TITLE:

# Phase III trial comparing sorafenib plus low-dose cisplatin/fluorouracil hepatic arterial infusion chemotherapy with sorafenib alone in patients with advanced hepatocellular carcinoma: SILIUS Trial

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Running head: Sorafenib plus low-dose HAIC versus sorafenib for advanced HCC

ABSTRACT

**Purpose**: To compare overall survival (OS) of patients with unresectable advanced hepatocellular carcinoma (HCC) treated with hepatic arterial infusion chemotherapy (HAIC) plus sorafenib or sorafenib alone.

**Patients and Methods**: In this multicenter, open-label, randomized, phase 3 trial, patients with advanced HCC were randomized (1:1) to sorafenib 400 mg BID orally or sorafenib plus HAIC (cisplatin 20 mg/m$^2$ on days 1 and 8 and 5-fluorouracil 330 mg/m$^2$ continuously on days 1–5 and 8–12 of every 28-day cycle via an implanted catheter system). The primary endpoint was OS. Key secondary endpoints were time to progression (TTP), progression-free survival (PFS), objective response rate (ORR), disease control rate, and safety.

**Results**: Of the 205 patients in the intent-to-treat population, 86.3% were male, 87.4% had ECOG-PS of 0, 72.2% had macrovascular invasion or extrahepatic spread, and 88.8% had Child-Pugh A liver function. Median OS was similar in the sorafenib plus HAIC and sorafenib groups (11.8 vs. 11.5 months; P=.955), whereas TTP (5.3 vs. 3.5 months; P=.004), PFS (4.8 vs. 3.5 months; P=.051), and ORR (36.3% vs 17.5%, P=.003) were significantly greater in the combined than in the monotherapy group. OS was tended to be longer in patients with main portal vein invasion (MPVI) treated with sorafenib plus HAIC than with sorafenib alone (11.4 vs. 6.5 months; P=.050). Grade 3–4 adverse events more frequent in the sorafenib plus HAIC group included anemia (15.9% vs. 5.9%), neutropenia (17.0% vs. 1.0%), and thrombocytopenia (33.0% vs. 11.8%).

**Conclusion**: The addition of HAIC to sorafenib did not significantly improve OS in patients with advanced HCC, but did significantly improve TTP,  and ORR. Combination therapy tended to improve OS in HCC patients with MPVI.

ClinicalTrials.gov Identifier NCT01214343.

## Introduction

Although surgical resection and local ablation therapy such as percutaneous ethanol injection and percutaneous radiofrequency ablation are considered curative in patients with hepatocellular carcinoma (HCC) (1-3), most patients with HCC are not diagnosed until the disease is unresectable (4-6). Locoregional treatments for unresectable HCC include transarterial chemoembolization (TACE), systemic chemotherapy, and hepatic arterial infusion chemotherapy (HAIC) (7-11). In HAIC, anticancer drugs are infused directly into the hepatic artery, increasing local intratumoral drug concentrations (12). Drugs infused as monotherapy during HAIC include cisplatin, with a response rate of 30-40% (13-17). Combination regimens infused during HAIC include cisplatin plus 5-fluorouracil (low-dose FP), with response rates ranging from 7-71% (18-36).

HAIC with either low-dose FP or another regimen is widely utilized in Japan, Korea, and Taiwan. In retrospective comparative cohort studies, HAIC has shown survival benefits when compared with historical controls (37). Moreover, HAIC showed better survival than best supportive care in the large cohort of Liver Cancer Study Group of Japan after propensity score matching (38). Nevertheless, HAIC is not regarded as standard of care, as no prospective randomized phase III trials to date have shown survival benefits in patients with advanced HCC.

A phase II trial in patients with advanced HCC showed better outcomes with single-dose cisplatin arterial infusion chemotherapy plus sorafenib than with sorafenib monotherapy (39). The arterial infusion technique in that study however, differed completely from continuous HAIC with an implanted catheter port system. Thus, prospective trials are needed to assess the safety and efficacy of continuous infusion of low-dose FP in patients with advanced HCC.

Sorafenib is an oral inhibitor of serine/threonine kinases, including those of vascular endothelial growth factor receptors (VEGFR)-2 and -3, platelet-derived growth factor receptor (PDGFR)-β, and the Flt-3, kit, and Ret gene products (40). Two randomized, placebo-controlled, phase III clinical trials showed that sorafenib improved overall survival in patients with unresectable advanced HCC (41, 42). Sorafenib has been approved worldwide and has become the standard treatment for patients with advanced unresectable HCC. Two retrospective analyses of propensity score-matched patients showed that HAIC did not have survival benefits compared with sorafenib monotherapy in patients with advanced HCC (43, 44). However, the combination of sorafenib and HAIC may have complementary effects in advanced HCC, with sorafenib

prolonging survival through disease stabilization and HAIC shrinking tumors through high response rate (45). A phase I/II study showed that sorafenib plus low-dose FP resulted in favorable tumor control and a generally manageable safety profile in patients with advanced HCC (45). Combination treatment with sorafenib and HAIC may, therefore, benefit patients with advanced HCC more than either treatment alone.

The SILIUS trial was a multicenter, phase 3 study comparing sorafenib plus low-dose FP with sorafenib monotherapy in patients with advanced, unresectable HCC who had progressed to TACE failure, portal vein invasion, or extrahepatic spread.

## Methods

### Description of patients

This prospective, randomized, open-label, active-controlled, parallel-group study enrolled patients with advanced HCC not suitable for resection, local ablation, or TACE. Advanced HCC was defined as ≥4 tumors refractory to TACE or tumors with vascular invasion or extrahepatic spread (EHS) based on histologic examination of biopsy samples or findings by dynamic CT, dynamic MRI, or CT during hepatic arteriography or arterioportography (CTHA/CTAP), according to AASLD criteria.

### Inclusion criteria

Patients with advanced HCC were eligible if they were aged ≥20 years, had a life expectancy ≥12 weeks, and were not candidates for hepatectomy, local ablation therapy, or TACE. All patients had an ECOG PS of 0–1, a Child-Pugh score ≤7, and adequate bone marrow, liver, and renal function.

### Exclusion criteria

Patients were excluded if they had another previous or current malignancy except for curatively treated intraepithelial cervical cancer, basal cell carcinoma, superficial bladder cancer, early gastric cancer, or other early cancers with a low risk of recurrence. Also excluded were patients with renal failure requiring hemodialysis or peritoneal dialysis; those with congestive heart failure, active coronary artery disease, ischemic heart disease, or serious cardiac arrhythmia; patients with poorly controlled hypertension, active clinically serious infection (grade ≥3), hearing impairment, history of HIV infection, or significant gastrointestinal bleeding within 4 weeks of study entry; and patients currently taking a CYP3A4 inhibitor.

All study subjects provided written informed consent. The study protocol was approved by the ethics committees of all participating institutions. The trial was registered at Clinical Trials.gov under Identifier NCT01214343.

**Treatment protocol**

Subjects were randomized 1:1 to receive either sorafenib 400 mg bid or sorafenib 400 mg bid plus low-dose FP HAIC. Stratification factors for randomization using the minimization method included institution; the presence or absence of EHS, macroscopic vascular invasion (MVI; Vp0, Vp1-3, or Vp4), where Vp0 through Vp4 indicated no, third branch, second branch (segmental invasion), first branch (branch invasion) and main portal vein invasion, respectively, according to Liver Cancer Study Group of Japan criteria.

Patients in the sorafenib plus HAIC group underwent catheter placement in the hepatic artery for 24-hour continuous delivery of low-dose cisplatin and 5-fluorouracil through a subcutaneously implanted port system. The gastroduodenal artery and/or right gastric vein was embolized using a metallic coil to avoid drug flowing to the stomach, duodenum or pancreas. The arterial catheters were placed in a manner allowing for proper drug distribution throughout the liver, with the flow checked by contrast CT through the port or by DSA before starting treatment.

Treatment was divided into 28-day cycles. All patients in both groups were treated with oral sorafenib 400 mg bid on days 1-28. In the HAIC combination therapy group, cisplatin was administered at a dose of 20 mg/m$^2$/day on days 1 and 8 and fluorouracil was administered at a dose of 330 mg/m$^2$/day on days 1–5 and 8–12 of every 28-day cycle, followed by 2 weeks off. The first treatment cycle was started within 28 days of randomization. Treatment with sorafenib prior to HAIC was allowed, but patients were required to be off sorafenib for 2 days before and 7 days after reservoir port placement. Treatment was continued until patients experienced progressive disease (PD), as defined by modified RECIST criteria and confirmed by imaging, or worsening of general condition. Treatment was also discontinued for adverse events, death, patient request, or if HAIC became technically infeasible. Patients who experienced a complete response (CR) were also discontinued.

Criteria for delaying the start of the next cycle of treatment included neutrophil count ≤1,000/μl, platelet count ≤50,000/μl, total bilirubin ≥2 mg/dl, ALT or AST ≥6 times the institutional upper limit of normal, serum creatinine ≥1.5 times the institutional upper limit of normal, and amylase ≥2 times the institutional upper limit of normal. If these criteria were not met, and the start of the next cycle delayed for >8 weeks, the patient was discontinued. Sorafenib doses were adjusted, by interruption or reduction, in patients who experienced clinically significant hematologic or non-hematologic toxicities attributed to sorafenib. As warranted, sorafenib doses were reduced

stepwise from 400 mg bid to 400 mg once daily to 400 mg every other day to 200 mg every other day. Stepwise increases were allowed after resolution of the adverse event.

HAIC was interrupted in patients who experienced hematologic and non-hematologic toxicities attributed to HAIC. Sorafenib treatment was continued if infusions alone were interrupted. Infusions were resumed at the same or a lower dose. Two dose reduction levels of HAIC were allowed: 20 mg/m$^2$/day cisplatin and 170 mg/m$^2$/day fluoruracil, and 10 mg/m$^2$/day cisplatin and 170 mg/m$^2$/day fluoruracil. Cisplatin alone was discontinued without reducing fluoruracil dose in patients who experienced adverse events caused by renal dysfunction.

**Study endpoints**

The primary study endpoint was overall survival (OS), calculated from the date of randomization until death from any cause or date of last evaluation. Secondary study endpoints included time to progression (TTP), calculated from the date of randomization until diagnosis of progression by modified RECIST criteria; progression-free survival (PFS), calculated from the date of randomization until diagnosis of tumor progression or death from any cause, whichever was sooner; overall response rate (ORR), calculated as the percentage of patients who achieved either a complete response (CR), or partial response (PR) to treatment; disease control rate (DCR), calculated as the percentage of patients who achieved CR, PR, and stable disease (SD); and safety.

**Statistical analysis**

Calculation of sample size

Sample size was based on assumptions that the median OS in patients receiving sorafenib monotherapy would be 10 months and that HAIC would improve median OS by 70% (hazard ratio [HR] 0.59). Thus, 112 events would be necessary to achieve a power of 80% for a one-sided $\alpha$ of 0.05 and 1:1 group assignment. The necessary number of events would be observed if 164 patients were followed for 36 months (enrollment period of 24 months and follow-up period of 12 months). Based on a drop-out rate of 15%, target enrollment was set at 190 patients (95 per group).

**Other statistical methods**

Results were reported as mean ± SD, number (%), or median (95% confidence interval [CI]), as warranted, and compared by Student's t-tests or Chi-squared tests. Survival outcomes were calculated using the Kaplan-Meier method and compared by log-rank tests. Outcomes in the two groups were reported as HR and 95% CI. All statistical analyses were performed using SPSS version 23 statistical software, with a p-value $<0.05$ defined as statistically significant.

## Results

Patient population

A total of 206 patients were randomized, 103 to treatment with sorafenib monotherapy and 103 to sorafenib plus HAIC combination therapy. One patient who was randomized to sorafenib plus HAIC withdrew after randomization, leaving 205 patients in the intent-to-treat (ITT) population. Fifteen patients, one in the sorafenib group and 14 in the sorafenib plus HAIC group, were not treated, leaving 190 patients in the safety population (**Figure 1**).

The two groups were generally well matched (**Table 1**). Mean ages of patients in the ITT population randomized to sorafenib and sorafenib plus HAIC were 68.1 ± 9.1 years and 66.7 ± 10.2 years, respectively, and 85.4% and 87.3%, respectively, were male. There were also no significant differences between the two groups in terms of Child-Pugh grade, disease etiology, BCLC stage, and the presence of EHS and MVI.

Although the mean duration of sorafenib treatment was slightly longer in the sorafenib plus HAIC treatment group, the median duration was slightly longer in the sorafenib monotherapy group (**Supplementary Table 1**). Mean and median relative sorafenib dose intensities were greater in the group treated with sorafenib alone. The mean and median numbers of HAIC cycles in the sorafenib plus HAIC group were 4.0 and 2.0, respectively.

## Efficacy outcomes

Kaplan-Meier analysis showed that OS, the primary endpoint, was similar in the two treatment groups (**Figure 2A**). Median OS was 11.5 months (95% CI, 8.2–14.8 months) in patients treated with sorafenib monotherapy and 11.8 months (95% CI, 9.1–14.5 months) in patients treated with sorafenib plus HAIC (HR 1.009; 95% CI, 0.743–1.371, P=.955).

Differences in OS were observed when patients were stratified by MVI (**Figure 3**). Median OS in patients with Vp1-3 (branch-segmental portal vein invasion) was longer with sorafenib monotherapy (14.4 months; 95% CI, 9.3–19.5 months) than with sorafenib plus HAIC (12.6 months; 95% CI, 4.3–20.9 months), although the difference was not statistically significant (HR 1.367; 95% CI, 0.829–2.255, P=.218). In contrast, median OS in patients with Vp4 (main portal vein invasion: MPVI) tended to be longer in those treated with sorafenib plus HAIC (11.4

months; 95% CI, 7.0–15.9 months) than in those treated with sorafenib alone (6.5 months; 95% CI, 4.5–8.4 months; HR 0.493; 95% CI, 0.240–1.014, P=.050). Forest plot analysis of factors associated with OS also showed that OS was greater in patients with Child-Pugh score 6 treated with sorafenib monotherapy than with sorafenib plus HAIC (**Figure 4**). However, sorafenib plus HAIC resulted in longer OS in patients with MPVI and in those with Child-Pugh score 7 than did sorafenib alone.

Analysis of secondary outcomes showed TTP was significantly longer and PFS tended to be longer in patients treated with sorafenib plus HAIC than in patients treated with sorafenib alone (**Figure 2B, C**). ORR was significantly greater in patients treated with sorafenib plus HAIC than in those treated with sorafenib monotherapy (36.3% vs 17.5%, P=.003). DCR rates were similar (72.8% vs 64.7%, P=.230; **Table 2**). Patients in each arm were stratified by whether they achieved CR/PR or SD/PD. Kaplan-Meier analysis showed that OS was significantly greater in the CR/PR than in the SD/PD subgroups (**Supplementary Figure 1A, B**). Moreover, a comparison of patients who achieved CR/PR showed that OS was longer for those in the sorafenib monotherapy group than in the sorafenib plus HAIC group, although the difference was not statistically significant (**Supplementary Figure 1C**).

**Safety outcomes**

Adverse event rates were generally similar in the two groups (**Table 3**). However, rates of all grade and grades 3/4 reductions in neutrophil and platelet counts were significantly higher in the sorafenib plus HAIC than in the sorafenib monotherapy group. In contrast, rates of all-grade alopecia, hoarseness, diarrhea, and increased ALT were significantly higher in the sorafenib monotherapy than in the sorafenib plus HAIC group, whereas rates of all-grade nausea, vomiting, and decreased white blood cell counts were significantly higher in the sorafenib plus HAIC group. Adverse events associated with the implanted catheter system were observed only in the sorafenib plus HAIC group.

## Discussion

Systemic chemotherapy agents have shown little efficacy in patients with advanced HCC (46, 47). In contrast, the phase III Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) and Asia-Pacific trials showed that sorafenib significantly prolonged OS in patients with advanced HCC, resulting in a significant advance in the treatment of this disease (41, 42). Other new agents tested in a first-line setting, including sunitinib, brivanib, and linifanib, and combinations of sorafenib with other agents, including the anti-angiogenic agent erlotinib and the cytotoxic agent doxorubicin (48-52), failed to show better survival benefit than sorafenib alone.

A phase I/II study in patients with advanced HCC found that sorafenib plus low-dose FP resulted in favorable tumor control and a generally manageable safety profile (45). These findings suggested that the combination of sorafenib and low-dose FP HAIC would improve OS in patients with advanced HCC. However, the current phase III SILIUS trial found that, compared with sorafenib monotherapy, this combination did not improve OS in patients with advanced unresectable HCC.

In SILIUS, combination therapy with sorafenib plus low-dose FP HAIC resulted in significantly higher TTP and ORR than did sorafenib monotherapy, suggesting that HAIC may have an additive anti-cancer effect on sorafenib. This is similar to findings reported previously in retrospective cohort studies of patients with advanced HCC (18-38). In a large, nationwide cohort study of patients with advanced HCC who were treated with low-dose FP HAIC, median OS was significantly longer in responders to low-dose FP HAIC (CR+PR) than in nonresponders (SD+PD) (25.8 months vs. 6.0 months, respectively) (38), with similar findings reported in another study (37). This phase III SILIUS trial also demonstrated survival benefits in responders (CR+PR) to combination therapy, through high response rate and slower TTP, compared with n responders to sorafenib alone. The finding that ORR was significantly higher with the use of combination therapy than with sorafenib monotherapy indicated that a much higher fraction of the enrichable patient population experienced survival benefits from combination therapy than from sorafenib alone.

The present study also found that combination therapy tended to improve OS and 1- and 2-year survival rates in HCC patients with MPVI (Vp4) when compared with sorafenib monotherapy, a finding consistent with previous reports (18-21, 38). An analysis of 57,445 patients with

advanced HCC prospectively registered in the nationwide database of the Liver Cancer Study Group of Japan from 2000 through 2005 compared 476 patients who received low-dose FP HAIC using a subcutaneous infusion port with 1,466 patients who received best supportive care (48). After propensity score matching, median OS was significantly longer in the 189 patients with MPVI who received low-dose FP HAIC than in the 189 who did not (7.9 months vs. 3.1 months). In comparison, the average OS in patients with MPVI was found to be <3 months (53-56). In SILIUS, the median OS in patients treated with low-dose FP HAIC plus sorafenib was 11.4 months compared with 6.5 months in patients treated with sorafenib monotherapy.

Overall, these findings suggest that, compared with sorafenib alone, the combination of low-dose FP HAIC and sorafenib may benefit selected patients with advanced HCC. These include older patients, those with MPVI (Vp4), patients with Child-Pugh scores of 7 and responders to this combination therapy. No unexpected AEs were reported.

The major limitation of this study was the small numbers of patients in the various subgroups, making it difficult to determine the statistical significance of outcomes in these groups. Additional studies with larger numbers of patients are required to determine whether sorafenib plus low-dose FP HAIC has advantages over sorafenib alone in patients with advanced HCC, especially in patients with MPVI.

In conclusion, low-dose FP HAIC plus sorafenib did not improve OS in patients with advanced HCC and MVI and/or EHS compared with sorafenib monotherapy. However, combination treatment did increase ORR and TTP, suggesting that this combination may benefit some selected patients. These results are consistent with those of retrospective cohort studies, which found that response rate was higher in patients treated with low-dose FP HAIC plus sorafenib compared with sorafenib alone, with the higher percentage of responders to combination therapy resulting in longer survival in responder subgroups. Furthermore, patients with MPVI may benefit from low-dose FP HAIC combination therapy. Further large-scale trials are warranted.

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References


1. Donadon M, Solbiati L, Dawson L, Barry A, Sapisochin G, Greig PD, Shiina S, et al. Hepatocellular Carcinoma: The Role of Interventional Oncology. Liver Cancer 2016;6:34-43.
2. Lanza E, Donadon M, Poretti D, Pedicini V, Tramarin M, Roncalli M, Rhee H, et al. Transarterial Therapies for Hepatocellular Carcinoma. Liver Cancer 2017;6:27-33.
3. Kudo M, Izumi N, Sakamoto M, Matsuyama Y, Ichida T, Nakashima O, Matsui O, et al. Survival Analysis over 28 Years of 173,378 Patients with Hepatocellular Carcinoma in Japan. Liver Cancer 2016;5:190-197.
4. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362:1907-1917.
5. Geschwind JF, Gholam PM, Goldenberg A, Mantry P, Martin RC, Piperdi B, Zigmont E, et al. Use of Transarterial Chemoembolization (TACE) and Sorafenib in Patients with Unresectable Hepatocellular Carcinoma: US Regional Analysis of the GIDEON Registry. Liver Cancer 2016;5:37-46.
6. Chow PK, Choo SP, Ng DC, Lo RH, Wang ML, Toh HC, Tai DW, et al. National Cancer Centre Singapore Consensus Guidelines for Hepatocellular Carcinoma. Liver Cancer 2016;5:97-106.
7. Bruix J, Reig M, Sherman M. Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma. Gastroenterology 2016;150:835-853.
8. Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, Tateishi R, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int 2017;11:317-370.
9. Kokudo N, Hasegawa K, Akahane M, Igaki H, Izumi N, Ichida T, Uemoto S, et al. Evidence-based Clinical Practice Guidelines for Hepatocellular Carcinoma: The Japan Society of Hepatology 2013 update (3rd JSH-HCC Guidelines). Hepatol Res 2015;45:123-127.
10. Kudo M, Matsui O, Izumi N, Iijima H, Kadoya M, Imai Y, Okusaka T, et al. JSH Consensus-Based Clinical Practice Guidelines for the Management of Hepatocellular Carcinoma: 2014 Update by the Liver Cancer Study Group of Japan. Liver Cancer 2014;3:458-468.
11. Kudo M, Trevisani F, Abou-Alfa GK, Rimassa L. Hepatocellular Carcinoma: Therapeutic Guidelines and Medical Treatment. Liver Cancer 2017;6:16-26.
12. Moriguchi M, Aramaki T, Nishiofuku H, Sato R, Asakura K, Yamaguchi K, Tanaka T, et al. Sorafenib versus Hepatic Arterial Infusion Chemotherapy as Initial Treatment for Hepatocellular Carcinoma with Advanced Portal Vein Tumor Thrombosis. Liver Cancer 2017;6:275-286.
13. Court WS, Order SE, Siegel JA, Johnson E, DeNittis AS, Principato R, Martz K, et al. Remission and survival following monthly intraarterial cisplatinum in nonresectable hepatoma. Cancer Invest 2002;20:613-625.
14. Tzoracoleftherakis EE, Spiliotis JD, Kyriakopoulou T, Kakkos SK. Intra-arterial versus systemic chemotherapy for non-operable hepatocellular carcinoma. Hepatogastroenterology 1999;46:1122-1125.
15. Yoshikawa M, Ono N, Yodono H, Ichida T, Nakamura H. Phase II study of hepatic arterial infusion of a fine-powder formulation of cisplatin for advanced hepatocellular carcinoma. Hepatol Res 2008;38:474-483.
16. Iwasa S, Ikeda M, Okusaka T, Ueno H, Morizane C, Nakachi K, Mitsunaga S, et al. Transcatheter arterial infusion chemotherapy with a fine-powder formulation of cisplatin for advanced hepatocellular carcinoma refractory to transcatheter arterial chemoembolization. Jpn J Clin Oncol 2011;41:770-775.
17. Intra-arterial administration of epirubicin in the treatment of nonresectable hepatocellular carcinoma. Epirubicin Study Group for Hepatocellular Carcinoma. Cancer Chemother Pharmacol 1987;19:183-189.
18. Ando E, Tanaka M, Yamashita F, Kuromatsu R, Yutani S, Fukumori K, Sumie S, et al. Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis: analysis of 48 cases. Cancer 2002;95:588-595.
19. Ando E, Yamashita F, Tanaka M, Tanikawa K. A novel chemotherapy for advanced hepatocellular carcinoma with tumor thrombosis of the main trunk of the portal vein. Cancer 1997;79:1890-1896.

20. Itamoto T, Nakahara H, Tashiro H, Haruta N, Asahara T, Naito A, Ito K. Hepatic arterial infusion of 5-fluorouracil and cisplatin for unresectable or recurrent hepatocellular carcinoma with tumor thrombus of the portal vein. J Surg Oncol 2002;80:143-148.
21. Lai YC, Shih CY, Jeng CM, Yang SS, Hu JT, Sung YC, Liu HT, et al. Hepatic arterial infusion chemotherapy for hepatocellular carcinoma with portal vein tumor thrombosis. World J Gastroenterol 2003;9:2666-2670.
22. Okuda K, Tanaka M, Shibata J, Ando E, Ogata T, Kinoshita H, Eriguchi N, et al. Hepatic arterial infusion chemotherapy with continuous low dose administration of cisplatin and 5-fluorouracil for multiple recurrence of hepatocellular carcinoma after surgical treatment. Oncol Rep 1999;6:587-591.
23. Tanioka H, Tsuji A, Morita S, Horimi T, Takamatsu M, Shirasaka T, Mizushima T, et al. Combination chemotherapy with continuous 5-fluorouracil and low-dose cisplatin infusion for advanced hepatocellular carcinoma. Anticancer Res 2003;23:1891-1897.
24. Toyoda H, Nakano S, Kumada T, Takeda I, Sugiyama K, Osada T, Kiriyama S, et al. The efficacy of continuous local arterial infusion of 5-fluorouracil and cisplatin through an implanted reservoir for severe advanced hepatocellular carcinoma. Oncology 1995;52:295-299.
25. Ueshima K, Kudo M, Takita M, Nagai T, Tatsumi C, Ueda T, Kitai S, et al. Hepatic arterial infusion chemotherapy using low-dose 5-fluorouracil and cisplatin for advanced hepatocellular carcinoma. Oncology 2010;78 Suppl 1:148-153.
26. Saeki I, Yamasaki T, Tanabe N, Iwamoto T, Matsumoto T, Urata Y, Hidaka I, et al. A new therapeutic assessment score for advanced hepatocellular carcinoma patients receiving hepatic arterial infusion chemotherapy. PLoS One 2015;10:e0126649.
27. Oh MJ, Lee HJ, Lee SH. Efficacy and safety of hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma as first-line therapy. Clin Mol Hepatol 2013;19:288-299.
28. Woo HY, Bae SH, Park JY, Han KH, Chun HJ, Choi BG, Im HU, et al. A randomized comparative study of high-dose and low-dose hepatic arterial infusion chemotherapy for intractable, advanced hepatocellular carcinoma. Cancer Chemother Pharmacol 2010;65:373-382.
29. Tsai WL, Lai KH, Liang HL, Hsu PI, Chan HH, Chen WC, Yu HC, et al. Hepatic arterial infusion chemotherapy for patients with huge unresectable hepatocellular carcinoma. PLoS One 2014;9:e92784.
30. Lin CP, Yu HC, Cheng JS, Lai KH, Lo GH, Hsu PI, Lin CK, et al. Clinical effects of intra-arterial infusion chemotherapy with cisplatin, mitomycin C, leucovorin and 5-flourouracil for unresectable advanced hepatocellular carcinoma. J Chin Med Assoc 2004;67:602-610.
31. Song MJ, Bae SH, Chun HJ, Choi JY, Yoon SK, Park JY, Han KH, et al. A randomized study of cisplatin and 5-FU hepatic arterial infusion chemotherapy with or without adriamycin for advanced hepatocellular carcinoma. Cancer Chemother Pharmacol 2015;75:739-746.
32. Ma MC, Chen YY, Li SH, Cheng YF, Wang CC, Chiu TJ, Pei SN, et al. Intra-arterial chemotherapy with doxorubicin and cisplatin is effective for advanced hepatocellular cell carcinoma. ScientificWorldJournal 2014;2014:160138.
33. Chung YH, Song IH, Song BC, Lee GC, Koh MS, Yoon HK, Lee YS, et al. Combined therapy consisting of intraarterial cisplatin infusion and systemic interferon-alpha for hepatocellular carcinoma patients with major portal vein thrombosis or distant metastasis. Cancer 2000;88:1986-1991.
34. Uka K, Aikata H, Takaki S, Miki D, Kawaoka T, Jeong SC, Takahashi S, et al. Pretreatment predictor of response, time to progression, and survival to intraarterial 5-fluorouracil/interferon combination therapy in patients with advanced hepatocellular carcinoma. J Gastroenterol 2007;42:845-853.
35. Nagano H, Wada H, Kobayashi S, Marubashi S, Eguchi H, Tanemura M, Tomimaru Y, et al. Long-term outcome of combined interferon-alpha and 5-fluorouracil treatment for advanced hepatocellular carcinoma with major portal vein thrombosis. Oncology 2011;80:63-69.
36. Yamashita T, Arai K, Sunagozaka H, Ueda T, Terashima T, Yamashita T, Mizukoshi E, et al. Randomized, phase II study comparing interferon combined with hepatic arterial infusion of fluorouracil plus cisplatin and fluorouracil alone in patients with advanced hepatocellular carcinoma. Oncology 2011;81:281-290.

37. Obi S, Yoshida H, Toune R, Unuma T, Kanda M, Sato S, Tateishi R, et al. Combination therapy of intraarterial 5-fluorouracil and systemic interferon-alpha for advanced hepatocellular carcinoma with portal venous invasion. Cancer 2006;106:1990-1997.
38. Nouso K, Miyahara K, Uchida D, Kuwaki K, Izumi N, Omata M, Ichida T, et al. Effect of hepatic arterial infusion chemotherapy of 5-fluorouracil and cisplatin for advanced hepatocellular carcinoma in the Nationwide Survey of Primary Liver Cancer in Japan. Br J Cancer 2013;109:1904-1907.
39. Ikeda M, Shimizu S, Sato T, Morimoto M, Kojima Y, Inaba Y, Hagihara A, et al. Sorafenib plus hepatic arterial infusion chemotherapy with cisplatin versus sorafenib for advanced hepatocellular carcinoma: randomized phase II trial. Ann Oncol 2016;27:2090-2096.
40. Wilhelm SM, Carter C, Tang L, Wilkie D, McNabola A, Rong H, Chen C, 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;64:7099-7109.
41. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-390.
42. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34.
43. Fukubayashi K, Tanaka M, Izumi K, Watanabe T, Fujie S, Kawasaki T, Yoshimaru Y, et al. Evaluation of sorafenib treatment and hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma: a comparative study using the propensity score matching method. Cancer Med 2015;4:1214-1223.
44. Shiozawa K, Watanabe M, Ikehara T, Kogame M, Matsui T, Okano N, Kikuchi Y, et al. Comparison of Sorafenib and Hepatic Arterial Infusion Chemotherapy for Advanced Hepatocellular Carcinoma: A Propensity Score Matching Study. Hepatogastroenterology 2014;61:885-891.
45. Ueshima K, Kudo M, Tanaka M, Kumada T, Chung H, Hagiwara S, Inoue T, et al. Phase I/II Study of Sorafenib in Combination with Hepatic Arterial Infusion Chemotherapy Using Low-Dose Cisplatin and 5-Fluorouracil. Liver Cancer 2015;4:263-273.
46. Yeo W, Mok TS, Zee B, Leung TW, Lai PB, Lau WY, Koh J, 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;97:1532-1538.
47. Thomas MB, O'Beirne JP, Furuse J, Chan AT, Abou-Alfa G, Johnson P. Systemic therapy for hepatocellular carcinoma: cytotoxic chemotherapy, targeted therapy and immunotherapy. Ann Surg Oncol 2008;15:1008-1014.
48. Cainap C, Qin S, Huang WT, Chung IJ, Pan H, Cheng Y, Kudo M, et al. Linifanib versus Sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. J Clin Oncol 2015;33:172-179.
49. Cheng AL, Kang YK, Lin DY, Park JW, Kudo M, Qin S, Chung HC, et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. J Clin Oncol 2013;31:4067-4075.
50. Johnson PJ, Qin S, Park JW, Poon RT, Raoul JL, Philip PA, Hsu CH, et al. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. J Clin Oncol 2013;31:3517-3524.
51. Zhu AX, Rosmorduc O, Evans TR, Ross PJ, Santoro A, Carrilho FJ, Bruix J, et al. SEARCH: a phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. J Clin Oncol 2015;33:559-566.
52. Abou-Alfa GK, Johnson P, Knox JJ, Capanu M, Davidenko I, Lacava J, Leung T, et al. Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma: a randomized trial. Jama 2010;304:2154-2160.
53. Chung GE, Lee JH, Kim HY, Hwang SY, Kim JS, Chung JW, Yoon JH, et al. Transarterial chemoembolization can be safely performed in patients with hepatocellular carcinoma invading the main portal vein and may improve the overall survival. Radiology 2011;258:627-634.

54. Lee HS, Kim JS, Choi IJ, Chung JW, Park JH, Kim CY. The safety and efficacy of transcatheter arterial chemoembolization in the treatment of patients with hepatocellular carcinoma and main portal vein obstruction. A prospective controlled study. Cancer 1997;79:2087-2094.
55. Yoon JH, Kim HC, Chung JW, Yoon JH, Jae HJ, Park JH. CT findings of completely regressed hepatocellular carcinoma with main portal vein tumor thrombosis after transcatheter arterial chemoembolization. Korean J Radiol 2010;11:69-74.
56. Woo HY, Heo J. New perspectives on the management of hepatocellular carcinoma with portal vein thrombosis. Clin Mol Hepatol 2015;21:115-121.

Table 1. Baseline demographic and clinical characteristics of the intent-to-treat (efficacy) population

| | **Sorafenib (n=103)** | **Sorafenib + HAIC (n=102)** |
|---|---|---|
| Age, yrs, mean ± SD | 68.1 ± 9.1 | 66.7 ± 10.2 |
| Sex, n (%) | | |
| Male | 88 (85.4) | 89 (87.3) |
| Female | 15 (14.6) | 13 (12.7) |
| Child-Pugh grade, n (%) | | |
| A | 92 (89.3) | 90 (88.2) |
| B | 11 (10.7) | 12 (11.8) |
| Etiology, n (%) | | |
| Hepatitis B | 22 (21.4) | 26 (25.5) |
| Hepatitis C | 46 (44.7) | 47 (46.1) |
| BCLC Stage, n (%) | | |
| B | 27 (26.2) | 32 (31.4) |
| C | 76 (73.8) | 70 (68.6) |
| MVI present, n (%) | 64 (62.1) | 58 (56.9) |
| EHS present, n (%) | 26 (25.2) | 27 (26.5) |
| MVI/EHS present, n (%) | 75 (72.8) | 73 (71.6) |
| AFP (ng/dl) | 195.0 | 440.5 |
| DCP (mAU/ml) | 1487.0 | 2780.5 |
| AFP-L3 (ng/dl) | 24.6 | 21.6 |

Abbreviations: AFP, alfa-fetoprotein; AFP-L3, L3 fraction of AFP; BCLC, Barcelona clinic liver cancer; DCP, des-γ–carboxyprotein; EHS; extra hepatic spread; MVI, macrovascular invasion.

Table 2. Summary of best response by mRECIST criteria in the randomized population.

| | **Sorafenib (n=103)** | **Sorafenib + HAIC (n=102)** | **P-value** |
|---|---|---|---|
| Best response, n (%) | | | <0.001 |
| Complete response (CR) | 2 (1.9) | 8 (7.8) | |
| Partial response (PR) | 16 (15.5) | 29 (28.4) | |
| Stable disease (SD) | 57 (55.3) | 29 (28.4) | |
| Progressive disease (PD) | 21 (20.4) | 16 (15.7) | |
| Not evaluable | 7 (6.8) | 20 (19.6) | |
| ORR (CR + PR), n (%) | 18 (17.5) | 37 (36.3) | 0.003 |
| DCR (CR + PR + SD), n (%) | 75 (72.8) | 66 (64.7) | 0.230 |

Abbreviations: CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Table 3. All-grade treatment-emergent adverse events with frequency >15% in either group and corresponding grade 3/4 adverse events

| | Sorafenib, % (n=102) | | Sorafenib + HAIC, % (n=88) | | P-value | |
|---|---|---|---|---|---|---|
| | **All-Grade** | **Grade 3/4** | **All-Grade** | **Grade 3/4** | **All-Grade** | **Grade 3/4** |
| Elevated AST | 96.1 | 29.4 | 94.3 | 27.3 | 0.841 | 0.744 |
| Elevated ALT | 87.3 | 14.7 | 72.7 | 13.6 | 0.015 | 0.833 |
| Thrombocytopenia | 80.4 | 11.8 | 89.8 | 33.0 | 0.036 | <0.001 |
| Anemia | 77.5 | 5.9 | 85.2 | 15.9 | 0.071 | 0.025 |
| Hypertension | 76.5 | 25.5 | 76.1 | 25.0 | 0.912 | 0.938 |
| Elevated lipase | 65.7 | 34.3 | 61.4 | 28.4 | 0.318 | 0.383 |
| Elevated bilirubin | 64.7 | 11.8 | 62.5 | 8.0 | 0.843 | 0.383 |
| Hand-foot skin reaction | 58.8 | 13.7 | 48.9 | 9.1 | 0.197 | 0.319 |
| Elevated serum amylase | 56.9 | 10.8 | 48.9 | 11.4 | 0.184 | 0.899 |
| Malaise | 52.9 | 0.0 | 46.6 | 0.0 | 0.430 | NA |
| Anorexia | 52.9 | 5.9 | 55.7 | 12.5 | 0.630 | 0.111 |
| Diarrhea | 48.0 | 9.8 | 33.0 | 3.4 | 0.041 | 0.082 |
| Decreased WBC count | 48.0 | 4.9 | 67.0 | 12.5 | 0.006 | 0.060 |
| Elevated INR | 48.0 | 0.0 | 43.2 | 0.0 | 0.604 | NA |
| Neutropenia | 41.2 | 1.0 | 67.0 | 17.0 | <0.001 | <0.001 |
| Fatigue | 39.2 | 7.8 | 30.7 | 9.1 | 0.243 | 0.757 |
| Weight loss | 32.4 | 1.0 | 37.5 | 0.0 | 0.774 | 0.352 |
| Hoarseness | 32.4 | 1.0 | 15.9 | 0.0 | 0.010 | 0.352 |
| Alopecia | 25.5 | 0.0 | 8.0 | 0.0 | 0.002 | NA |
| Fever | 24.5 | 2.9 | 22.7 | 0.0 | 0.811 | 0.105 |
| Nausea | 16.7 | 2.0 | 35.2 | 4.5 | 0.003 | 0.310 |
| Vomiting | 6.9 | 1.0 | 19.3 | 3.4 | 0.009 | 0.245 |
| Implanted catheter system trouble | 0.0 | 0.0 | 18.2 | 12.5 | NA | NA |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio.

**Figure 1.** Patient disposition during the study.

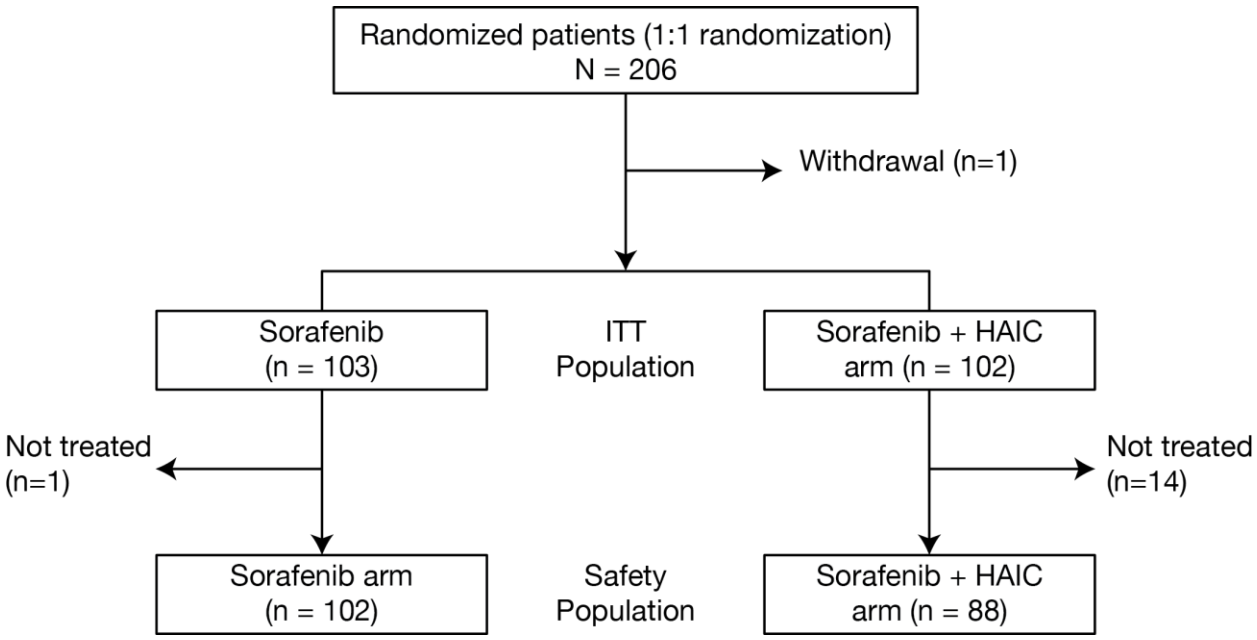
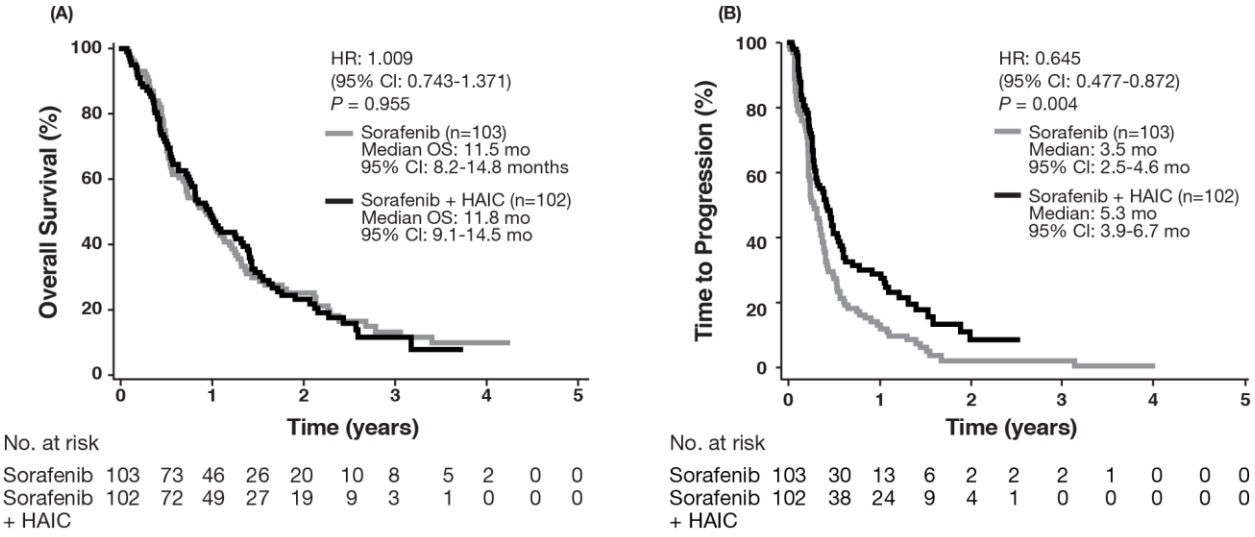


**Figure 2.** Kaplan-Meier analysis of (A) overall survival, (B) time to progression, and (C) progression-free survival in patients treated with sorafenib alone and sorafenib plus HAIC.



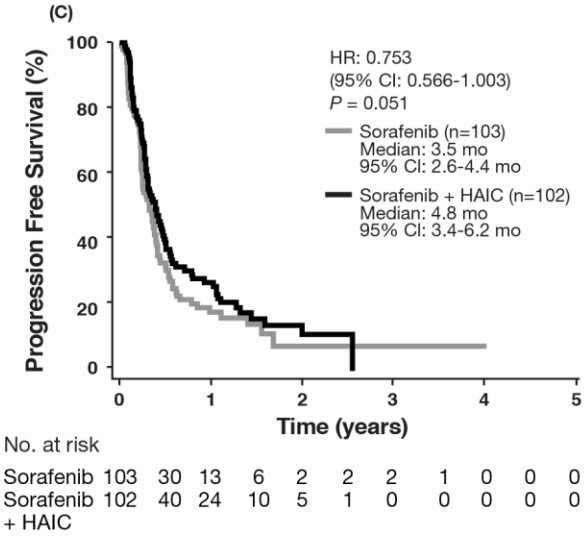



**Figure 3.** Kaplan-Meier analysis of overall survival in patients treated with sorafenib alone and sorafenib plus HAIC and stratified by MVI. (A) Vp1–3 and (B) Vp4.

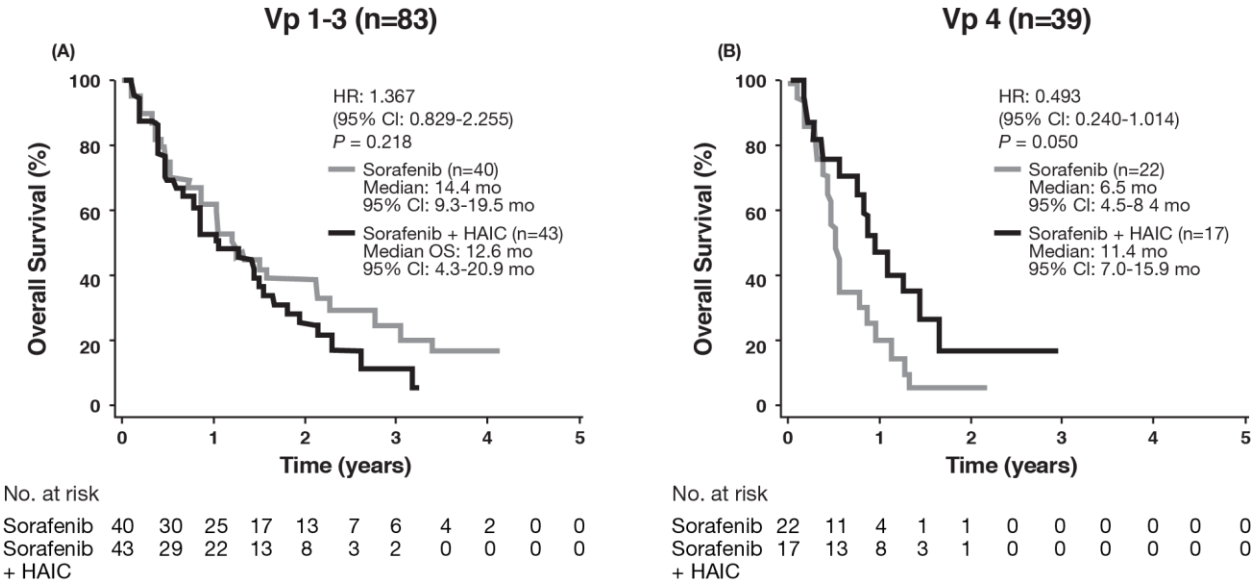
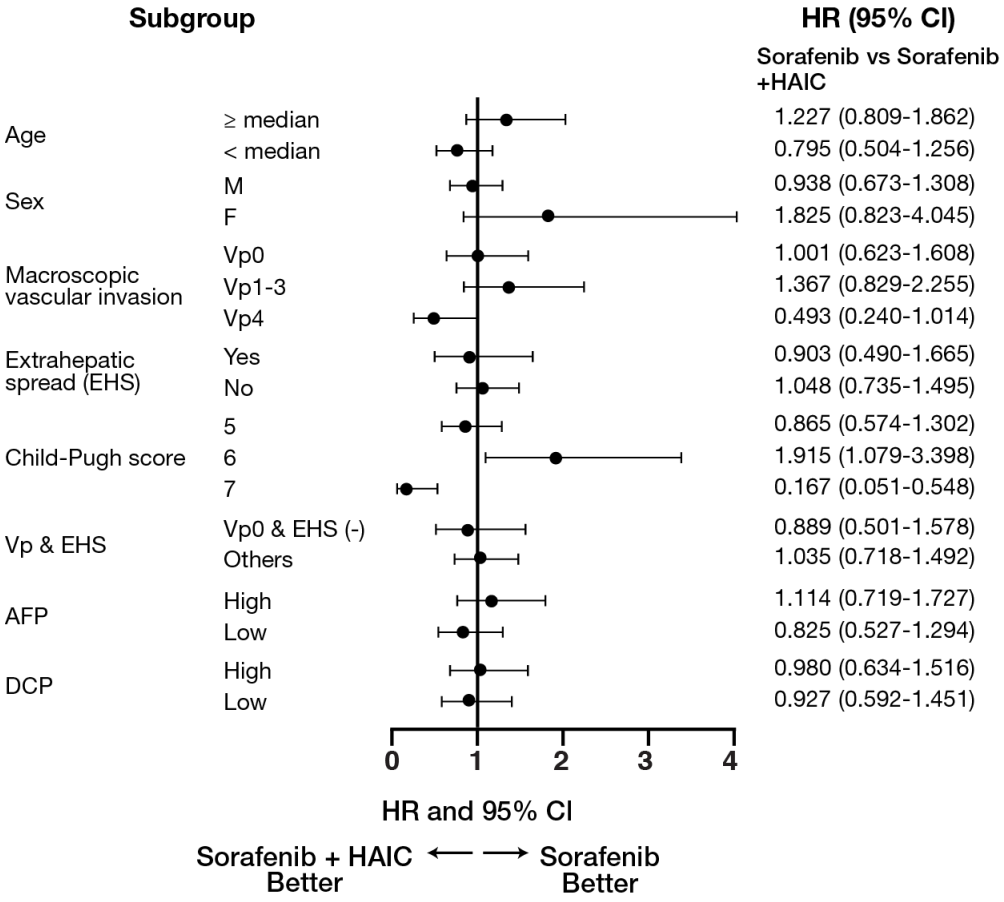


**Figure 4.** Forest plot of factors associated with overall survival in patients treated with sorafenib alone and sorafenib plus HAIC.



Supplementary Table 1. Dose intensities of sorafenib and number of HAIC cycles in the safety population.

| | **Sorafenib (n=102)** | **Sorafenib + HAIC (n=88)** |
|---|---|---|
| Duration of sorafenib treatment, weeks | | |
| Mean ± SD | 23.9 ± 29.0 | 25.0 ± 31.9 |
| Median (range) | 14.4 (159.3) | 13.6 (216.0) |
| Relative sorafenib dose intensity, % | | |
| Mean ± SD | 60.0 ± 25.6 | 53.7 ± 26.6 |
| Median | 55.6 (100.0) | 53.1 (100.0) |
| Total number of HAIC cycles (1 cycle = 28 days) | | **(n=85)** |
| Mean ± SD | | 4.0 ± 4.0 |
| Median (range) | | 2.0 (19.0) |

Supplementary Figure 1. Kaplan-Meier analysis of overall survival in patients stratified by tumor response. (A, B) OS was significantly longer in patients who achieved CR+PR than in those who achieved SD+PD in response to sorafenib alone (A) and sorafenib plus HAIC (B). (C) OS was similar in patients who achieved CR+PR in response to sorafenib alone and sorafenib plus HAIC.