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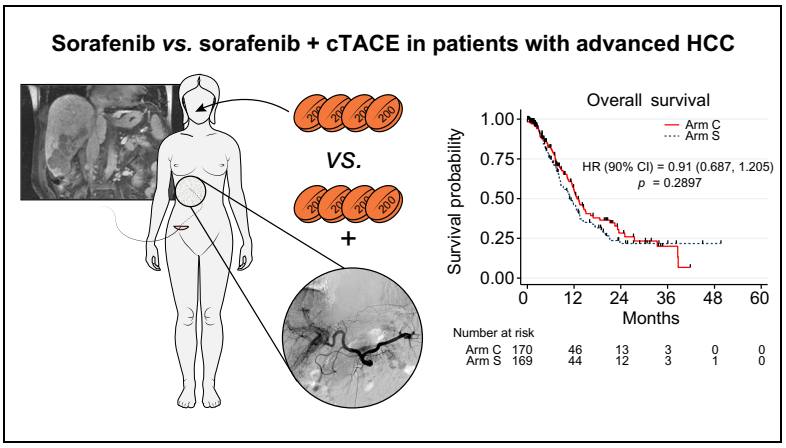
Sorafenib with or without concurrent transarterial chemoembolization in patients with advanced hepatocellular carcinoma: The phase III STAH trial

Graphical abstract



Highlights

- Sorafenib combined with concurrent chemoembolization did not improve overall survival.
- Combination therapy significantly improved tumor response and secondary outcomes.
- Sorafenib alone remains first-line standard of care for advanced hepatocellular carcinoma.

Authors

Joong-Won Park, Yoon Jun Kim, Do Young Kim, ..., Jong Eun Yeon, Bo Hyun Kim, Jaeseok Hwang

Correspondence

jwpark@ncc.re.kr
(J.-W. Park)

Lay summary

For patients with advanced hepatocellular carcinoma requiring sorafenib therapy, co-administration with conventional transarterial chemoembolization did not improve overall survival compared to sorafenib alone. Therefore, sorafenib alone remains the first-line standard of care for patients with advanced hepatocellular carcinoma.

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Sorafenib with or without concurrent transarterial chemoembolization in patients with advanced hepatocellular carcinoma: The phase III STAH trial

Joong-Won Park[1,*,†], Yoon Jun Kim[2,†], Do Young Kim[3], Si-Hyun Bae[4,5], Seung Woon Paik[6], Youn-Jae Lee[7], Hwi Young Kim[8,††], Han Chu Lee[9], Sang Young Han[10], Jae Youn Cheong[11], Oh Sang Kwon[12], Jong Eun Yeon[13], Bo Hyun Kim[1], Jaeseok Hwang[14]

[1]*National Cancer Center, Korea, South Korea;* [2]*Seoul National University Hospital, South Korea;* [3]*Severance Hospital, South Korea;* [4]*The Catholic University of Korea, South Korea;* [5]*Seoul St. Mary's Hospital, South Korea;* [6]*Samsung Medical Center, South Korea;* [7]*Inje University Busan Paik Hospital, South Korea;* [8]*SNU Boramae Medical Center, South Korea;* [9]*Asan Medical Center, University of Ulsan, South Korea;* [10]*Dong-A University Hospital, South Korea;* [11]*Ajou University Hospital, South Korea;* [12]*Gachon University Gil Medical Center, South Korea;* [13]*Korea University Guro Hospital, South Korea;* [14]*Keimyung University Dongsan Medical Center, South Korea*

Background & Aims: Sorafenib is first-line standard of care for patients with advanced hepatocellular carcinoma (HCC), yet it confers limited survival benefit. Therefore, we aimed to compare clinical outcomes of sorafenib combined with concurrent conventional transarterial chemoembolization (cTACE) *vs.* sorafenib alone in patients with advanced HCC.

Methods: In this investigator-initiated, multicenter, phase III trial, patients were randomized to receive sorafenib alone (Arm S, n = 169) or in combination with cTACE on demand (Arm C, n = 170). Sorafenib was started within 3 days and cTACE within 7–21 days of randomization. The primary endpoint was overall survival (OS).

Results: For Arms C and S, the median OS was 12.8 *vs.* 10.8 months (hazard ratio [HR] 0.91; 90% CI 0.69–1.21; $p = 0.290$); median time to progression, 5.3 *vs.* 3.5 months (HR 0.67; 90% CI 0.53–0.85; $p = 0.003$); median progression-free survival, 5.2 *vs.* 3.6 months (HR 0.73; 90% CI 0.59–0.91; $p = 0.01$); and tumor response rate, 60.6% *vs.* 47.3% ($p = 0.005$). For Arms C and S, serious (grade ≥3) adverse events occurred in 33.3% *vs.* 19.8% ($p = 0.006$) of patients and included increased alanine aminotransferase levels (20.3% *vs.* 3.6%), hyperbilirubinemia (11.8% *vs.* 3.0%), ascites (11.8% *vs.* 4.2%), thrombocytopenia (7.2% *vs.* 1.2%), anorexia (7.2% *vs.* 1.2%), and hand-foot skin reaction (10.5% *vs.* 11.4%). A *post hoc* subgroup analysis compared OS in Arm C patients (46.4%) receiving ≥2 cTACE sessions to Arm S patients (18.6 *vs.* 10.8 months; HR 0.58; 95% CI 0.40–0.82; $p = 0.006$).

Conclusion: Compared with sorafenib alone, sorafenib combined with cTACE did not improve OS in patients with advanced HCC. However, sorafenib combined with cTACE significantly improved time to progression, progression-free survival, and tumor response rate. Sorafenib alone remains the first-line standard of care for patients with advanced HCC.

Lay summary: For patients with advanced hepatocellular carcinoma requiring sorafenib therapy, co-administration with conventional transarterial chemoembolization did not improve overall survival compared to sorafenib alone. Therefore, sorafenib alone remains the first-line standard of care for patients with advanced hepatocellular carcinoma.

Clinical Trial Number: NCT01829035.

Introduction

Worldwide, primary liver cancer, including hepatocellular carcinoma (HCC), is the fifth most common cancer and the second leading cause of cancer-related mortality.[1] HCC prognosis remains poor because of the underlying chronic liver disease; late diagnosis, often at advanced stages of disease; and frequent recurrence/progression after treatment.[2,3]

Because there is no global consensus on the definition of advanced HCC, it encompasses a heterogenous group,[4] generally indicated in cases with macrovascular invasion and extrahepatic spread or progression on curative treatments. In patients with advanced HCC, sorafenib, the first approved oral multityrosine kinase inhibitor, is the standard first-line therapy;[4–9] however, outcomes of most patients remain unsatisfactory. To augment or improve the modest effects of sorafenib, several trials have studied the effects of combining it with other systemic therapies[10–12] or locoregional treatments, including radiofrequency ablation,[13] transarterial chemoembolization (TACE),[14,15] and radiotherapy.[16] Conventional TACE (cTACE) is an effective treatment for unresectable HCC, and most guidelines for HCC management recommend cTACE for intermediate stage or multifocal HCC.[4,7–9] In many countries, including South Korea, most patients with HCC present with unresectable disease, and TACE is most frequently performed across all disease stages, including advanced stage.[2] Contrary to Western guidelines,

Keywords: Hepatocellular carcinoma; Sorafenib; Transarterial chemoembolization; Combination treatment.
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* Corresponding author. Address: Center for Liver Cancer, National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang, Gyeonggi-do 10408, Republic of Korea. Tel.: +82 31 920 1605, fax: +82 31 920 1520.
E-mail address: jwpark@ncc.re.kr (J.-W. Park).
† These authors contributed equally as first authors to this article.
†† Present affiliation: Department of Internal Medicine, College of Medicine, Ewha Womans University, South Korea.

Asian guidelines recommend cTACE as an alternative treatment for advanced HCC according to low-level evidence.[8,17]

In a previous phase II study of patients with unresectable or advanced HCC, sorafenib combined with concurrent cTACE (SOR+T) demonstrated manageable safety and tended to improve outcomes.[15] TACE, inducing the upregulation of angiogenic factors by ischemic liver injury,[18] plus an anti-angiogenic agent (sorafenib) may complementarily inhibit angiogenic factors and tumor growth.[19]

Given the possibility of improved efficacy of the phase II study, we conducted an investigator-initiated phase III randomized, multicenter controlled study (STAH; NCT01829035) to compare the efficacy and safety of SOR+T with those of sorafenib alone as first-line treatment in patients with advanced HCC.

Patients and methods

Study population

In this phase III trial, 339 patients from 13 hospitals in South Korea were enrolled. HCC diagnosis was confirmed either histologically or clinically according to the Korean Liver Cancer Study Group and National Cancer Center Korea guidelines.[8,20] Abdominal and chest imaging was performed within 4 weeks of treatment initiation to determine treatment eligibility. Patients were eligible if they met any of the following criteria: stages III, IVa, or IVb HCC according to the modified Union for International Cancer Control (mUICC) TNM staging criteria (with vascular invasion, lymph node metastasis [any lymph node ≥1 cm] or extrahepatic tumor spread);[21] advanced HCC (mUICC stages III, IVa-b) indicated for systemic chemotherapy (but not curative therapy) as treatment of choice;[8,20] advanced HCC (mUICC stages III or IVa-b) that progressed despite prior local treatment; and advanced HCC progression and the requirement for 3 TACE sessions within the first 6 months (TACE refractoriness). Eligible patients were aged ≥20 years and had ≥1 typical enhanced measurable target lesion of ≤15 cm based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, Child-Pugh scores ≤7, Eastern Cooperative Oncology Group (ECOG) performance status score ≤2.

Patients were excluded if they had no measurable tumor of a diffuse infiltrative HCC type or brain metastases, a complete obstructive invasion of the main portal vein (Vp4), inferior vena cava invasion (Vv3), first order branch of the biliary duct invasion (B3), or had received any previous systemic therapy. Furthermore, patients were excluded if they received any locoregional therapy for HCC or radiotherapy for intrahepatic lesions 4 weeks or 3 months, respectively, prior to signing the informed consent (see appendix for full inclusion and exclusion criteria).

All patients provided written informed consent. The trial was approved by the institutional review boards of each participating hospital and complied with the Declaration of Helsinki and Good Clinical Practice guidelines.

Study design and treatment

Patients were randomly assigned to receive sorafenib with cTACE (combination; Arm C) or without cTACE (sorafenib alone; Arm S); they were stratified by mUICC stage (stage III *vs.* IV), degree of vascular invasion (none or Vp 1–2 *vs.* 3–4 or any other presence), Child-Pugh score (5 *vs.* 6–7), and alpha-fetoprotein level (<200 *vs.* ≥200 ng/ml) using the block randomization method (block sizes 2 or 4).

All patients initially received sorafenib 600 mg/day (200–400 mg twice daily) within 3 days of randomization. The daily sorafenib dose was increased to 800 mg (400 mg twice daily) if the 600 mg daily dose was well tolerated. Dose reduction was allowed by protocol (400 mg twice daily, 200–400 mg twice daily, 400 mg once daily, and 200 mg once daily) for patients experiencing sorafenib-related grade 3 non-hematologic or hematologic toxicities.

Patients randomized to Arm C received the first cTACE between 7 and 21 days after randomization (Fig. S1). Patients in Arm C then resumed sorafenib between 3 and 28 days after the first cTACE when they met the sorafenib treatment initiation criteria (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] levels ≤5 times the upper limit of normal [ULN], total bilirubin level <3.0 mg/dl, and albumin level ≥2.8 g/dl; see appendix for details).

For cTACE, lipiodol mixed with antitumor drug (doxorubicin or cisplatin) was used, and additional embolization materials, such as gelatin sponges, were allowed. Unapproved drugs or embolization materials were not permitted. Super-selective cTACE was recommended to chemoembolize all feeding arteries and minimize impairment of non-cancerous liver tissues. Patients could receive subsequent cTACE on demand if they showed viable lesions or incomplete lipiodol uptake and met the pre-cTACE test criteria (AST or ALT ≤5 times ULN, total bilirubin <3.0 mg/dl, prothrombin time international normalized ratio ≤1.8 times ULN and albumin ≥2.8 g/dl; see the appendix for details). However, cTACE was discontinued in cases of obstructive main vascular invasion or arterial damage, making additional cTACE impossible; prolonged hepatic impairment (Child-Pugh score ≥9 over 4 weeks); or intractable intrahepatic target lesions seen on 3 consecutive imaging studies.

Treatment continued until radiological disease progression or recurrence (defined by RECIST criteria) or unacceptable adverse events (AEs). Treatment was also discontinued for patients unable to commence sorafenib within 28 days of cTACE administration or take sorafenib for 29 consecutive days.

Outcomes and assessments

The primary endpoint of this study was overall survival (OS), defined as the time from enrollment date to the date of death from any cause. In this study, the time-point of enrollment was the date of randomization. Patients who remained alive at cut-off time were censored at the last study follow-up date.

Secondary endpoints were time to progression (TTP), defined as the time from enrollment date to radiologic progression date; progression-free survival (PFS), time from enrollment date to radiologic progression or death date; tumor response rate (TRR), percentage of patients with best response of complete response (CR), partial response (PR), and stable disease (SD); and safety profile evaluation. Tumor response and progression were assessed by an investigator using the RECIST version 1.1 criteria. *Post hoc* assessments using RECIST 1.1 were performed by masked independent imaging review. Tumor assessment via contrast-enhanced multiphasic computed tomography or magnetic resonance imaging was performed every 8 weeks after initiating sorafenib. AEs were monitored and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Statistical analysis

Based on the 1-sided test with 0.05 alpha level, 80% power, 10% follow-up loss, and 241 events, 169 patients per treatment group were required to detect a significant difference in the primary endpoint OS (assuming a median OS of 9.5 and 13.0 months for Arms S and C, respectively). All efficacy evaluations were performed for both the intention-to-treat and full analysis sets. Safety analysis was performed for all randomized patients who received at least 1 sorafenib dose (the safety analysis set).

For OS, TTP, and PFS analyses, treatment groups were compared using 1-sided stratified log-rank test with a 5% significance level. Median durations and associated 90% CIs were estimated using the Kaplan-Meier method. The hazard ratio (HR) with 90% CI was calculated using Cox proportional hazards model with randomization stratification factors. Between-group TRRs were compared using the Cochran-Mantel-Haenszel method.

All subgroup analyses of OS, pre-specified by stratification factors and frequency of TACE session number, were performed using stratified log-rank test, whereas HR with 90% CI was estimated using a stratified Cox proportional hazards model.

All statistical analyses, except the log-rank test, were 2-sided, and p values <0.05 were considered significant. SAS (version 9.4; SAS Institute, Cary, North Carolina, USA) was used for all statistical analyses.

Results

Patient characteristics

Between January 2013 and December 2015, 373 patients were screened from 13 hospitals in South Korea, of whom 339 were enrolled and randomly assigned to receive sorafenib with or without concurrent cTACE (170 and 169 to Arms C and S, respectively; Fig. 1). The last patient completed the trial on June 2017. The median follow-up duration was 14 months (90% CI 9.4–20.2) (interquartile range [IQR] 4.0–27.1) for Arm C and 18.7 months (90% CI 11.1–23.3) (IQR 2.3–27.1) for Arm S. A total of 17 patients from Arm C and 2 from Arm S who did not receive cTACE or sorafenib were excluded from the full analysis set (Fig. 1). The mean age was 60.7 years and most patients were males (83.5%). Hepatitis B virus was the predominant etiology (74.9%). Overall, most patients had ECOG performance 0 (81.4%), cirrhosis (68.4%), Child-Pugh score 5 (61.1%), mUICC stage IV (65.5%), or Barcelona Clinic Liver Cancer (BCLC) C stage (74.6%). All 131 (38.6%) and 121 (35.7%) patients had vascular invasion and extrahepatic spread, respectively. Between both arms, baseline characteristics were well balanced (Table 1).

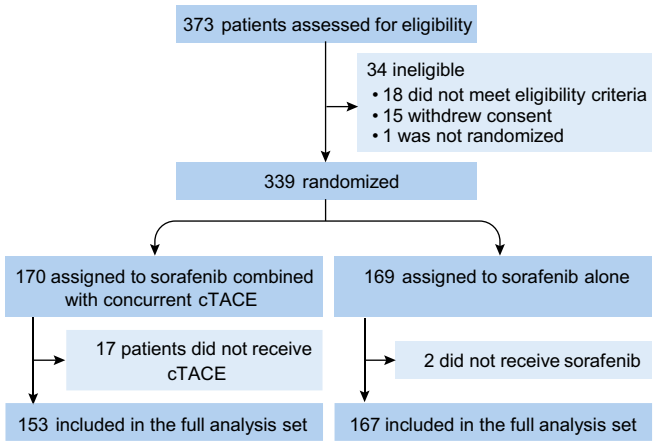

Fig. 1. Consort flow diagram. cTACE, conventional transarterial chemoembolization.

Sixty-one (18%), 74 (21.8%), and 245 (72.3%) patients received resection, radiofrequency ablation/percutaneous ethanol injection therapy, and TACE, respectively, before enrollment, and previous antitumor treatments were also well balanced between the 2 arms.

Efficacy

The median OS was 12.8 months (90% CI 11.5–15.0) for Arm C and 10.8 months (90% CI 8.7–12.7) for Arm S (Fig. 2A). Compared with Arm S, the HR was 0.91 (90% CI 0.687–1.205; $p = 0.2898$) for Arm C, meaning SOR+T did not lead to a statistically significant improvement in OS. Median TTP was 5.3 months (90% CI 3.7–5.7) for Arm C and 3.5 months (90% CI 2.1–3.7) for Arm S (HR 0.674; 90% CI 0.533–0.852; $p = 0.0028$) (Fig. 2B). Median PFS was 5.2 months (90% CI 3.7–5.6) for Arm C and 3.6 months (90% CI 2.6–3.7) for Arm S (HR 0.733; 90% CI 0.589–0.912; $p = 0.0097$) (Fig. 2C). Arm C showed a statistically significant improvement in median TTP and PFS. Arm C TRR was also significantly higher than Arm S TRR (60.6% *vs.* 47.3%; $p = 0.0053$; Table 2). These outcomes were analyzed by the intention-to-treat principle. Further analysis based on the full analysis set principle is presented in Figs. S4–6 and Table S4.

The mean sorafenib administration time was 166 (range 3–1,247) days for Arm C and 128 (range 7–1,453) days for Arm S ($p = 0.0678$). The mean daily dose of sorafenib was 557.9 ± 123.1 mg for Arm C and 584.7 ± 118.1 mg for Arm S ($p = 0.3088$).

Predefined subgroup analysis for OS failed to show a benefit for SOR+T with any stratification factors (Fig. 3). ECOG status also did not affect OS. However, for patients with Vp3-4 or any other vascular invasion, SOR+T tended to confer a survival benefit, although not statistically significant (HR 0.52; 95% CI 0.27–1.02).

A *post hoc* subgroup analysis for OS comparing patients according to the number of cTACE sessions in Arm C revealed a survival benefit in 71 Arm C patients (46.4%) who received ≥2 cTACE sessions compared with Arm S patients: 18.6 (90% CI 13.2–23.5) *vs.* 10.8 (90% CI 8.7–12.7) months (HR 0.575; 95% CI 0.402–0.823; $p = 0.0055$) (Fig. S7, Table S1). Median TTP and PFS were also significantly longer in Arm C patients who received ≥2 cTACE sessions than in Arm S patients (Figs. S2 and S3). The median OS of 82 Arm C patients (53.6%) who received only 1 cTACE session was 8.8 (90% CI 7.1–12.0) months (compared to Arm S patients: HR 1.559; 90% CI 1.077–2.257; $p = 0.0242$) (Fig. S7). The mean tumor diameter of Arm C patients who received ≥2 cTACE sessions was smaller than those who received cTACE once (71.2 mm *vs.* 62.8 mm; $p = 0.0418$). Additionally, patients who received ≥2 cTACE sessions had several different baseline characteristics compared to patients who received cTACE once (Table S2).

Compared with prior non-TACE treatment patients, prior TACE treatment patients showed better OS, with no statistical difference in Arm S: median 11.8 months (95% CI 8.7–14.1) *vs.* 8.6 months (95% CI 4.5–13.5) ($p = 0.3856$).

Sixty-eight (61.8%) Arm C and 84 (69.4%) Arm S patients received post-study anticancer treatment (Table S5). Of these

Table 1. Baseline characteristics of the study population.

Characteristics	Arm C n = 170	Arm S n = 169	Total n = 339
Age, mean (SD), years	60.2 (9.6)	61.3 (9.6)	60.7 (9.6)
Male sex, n (%)	136 (80.0)	147 (87.0)	283 (83.5)
ECOG performance status, n (%)			
0	136 (80.0)	140 (82.8)	276 (81.4)
1	33 (19.4)	28 (16.6)	61 (18.0)
2	1 (0.6)	1 (0.6)	2 (0.6)
Risk factors, n (%)			
HBV positive*	134 (78.8)	120 (71.0)	254 (74.9)
HCV positive	8 (4.7)	16 (9.5)	24 (7.1)
Others**	28 (16.5)	33 (19.5)	61 (18.0)
Cirrhosis*	116 (68.2)	116 (68.6)	232 (68.4)
Child-Pugh score, n (%)			
5	103 (60.6)	104 (61.5)	207 (61.1)
6	45 (26.5)	43 (25.4)	88 (26.0)
7	22 (12.9)	22 (13.0)	44 (13.0)
Modified UICC stage, n (%)			
III	56 (32.9)	61 (36.1)	117 (34.5)
IVa	51 (30.0)	46 (27.2)	97 (28.6)
IVb	63 (37.1)	62 (36.7)	125 (36.9)
BCLC stage, n (%)			
A	3 (1.8)	0 (0.0)	3 (0.9)
B	39 (22.9)	44 (26.0)	83 (24.5)
C	128 (75.3)	125 (74.0)	253 (74.6)
Vascular invasion status, n (%)†			
None	102 (60)	106 (62.7)	208 (61.4)
None or Vp1-2	122 (71.8)	121 (71.6)	243 (71.7)
Vp3-4 and any other presence	48 (28.2)	48 (28.4)	96 (28.3)
Extrahepatic spread, n (%)	62 (36.5)	59 (34.9)	121 (35.7)
Alpha fetoprotein			
Mean (SD), ng/ml	7,557.1 (22,642.52)	24,113.9 (168,194.81)	15,811.1 (119,942.18)
<200 ng/ml, n (%)	79 (46.5)	76 (45)	155 (45.7)
≥200 ng/ml, n (%)	91 (53.5)	93 (55)	184 (54.3)
Previous therapy, n (%)			
Surgery	30 (17.7)	31 (18.3)	61 (18.0)
RFA/PEIT	34 (20)	40 (23.7)	74 (21.8)
TACE	118 (69.4)	127 (75.2)	245 (72.3)
Radiotherapy	25 (14.7)	33 (19.5)	58 (17.1)

BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; RFA/PEIT, radiofrequency ablation/percutaneous ethanol injection therapy; SD, standard deviation; TACE, transarterial chemoembolization; UICC, Union for International Cancer Control; Vp3-4, severe vascular invasion.
*Missing values (1.5%) were included in the percentage calculation.
**Others included alcoholic chronic liver disease, non-alcoholic fatty liver disease, and cryptogenic liver disease.
†Vp1, portal vein invasion in portal branches distal to the second branches; Vp2, portal vein invasion in the second portal branches; Vp3, portal vein invasion in the first portal branches; Vp4, main portal vein invasion; any other presence, hepatic vein or vena cava or atrium invasion.

patients, 26 (23.6%), 16 (14.6%), and 10 (9.1%) in Arm C and 53 (43.8%), 8 (6.6%), and 10 (8.3%) in Arm S received cytotoxic chemotherapy, radiotherapy, and sorafenib, respectively, during survival follow-up, and 14 (6.1%) patients continued to receive sorafenib after progression.

Safety

Of patients in Arms C and S, 96.7% and 90.4%, respectively, experienced any AEs ($p = 0.0227$). AEs occurring in >15% of patients in either arms are listed (Table 3). Comparing AEs in Arms C and S, the most common grade ≥3 AEs in Arm C patients included increased AST (27.5% *vs.* 4.8%; $p < 0.0001$), increased ALT (20.3% *vs.* 3.6%; $p < 0.0001$), ascites (11.8% *vs.* 4.2%; $p = 0.0117$), hyperbilirubinemia (11.8% *vs.* 3.0%; $p = 0.0024$), and hand-foot skin reaction (10.5% *vs.* 11.4%; $p = 0.7923$). Hyponatremia (5.2% *vs.* 0%; $p < 0.05$), encephalopathy (5.2% *vs.* 1.2%), and diarrhea (5.2% *vs.* 4.2%) were other grade ≥3 AEs that occurred more frequently in Arm C patients. In Arms C and S, 33.3% and 19.8%, respectively, had serious AEs ($p = 0.0058$). Fatal AEs (including hypovolemic shock and esophageal variceal bleeding) occurred in 2 Arm S patients, whereas only 1 Arm C patient had a fatal AE (infectious pneumonia) following cTACE.

Discussion

Unlike previous studies comparing TACE alone and TACE plus sorafenib in patients with unresectable HCC,[22–24] this study comparing SOR+T *vs.* sorafenib alone demonstrated that SOR +T did not meet the expected primary endpoint of an improved OS in patients with advanced HCC. However, SOR+T led to a statistically significant improvement in all secondary outcomes (TTP, PFS, and TRR). Unfortunately, tumor response or suppression with combined cTACE did not prolong OS. Since the tumor response was measured using RECIST 1.1 rather than modified RECIST, the lipiodol staining would not interfere with the evaluation of radiological progression. Compared with other studies, the low response rate (CR+PR, 11.8%) with cTACE in Arm C may be related to the evaluation period (8 weeks), RECIST criteria,

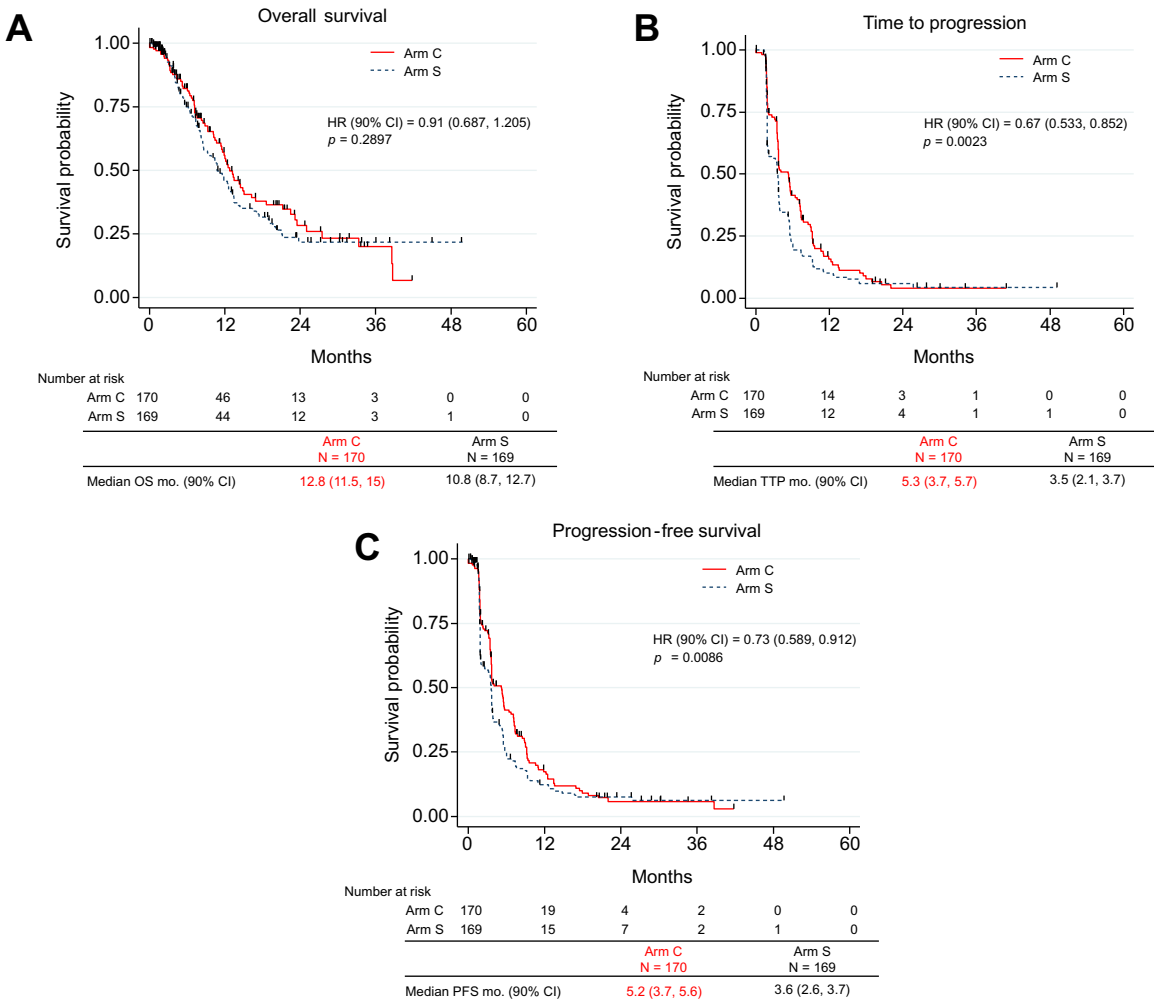

Fig. 2. Kaplan-Meier curves of overall survival, time to progression, and progression-free survival for the intention-to-treat population. HR, hazard ratio; OS, overall survival.

Table 2. Tumor response rate.

Best Response (%)	Arm C (n = 170)	Arm S (n = 169)	Total (n = 339)	*p* value
CR	3 (1.8)	0 (0.0)	3 (0.9)	–
PR	17 (10.0)	10 (5.9)	27 (8.0)	–
SD	83 (48.8)	70 (41.4)	153 (45.1)	–
PD	34 (20)	61 (36.1)	95 (28)	–
CR, PR, or SD	103 (60.6)	80 (47.3)	183 (54.0)	0.0053*
NA, NE	26 (15.3)	26 (15.4)	52 (15.3)	–
Missing value	7 (4.1)	2 (1.2)	9 (2.7)	–

CR, complete response; NA, not applicable; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.
*Cochran-Mantel-Haenszel test.

and tumor size (Tables 2, S2, S4). The main reason for the failure of all phase III drug development trials over the past 10 years after sorafenib was that "all-comers" were enrolled in the clinical trials.[25,26] This study also seems to have made a similar error.

A *post-hoc* subgroup analysis showed that SOR+T may have a worse prognosis than sorafenib alone in about half of patients in Arm C. The median OS of 82 (53.6%) Arm C patients who were unable to receive cTACE more than once was significantly shorter than that of Arm S patients (Fig. 3). This study clearly showed that the AE risk of concurrent combination TACE treatment is high. The overall incidence of AEs and serious AEs (especially grade 3–4 AEs associated with decreased liver function) were significantly more frequent and higher in the SOR+T group. In patients who received only 1 TACE session, disease progression (70.7%) was the most common reason for discontinuing the trial, but treatment associated AEs or not-satisfying the criteria for sorafenib re-administration after cTACE (14.6%) and patient refusal of combination sorafenib treatment (8.5%) were the other main reasons for discontinuing treatment (Table S3). Compared to other combination studies,[11,22,27] the incidence of grade 3–4 AEs was similar in this study, although a higher incidence in AST/ALT increase, possibly related to combined cTACE, occurred in this study. However, the mean total dose and duration of sorafenib administration were not significantly different between the 2 arms. In this study, we initiated 600 mg sorafenib (to enhance the compliance of patients to sorafenib) and adjusted the dose by 200 mg at 2–4-week intervals. The initiation of sorafenib therapy at reduced dosages was associated with better tolerance but not inferior OS.[28]

This study failed to achieve a survival gain; however, it showed that some patients could benefit from SOR+T (Fig. 3). In the subgroup analysis, SOR+T increased survival in patients with severe vascular invasion (Vp3-4 and any other vessel

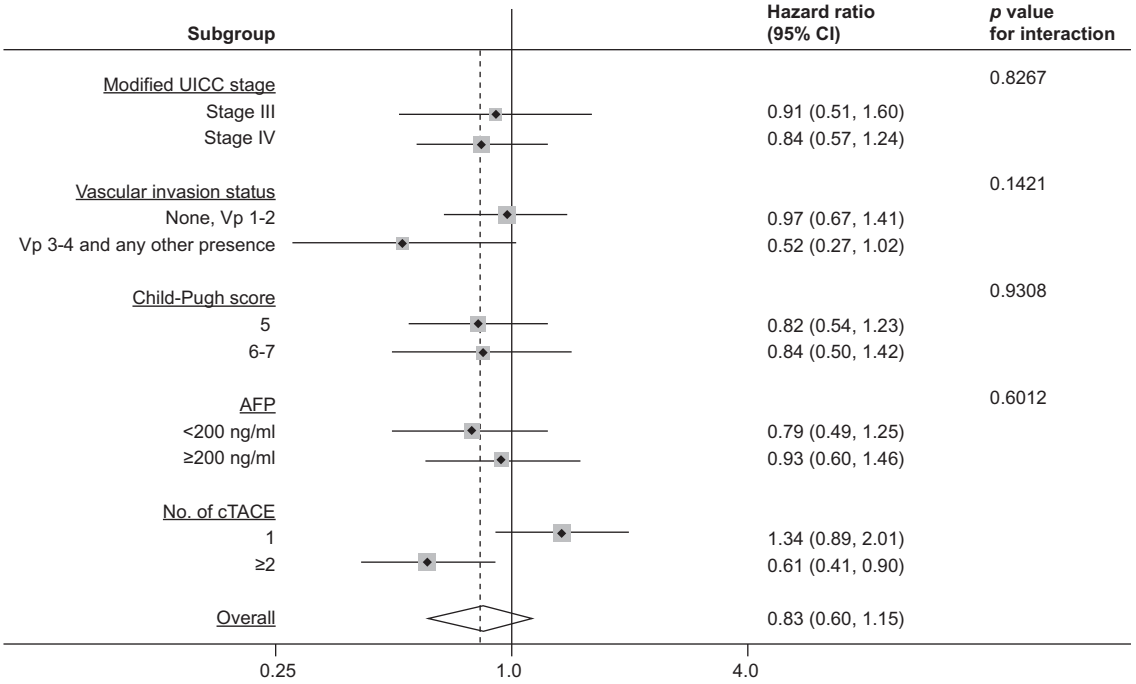

Fig. 3. Forest plots showing subgroup analyses of overall survival. AFP, alpha-fetoprotein; cTACE, conventional transarterial chemoembolization; UICC, Union for International Cancer Control.

Table 3. Adverse events.[*]

	All grades		Grade ≥3	
	Arm C (n = 153)	Arm S (n = 167)	Arm C (n = 153)	Arm S (n = 167)
Abdominal pain	82 (53.6%)	29 (17.4%)	5 (3.3%)	1 (0.6%)
Hand-foot skin reaction	74 (48.4%)	88 (52.7%)	16 (10.5%)	19 (11.4%)
Diarrhea	60 (39.2%)	54 (32.3%)	8 (5.2%)	7 (4.2%)
Nausea	58 (37.9%)	15 (9.0%)	0	2 (1.2%)
Fever	57 (37.3%)	8 (4.8%)	0	0
Anorexia	47 (30.7%)	37 (22.2%)	11 (7.2%)	2 (1.2%)
AST elevation	46 (30.1%)	12 (7.2%)	42 (27.5%)	8 (4.8%)
Pain - others	37 (24.2%)	17 (10.2%)	1 (0.7%)	1 (0.6%)
ALT elevation	36 (23.5%)	7 (4.2%)	31 (20.3%)	6 (3.6%)
Constipation	33 (21.6%)	20 (12.0%)	0	1 (0.6%)
Ascites	31 (20.3%)	18 (10.8%)	18 (11.8%)	7 (4.2%)
Vomiting	31 (20.3%)	11 (6.6%)	0	4 (2.4%)
Hyperbilirubinemia	29 (19.0%)	15 (9.0%)	18 (11.8%)	5 (3.0%)
Heartburn	28 (18.3%)	15 (9%)	0	0
Hypertension	27 (17.6%)	23 (13.8%)	1 (0.7%)	1 (0.6%)
Fatigue	24 (15.7%)	24 (14.4%)	9 (5.9%)	8 (4.8%)
Alopecia	23 (15.0%)	25 (15.0%)	0	0
Hypoalbuminemia	23 (15.0%)	7 (4.2%)	0	1 (0.6%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NCI-CTCAE; National Cancer Institute Common Terminology Criteria for Adverse Events.
[*]Data are n (%). Adverse events were graded using NCI-CTCAE version 3.0 and were listed if occurred in ≥15% patients in each arm.

invasion), although the upper HR margin was not statistically significant at 1.02. With more patients, there could have been positive results. For the first time, *post hoc* analysis suggested that fewer patients (46.4%) who could receive ≥2 cTACE sessions achieved a significantly prolonged survival compared to those who received sorafenib alone (Fig. S7, Table S2). However, *post hoc* analysis is not sufficient to conclude that combination therapy may be beneficial in specific subgroups of patients, because selection bias may be inherent. Further studies are needed in the future.

Our study had several limitations. First, at protocol development, survival time of sorafenib alone was assumed to be 9.5 months according to other studies reported at that time,[5,6,29,30] and concurrent combination treatment was assumed to extend survival by 3.5 months. However, patients on sorafenib alone survived longer than expected, and concurrent TACE combination extended survival for only 2 months. Second, despite the promising results of phase II trial of SOR +TACE,[15] the trial did not assess the efficacy of SOR+TACE in patients with far-advanced HCC, which was the main target in this trial. Third, this study protocol included patients with rather large tumors (size, ≤15 cm) considering the actual clinical situation in South Korea. Fourth, the proportion of patients with extrahepatic spread was 35.7%, which is lower than that noted

in other systemic therapy trials. This may be because the patients in our study may not have been a typical advanced population.

In conclusion, in patients with advanced HCC, compared to sorafenib alone, SOR+T therapy did not improve OS. However, SOR+T therapy significantly improved TTP, PFS, and TRR. Treatment with sorafenib alone remains the first-line standard of care for patients with advanced HCC.

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Conflict of interest

Employment or leadership position: none. Consultant or advisory role: **Joong-Won Park**, BMS, Ono, Bayer, Eisai, Midatech, Roche, Cue; **Yoon Jun Kim**, Gilead, Bayer, Ono, AbbVie; Seung Woon Paik, BMS, Ono, Bayer, Eisai; Han Chu Lee, BMS, Ono, Bayer, Sillajen; Jaeyoun Cheong, Bukwang. Stock Ownership: none. Honoraria: Joong-Won Park, Eisai, Bayer, Ono; Yoon Jun Kim, Bayer, Gilead. Research Funding: Yoon Jun Kim, BTG, Bayer, Ono, AstraZeneca, Roche, LG, BMS. Expert Testimony: None. Patents, Royalties, and Licenses: none. Other Remunerations: none.

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Authors' contributions

Conception and design: **Joong-Won Park**, Bo Hyun Kim. Administration support: **Joong-Won Park**. Provision of study materials or patients: All authors. Collection and assembly of data: All authors. Data analysis and interpretation: **Joong-Won Park, Yoon Jun Kim**, Do Young Kim, Si-Hyun Bae, Bo Hyun Kim, Jaeseok Hwang. Manuscript writing: **Joong-Won Park, Yoon Jun Kim**, Bo Hyun Kim. Final approval of manuscript: All authors.

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Supplementary data

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