipated, in particular because of adverse events and consent withdrawal, which led to a shorter than expected median duration of treatment of roughly 12 months. This finding is probably indicative of the fact that physicians and patients have a reduced acceptance of adverse events because of a perception that the disease is cured by surgery or ablation. Additionally, the treatment duration in this trial was longer than for clinical trials in patients with advanced-stage disease, and hence a higher rate of adverse events and discontinuation, overall, might be expected.

Median treatment duration in the sorafenib and placebo groups was shortest in the Americas and longest in Asia-Pacific. We noted more sorafenib dose modifications in the Americas compared with other regions, and a notably lower rate of consent withdrawal in Asia-Pacific. The regional differences recorded in treatment adherence suggest that length of treatment was not the reason for the absence of efficacy in this study because subgroup analysis showed that patients in Asia-Pacific received sorafenib for a median of 16·9 months, with no effect on RFS. Nonetheless, we recorded a trend for longer time to recurrence for patients in the sorafenib group who had HCC as a result of HCV, who are found mainly in western regions (ie, Europe and the Americas). Thus, the shorter treatment duration could have affected the efficacy of sorafenib in these patients, especially in view of results of exploratory subgroup analyses of the SHARP trial showing better outcomes in patients with HCC caused by HCV versus HBV.[28] However, because HCC was not a stratification factor in this study, and given the HRs for survival were consistent across regions in phase 3 trials,[19,29] the potentially greater effect of sorafenib in patients with HCV compared with HBV remains to be validated. However, these findings might still be useful in directing the design of future trials in HCC because they potentially reflect differences in clinical practice or cultural approaches across regions.

Most patients in the sorafenib group had a dose reduction, and the mean daily dose of sorafenib was much lower (578 mg) than the intended 800 mg. It is unclear if the low exposure to sorafenib treatment was a contributing factor to the negative findings reported. The use of a lower sorafenib dose has been suggested in the scientific literature, in particular based on the findings of the SOFIA study.[30] However, the study was biased by several methodological issues,[31] and there is not enough evidence to support a ramp-up strategy for sorafenib. Indeed, evidence suggests that the adverse-event profile for sorafenib in the advanced treatment setting is similar irrespective of starting dose,[32] and in the SHARP trial, 76% of patients received more than 80% of the planned daily dose of sorafenib.[19] As mentioned, physicians and patients have a reduced acceptance of adverse events in the absence of active disease, which more likely explains the low median dose and high rate of dose modifications recorded for sorafenib in this study.

The higher than expected treatment discontinuation meant fewer recurrence events were recorded than might have been anticipated based on the scientific literature. There are probably many reasons for this: first, patients were included only if they had a complete response after ablation 1 month after the procedure, or if they had R0 status on the pathology report after resection. Thus, the high rate of early recurrences reported in retrospective studies because of undetected tumoral remains was not observed in the STORM study. Second, the alpha fetoprotein cutoff level of 400 ng/mL might have excluded patients with disease undetectable by imaging. Patients with an unhealthier lifestyle who would naturally have a higher risk of recurrence might also have been less likely to participate in the study. Additionally, it is possible that the bespoke risk stratification used meant that the study included some patients who had a low or moderate risk of recurrence. Hence, as a result of the approach taken, the required number of events was adapted and the study power was reduced from 90% to 80%.

Hepatocarcinogenesis is a complex process including many signalling cascades, and the mechanisms driving recurrence are not fully elucidated. The absence of benefit in our study might reflect that angiogenesis is not the sole requirement for initial tumour regrowth after resection or ablation, thereby rendering the anti-angiogenic activity of sorafenib insufficient to prevent relapse. The tumour microenvironment also plays a fundamental part in the pathogenesis of HCC, and sorafenib is known to affect several cell types other than cancer cells, such as hepatic stellate cells and macrophages.[33] Thus, because of the dynamic nature of the tumour microenvironment, the cell mix at the initial phase of the metastatic process might differ from that seen at a more evolutionary stage.

Of relevance, despite the many successes of anti-angiogenic treatments, their efficacy differs between cancer types, and several other anti-angiogenic agents have failed in the adjuvant setting of cancers such as colorectal, renal cell, and ovarian.[34,35] Hence, the negative findings for sorafenib as an adjuvant therapy in HCC do not affect its current indication in advanced HCC.

In conclusion, this phase 3 randomised study of sorafenib as adjuvant treatment after potentially curative therapy for HCC showed no significant treatment effect with sorafenib, with regards to RFS, time to recurrence, or overall survival. The adjuvant setting remains an area of high unmet need in HCC management, and further research into strategies to prevent HCC recurrence is needed.

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