Sun Yat-Sen University Cancer Center

CLINICAL STUDY PROTOCOL

Title:	Sorafenib combined with hepatic arterial infusion of oxaliplatin plus 5 fluorouracil/leucovorin versus sorafenib alone in hepatocellular carcinoma with portal vein tumor thrombosis: a multicenter, open-label, randomized controlled trial.
Test Drug:	Sorafenib Oxaliplatin, leucovorin, 5-fluorouracil
Funding:	National Key R&D Program of China (2017YFA0505803) National Natural Science Foundation of China Grants (81625017 and 81572385) Fundamental Research Funds for the Central Universities of China no. 16ykjc36
Principal Investigator:	Ming Shi, MD, Professor
Study Number/Version/Date:	S021 / Version 2.2 / 17 March 2016
Development Phase:	Phase III
ClinicalTrials.gov ID:	NCT02774187

Table of Contents

1. INTRODUCTION

1.1. Hepatocellular Carcinoma (HCC)

Globally, liver cancer ranked fourth for cancer deaths in 2015, and approximately 90% of these are hepatocellular carcinoma (HCC)[1]. China alone accounts for 55% of global HCC incidence, and HCC is the second leading cause of cancer death in China[2]. Unlike in the United States and Europe, where HCC is associated with chronic hepatitis caused by persistent infection with hepatitis C virus (HCV), the etiology of HCC in China is hepatitis B virus (HBV)[3].

A variety of treatments including surgical resection, local ablation therapy (e.g., percutaneous ethanol injection therapy and percutaneous radiofrequency), transcatheter arterial chemoembolization, chemotherapy, and liver transplantation are performed for HCC. Surgical resection and local ablation therapy are considered curative treatments for localized lesions, and transcatheter arterial chemoembolization has also produced good outcomes. Surgical resection leads to 60−70% 5-year survival for patients with HCC who present with solitary tumors and have excellent liver function. However, because most patients present with advanced disease or insufficient liver function, surgical resection is an option for less than 20% of patients[4]. Portal vein tumor thrombus (PVTT) occurs in 13–32% of HCC patients at the time of diagnosis and has a profound adverse effect on prognosis[5,6], so the subjects of this study are patients with HCC and PVTT who are not candidates for surgical resection, or local ablation therapy.

1.2. Sorafenib is the Standard Treatment for HCC with PVTT

HCC with PVTT has a median survival of 2.7–4.0 months if left untreated[7,8]. Sorafenib is the current standard of care for advanced HCC[9,10]. Sorafenib is a multikinase inhibitor that inhibits various kinases, including Raf kinases, and vascular endothelial growth factor receptors. Specifically, it inhibits serine/threonine kinases in the Raf family as well as vascular endothelial growth factor receptors (VEGFR-2 and 3), platelet-derived growth factor receptor (PDGFR−β), and receptor tyrosine kinases such as Flt-3, kit, and Ret[11].

When the SHARP and AP study demonstrated that sorafenib improved the overall survival (OS) rate in patients with unresectable HCC[12,13], sorafenib became the first oral drug approved to treat HCC. In the SHARP study, median OS was 10.7 months in the sorafenib group and 7.9 months in the placebo group, with a hazard ratio of 0.69 ($p<0.001$). In the AP study, median OS was 6.5 months in the sorafenib group and 4.2 months in the placebo group, with a hazard ratio of 0.68 ($p=0.014$). Sorafenib significantly prolonged OS in patients with HCC compared with the placebo group. Based on the above data, Nexavar® (sorafenib) was approved by the European Medicines Agency (EMA) on October 30, 2007, and by the United States Food and Drug Administration (FDA) on November 19, 2007. As of October 2008, it was in use in 67 countries. In China, the indications were expanded to include unresectable HCC on August 2009, and the drug is now considered the standard therapy for unresectable advanced HCC.

1.3 Hepatic Arterial Infusion Chemotherapy

For patients with HCC and PVTT treated with sorafenib monotherapy, outcome remains poor, with a median survival time of 5.5–7.2 months[14-16]. It would be desirable to develop new effective drugs and treatment methods for HCC.

In Japan and Korea, hepatic arterial infusion chemotherapy (HAIC) is selected for patients with advanced HCC who are not candidates for surgical resection, or local ablation therapy. HAIC provides direct chemotherapeutic agent delivery into the tumor feeding arteries and minimizes systemic toxicities through a first-pass effect in the liver[17,18]. However, the disease commonly begins to progress again even after the treatment shrinks the tumor, and the cancer recurs, or the tumor starts growing again. Thus, treatment is often repeated as long as liver function will allow.

Hepatic arterial infusion of a cisplatin-based regimen was first investigated as a combination therapy with sorafenib [19,20]. In one randomized clinical trial, sorafenib plus hepatic arterial infusion of cisplatin extended OS by 22% or 1.9 months compared with sorafenib alone (10.6 months vs 8.7 months; hazard ratio [HR] 0.60, 95% CI 0.38–0.96; p=0.03)[21]. In another randomized trial, a combination of sorafenib and a hepatic arterial infusion of cisplatin and fluorouracil failed to demonstrate survival superiority over sorafenib alone[22]. In summary, there is no sufficient evidence of a survival benefit associated with the addition of hepatic arterial infusion of a cisplatin-based regimen to sorafenib, despite impressive higher tumor response rates (22–36%)[21,22].

1.4 Rationale for Synergistic Effects of Sorafenib and HAIC of FOLFOX

Compared with cisplatin, oxaliplatin has distinct cytotoxic, immunological, and pharmacological properties.[23-26] First, oxaliplatin kills cancer cells by inducing ribosome biogenesis stress rather than by engaging a DNA damage response.[23] Second, immunogenic tumor cell death induced by oxaliplatin (but not cisplatin) can promote a permanent antitumor immune response.[25,26] Furthermore, there is a significant pharmacokinetic advantage to using oxaliplatin for HAIC compared with cisplatin.[24] In brief, oxaliplatin might be a better option than cisplatin for HAIC.

Oxaliplatin, fluorouracil, and leucovorin (FOLFOX) is a regimen first used in colorectal cancer with liver metastases and was reported to be effective both by systemic delivery and HAIC in clinical trials[27,28]. EACH study showed that the systemic FOLFOX regimen provided better outcomes than doxorubicin for advanced HCC[29]. A retrospective study also showed that HAIC of FOLFOX therapy may improve survival compared to sorafenib in patients with advanced HCC[30]. Our phase II study of sorafenib plus HAIC of FOLFOX demonstrated a safe toxicity profile and a 12-month survival rate of 52.7% in patients with HCC and major PVTT[31].

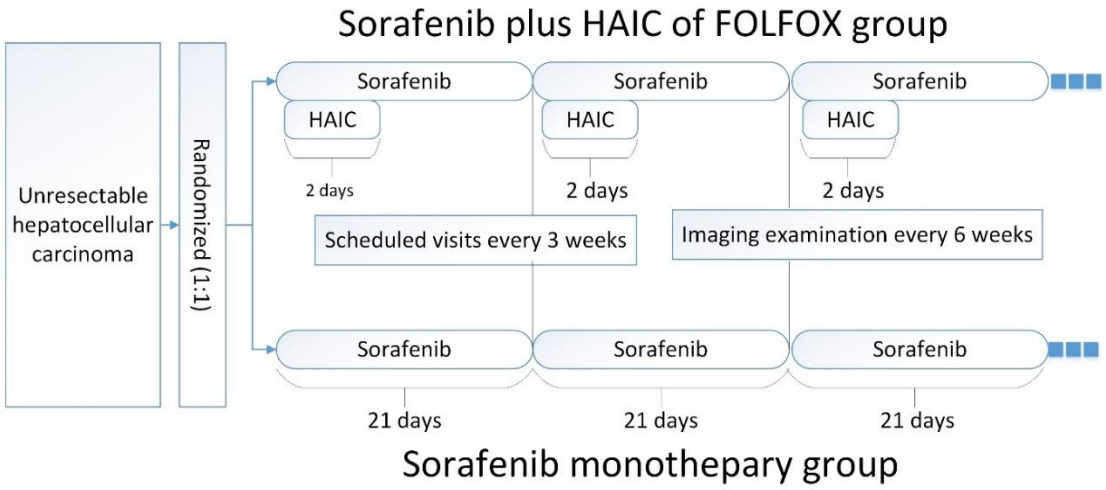
Since sorafenib improves survival through disease stabilization and has been shown to exert a synergistic anticancer effect with chemotherapeutic agents in preclinical research,[32-34] sorafenib combined with HAIC might benefit patients with advanced HCC more than either treatment alone. Therefore, this study was designed to assess the additive effects of HAIC of FOLFOX on the current standard therapy of sorafenib monotherapy and to establish this new therapy as the standard therapy for this patient

population. It is the first randomized phase III trial to compare oral sorafenib plus hepatic arterial infusion of FOLFOX with sorafenib monotherapy in patients with unresectable HCC and portal vein tumor thrombosis.

2. STUDY OBJECTIVES

To investigate the superiority of combination therapy with sorafenib and hepatic arterial infusion of oxaliplatin, 5-fluorouracil and leucovorin over the standard treatment of sorafenib monotherapy in terms of the primary endpoint of prolongation of OS in patients with HCC and PVTT who are not candidates for surgical resection, or local ablation therapy.

Figure 2-1. Schematic of the study design



Primary endpoint

Overall survival (OS)

Secondary endpoints

Progression-free survival (PFS)

Objective response rate (ORR) by RECIST criteria

Safety

3. STUDY INSTITUTE AND INVESTIGATORS

Study Institute	Principal Investigators
Sun Yat-sen University Cancer Center	Ming Shi
First Affiliated Hospital of Sun Yat-sen University	Guo-Sheng Tan
Guangzhou No.12 People's Hospital	Yuan-Min Zhou
Kaiping Central Hospital	Wan-Qiang Fang
The First Affiliated Hospital of University of South China	Xiao-Ping Wu

Coordinating/Principal Investigator for the study:

Name: Ming Shi

Address: Department of Hepatobiliary Oncology, Sun Yat-sen University Cancer Center, 651 Dongfeng East Road, Guangzhou, China

Telephone: (8620)-87343938Fax: (8620)-87343938

Email: shiming@sysu.edu.cn

4. INVESTIGATIONAL PLAN

4.1. Study Design

This is a multicenter, prospective, randomized, open-label, multicenter,

parallel-group trial to verify the superiority of combination therapy with sorafenib and HAIC of oxaliplatin, 5-fluorouracil and leucovorin compared with sorafenib monotherapy in patients with HCC and PVTT who are not candidates for surgical resection, or local ablation therapy.

4.1.1. Sorafenib plus HAIC of FOLFOX group (SoraHAIC group) (Figure 4-1)

This study will use the following doses demonstrated as safe in our II study of sorafenib plus HAIC of FOLFOX for HCC with major portal vein thrombosis. The following regimen will be administered via the hepatic artery: oxaliplatin 85 mg/m2 from hours 0 to 2 on day 1; leucovorin 400 mg/m2 from hours 2 to 3 on day 1; and 5-fluorouracil 400 mg/m2 bolus at hour 3 and then 2400 mg/m2 over 46 hours on days 1 and 2. Sorafenib will be administered continuously at a dose of 400 mg twice daily for 21 days from day 1 to day 21. This 3-week period constitutes one cycle, and cycles will be repeated until discontinuation of the protocol treatment.

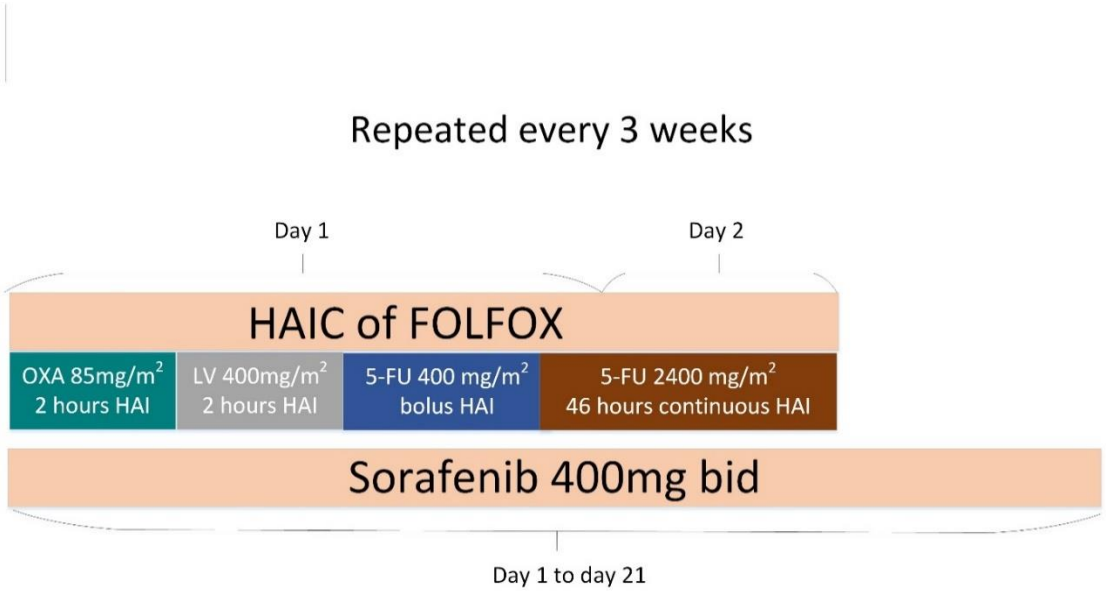
Patients will be allowed to have sorafenib as a single agent and still be considered on study when HAIC is delayed or discontinued in the absence of disease progression. Earlier treatment with sorafenib will be allowed. This combination therapy will be repeated until progressive disease (PD) according to the RECIST criteria is documented.

If an adverse event is observed, treatment will be interrupted or the dose will be reduced as appropriate in accordance with **Section 4.7.3. Criteria for adjusting the sorafenib dose (dose interruption and reduction)** and **Section 4.7.2. Criteria for**

HAIC (FOLFOX) dose adjustment (dose interruption and reduction). After the protocol treatment is discontinued, appropriate treatment as described in **Section 4.7.5. Subsequent treatment** will be instituted.

A 3.5 French catheter will be inserted into the celiac trunk or superior mesenteric artery for arteriography. Depending on the arterial supply of the tumor identified by arteriography, coil embolization of the gastroduodenal artery and the right gastric artery will be performed routinely. Then, a 2.7 French microcatheter will be superselectively placed into the feeding arteries of the tumor and the tumor thrombus. If the tumors simultaneously accept blood supply from the celiac trunk and superior mesenteric artery, the microcatheter will be placed into the largest tumor feeding arteries. The peripheral end of the micro-catheter will be locked with a heparin lock (10 ml, 10,000 units, 1: 1,000 dilution) to prevent clotting of the catheter. The peripheral part of the catheter exposed outside the body will be covered with medical sterile gauze and fastened on the skin of the thigh using medical rubberized fabric and a bandage. Then, the patient will be transferred to the ward and confined to bed for 48 hours. After confirming the location of the tips of the microcatheter by bedside X-ray radiography, the microcatheter will be connected to the artery infusion pump to administer the chemotherapy agent. After HAIC is completed, the catheter and sheath will be removed. The catheter will be placed again at the next treatment. The entire chemoembolization procedure will be performed under continuous fluoroscopic guidance with cone-beam computed tomography.

Figure 4-1. Treatment schedule (Sorafenib plus HAIC of FOLFOX group)

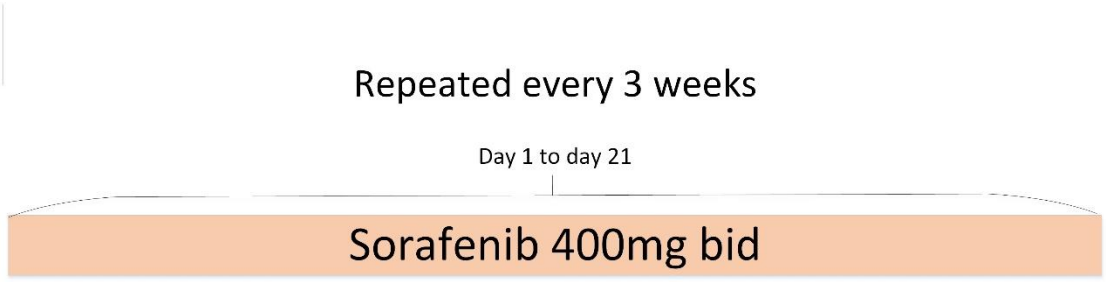


4.1.2. Sorafenib group (sorafenib group) （Figure 4-2）

Sorafenib will be administered continuously at a dose of 400 mg twice daily for 21 days from day 1 to day 21. This 3-week period constitutes one cycle, and cycles will be repeated until discontinuation of the protocol treatment. Treatment will be repeated until progressive disease (PD) is diagnosed by the RECIST criteria.

If an adverse event is observed during treatment with sorafenib, treatment will be interrupted or the dose will be reduced as appropriate in accordance with **4.7.3. Criteria for adjusting the sorafenib dose (dose interruption and reduction)**. After the protocol treatment is discontinued, appropriate treatment as described in **Section 4.7.5. Subsequent treatment** will be performed.

Figure 4-2. Treatment schedule (Sorafenib group)



4.1.3. Description and rationale of design

For patients with HCC and PVTT treated with sorafenib monotherapy, the prognosis remains poor. HAIC provides direct chemotherapeutic agent delivery into the tumor feeding arteries and minimizes systemic toxicities through a first-pass effect in the liver. Our phase II study of sorafenib plus HAIC of FOLFOX demonstrated a safe toxicity profile and a 12-month survival rate of 52.7% in patients with HCC and major PVTT. Because sorafenib is standard therapeutic modality for patients with advanced HCC, the control group is the sorafenib monotherapy and the experimental group is sorafenib plus HAIC of FOLFOX.

4.1.4. Data Monitoring Committee (DMC)

A Data Monitoring Committee (DMC) will be instituted for this study to ensure its ongoing safety. Recommendation for trial continuation will be guided by safety evaluations at all safety data reviews.

The committee will include an independent statistician and independent oncologists. Safety review meetings will be held as per a separate DMC charter, approximately every 6 months.

Decisions on trial termination, amendment or cessation of patient recruitment based

on safety or outcome findings will be made after recommendations from the DMC have been assessed by Sun Yat-sen University Cancer Center.

4.2. Selection of Study Population

4.2.1. Primary diagnosis

Patients with unresectable HCC and PVTT, ECOG PS 0, 1, or 2, Child-Pugh status A who have not received prior anticancer treatment for HCC.

4.2.2. Number of patients

The planned 244 patients with advanced, measurable HCC who fulfill the inclusion criteria and exclusion criteria will be randomized in a ratio of 1:1 to either sorafenib plus HAIC of FOLFOX or sorafenib. These 244 patients will be recruited from Sun Yat-sen University Cancer Center (80 patients), First Affiliated Hospital of Sun Yat-sen University (52 patients), Guangzhou No.12 People's Hospital (52 patients), Kaiping Central Hospital (30 patients) and The First Affiliated Hospital of University of South China (30 patients).

4.2.3. Inclusion Criteria

Patients who meet all of the following criteria in screening tests and observations within 21 days before enrollment will be included in the study.

1) 18 years or older
2) Diagnosis of HCC based on the diagnostic criteria for HCC used by the European Association for the Study of the Liver (EASL)

3) At least one tumor lesion that can be accurately measured according to the Response Evaluation Criteria in Solid Tumors version 1·1

4) HCC with PVTT

Patients who meet any of the following criteria are considered to have HCC with PVTT:

a) Biopsy-confirmed HCC. Ultrasound-guided percutaneous tumor biopsy is performed with a gauge needle.

b) HCC and PVTT confirmed by two image techniques, including contrast-enhanced ultrasound, dynamic contrast-enhanced computerized tomography and dynamic contrast-enhanced magnetic resonance imaging.

5) Eastern Cooperative Oncology Group performance status of 0 to 2

6) No previous treatment

7) No cirrhosis or cirrhotic status of Child-Pugh class A only

8) Not amenable to surgical resection, local ablative therapy and any other cured treatment.

9) The following laboratory parameters:

a) Platelet count $\geq 75\times10^9$ per L

b) Hemoglobin ≥8.5 g/dL

c) Total bilirubin ≤30 mmol/L

d) Serum albumin ≥30 g/L

e) ASL and AST ≤5 x upper limit of normal

f) Serum creatinine ≤1.5 x upper limit of normal

g) INR ≤1.5 or PT/APTT within normal limits

h) white blood cell count ≥3.0×10⁹ per L

i) Absolute neutrophil count (ANC) >1.5×10⁹ per L

j) Left ventricular ejection ⩾45%

10) Provided written informed consent to participate in the study

4.2.4. Exclusion Criteria

Patients who meet one of the following criteria in screening tests and observations within 21 days before enrollment will be excluded from the study:

1) Evidence of hepatic decompensation including ascites, gastrointestinal bleeding or hepatic encephalopathy
2) Known history of HIV or organ allograft
3) Known or suspected allergy to the investigational agents or any agent given in association with this trial
4) Patients with clinically significant gastrointestinal bleeding within 30 days prior to study entry or evidence of bleeding diathesis
5) Known central nervous system tumors including metastatic brain disease
6) Patients who are pregnant or breastfeeding
7) Other invasive malignant diseases

4.3. Removal of Subjects from Study

Sorafenib discontinuation is protocol treatment discontinuation in both groups. In the SoraHAIC group, patients will be allowed to have sorafenib as a single agent and

still be considered on study when HAIC is delayed or discontinued in the absence of disease progression.

Patients will continue therapy with the study medication until death or until a criterion is met for stopping therapy. After the protocol treatment is generally discontinued, continuation of HAIC, sorafenib or other treatments are allowed if the investigator determines that the patient is responding clinically to these treatments, but these treatments belong to subsequent therapy. Decisions about continuing the study medication will be made at the discretion of the investigator based on the investigator's judgment about the patient's clinical status.

The criteria for stopping protocol therapy (sorafenib) are outlined in **Section 4.3.1.**

The criteria for stopping HAIC treatment are outlined in **Section 4.3.2.**

4.3.1. Criteria for protocol treatment (sorafenib) discontinuation

When one of the following situations occurs, sorafenib (protocol treatment) will be discontinued.

1) Tumor progression (both radiologic progression, as defined by RECIST[35], and symptomatic progression, as defined by the Functional Assessment of Cancer Therapy–Hepatobiliary Symptom Index 8 questionnaire[36])
2) Intolerable adverse event
    a) Patient cannot resume sorafenib after 30 days of interruption due to an adverse event
    b) An adverse event that meets the criteria for sorafenib dose

reduction occurs after the dose was already reduced to the lowest level

c) Life-threatening adverse event

3) The need for another anticancer treatment due to downstaging (such as surgery) at the physician's discretion

4) Patient requests to discontinue the study

5) Investigator determines that discontinuation is necessary for any reason

6) Deterioration of PS to ECOG 4

7) Death

The Investigator will make every reasonable effort to keep each patient on their randomized treatment unless it is in the patient's best interest to discontinue. If treatment is discontinued, every reasonable effort will be made to follow the patient to measure study outcomes.

After discontinuation/withdrawal from study drug treatment, patients must be entered in the follow-up period and contacted regularly (every 3 months) for survival status until death or study closure.

4.3.2. Criteria for HAIC treatment discontinuation

HAIC treatment will be discontinued in the following situations occur.

1) Tumor progression (both radiologic progression, as defined by RECIST[35], and symptomatic progression, as defined by the Functional Assessment of Cancer Therapy–Hepatobiliary Symptom Index 8 questionnaire[36])

2) Intolerable adverse event
    a) Patient cannot resume HAIC after 30 days of interruption due to an adverse event
    b) An adverse event that meets the criteria for HAIC dose reduction occurs after the dose was already reduced to the lowest level
    c) Life-threatening adverse event
3) The need for another anticancer treatment due to downstaging (such as surgery) at the physician's discretion
4) HAIC becomes technically infeasible
5) Patient requests to discontinue the study
6) Investigator determines that discontinuation is necessary for any reason
7) Deterioration of PS to ECOG 4
8) Death

4.4. Randomization and Stratification Factors

Patients will be randomly assigned on a 1:1 basis to sorafenib 400 mg twice daily or sorafenib 400 mg twice daily plus HAIC. To accomplish this, a computer-generated randomization sequence will be created by an independent organization. Randomization will be stratified by the following:

- Institution
- Degree of PVTT (Vp1-2, Vp3, Vp4)

4.5. Mask

As an open-label trial, all doctors, investigators and patients will know the assigned treatments.

4.6. Criteria for Treatment Adjustment

4.6.1. Criteria for starting the cycle (for both groups)

The next cycle will be started if the investigator confirms the following criteria are met within 1 week before the scheduled start date. If any of these criteria are not met, the cycle will be delayed until the criteria are met. If the criteria for starting the cycle are still not met for 30 days, the protocol treatment will be discontinued.

1) Neutrophil count ≥1,200/μL
2) Platelet count ≥60,000/μL
3) Total bilirubin ≤30 mmol/L
4) Albumin ≥3.0 mg/dL
5) Serum creatinine ≤1.5 times the institutional upper limit of normal

4.6.2. Criteria for HAIC (FOLFOX) dose adjustment (dose interruption and reduction)

If clinically significant hematological or nonhematological toxicity attributed to HAIC (FOLFOX) occurs, infusions alone will be interrupted. Sorafenib will be continued. The 5FU dose will be decreased to 300mg/m2 bolus and 1800mg/m2/cycle continuous infusion in case of grade 3 or 4 diarrhea or stomatitis, skin toxicity or

other grade 3 major organ drug-related toxicity. The oxaliplatin dose will be decreased to 65 mg/m2/cycle in case of grade 3 or 4 neutropenia or thrombocytopenia, any other grade 3 major organ drug-related toxicity, or paresthesia associated with pain.

4.6.3. Criteria for adjusting the sorafenib dose (dose interruption and reduction)

The dose of sorafenib will be delayed or reduced for clinically significant hematologic and other toxicities that are related to sorafenib therapy. If a patient experiences several toxicities and there are conflicting recommendations, the recommended dose adjustment that reduces the dose to the lowest level will be used. When grading events, investigators will consider not only whether the patient received a certain treatment but also whether that treatment was indicated for the patient's condition. However, they will also consider whether it is possible to continue treatment with sorafenib by increasing the frequency of tests. All dose modifications will follow predefined dose levels:

1) Standard dose: 400 mg twice daily, two 200 mg tablets of sorafenib per dose twice daily (morning and evening)
2) Dose level 1: 400 mg once daily, two 200 mg tablets of sorafenib per dose once daily (morning)
3) Dose level 2: 400 mg every other day, two 200 mg tablets of sorafenib per dose once every other day (morning)

If the dose is reduced below level 2, the patient should be discontinued from the study. In addition, at the discretion of the investigator, the dose may be re-escalated to

400 mg po bid after the resolution of the adverse event. When the dose is increased, it will be increased one level at a time.

The following tables (Table 4-1, Table 4-2 and Table 4-3) illustrate dose modifications and delays:

Table 4-1. Sorafenib dose delay and modification guidelines for nondermatological toxicities

Grade	Dose delay	Dose modification
Hematologic toxicities		
Grade 0─2	Treat on time	No change
Grade 3	Treat on time	Decrease one dose level
Grade 4	Delay* until ≤grade 2	Decrease one dose level
Nonhematologic toxicities (except skin toxicity) †		
Grade 0─2	Treat on time	No change
Grade 3	Delay* until ≤grade 2	Decrease one dose level‡
Grade 4	Off protocol therapy	Off protocol therapy

* If no recovery after a 30-day delay, treatment will be discontinued unless the patient is deriving clinical benefit.

† Also excludes nausea/vomiting that has not been premedicated and diarrhea.

‡ If more than two dose reductions are required, treatment will be discontinued.

Table 4-2. Sorafenib dose delay and modification guidelines for dermatological toxicities*

Grade	During a course of therapy	Dose for next cycle
Grade 1	Maintain dose level	Maintain dose level

Grade 2	1st appearance	Interrupt until resolved to grade 0–1	Maintain dose level
	2nd appearance	Interrupt until resolved to grade 0–1	400 mg every day
	3rd appearance	Interrupt until resolved to grade 0–1	400 mg every 2 days
	4th appearance	Discontinue treatment permanently	
Grade 3	1st appearance	Interrupt until resolved to grade 0–1	400 mg every day†
	2nd appearance	Interrupt until resolved to grade 0–1	400 mg every two days
	3rd appearance	Discontinue treatment permanently	

454 * Patients experiencing hand–foot skin reaction should have their signs and symptoms graded
455 according to table 3. Other skin toxicities will be graded according to CTCAE v4.0 Common Terminology Criteria
456 for Adverse Events version 4.0.
457 † For patients who require a dose reduction for grade 3 rash or hand–foot skin reaction, the dose of the study drug
458 may be increased to the starting dose after one full cycle of therapy has been administered at the reduced dose
459 without the appearance of rash or hand–foot skin reaction grade ≥1.
460
461 Table 4-3. Grades for hand-and-foot skin reaction

Grade	
Grade 1	numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort that does not disrupt normal activities
Grade 2	painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities
Grade 3	moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living

Patients who develop rash/desquamation or hand-foot skin reaction during treatment with sorafenib should have the involved area photographed if possible.

Patients with discomfort due to hand-foot syndrome may be treated with topical emollients, low-potency topical steroids, or urea-containing cream.

For patients who require a dose reduction for grade 3 rash or hand-foot syndrome, the dose of the study drug may be increased to the starting dose after one full cycle of therapy has been administered with the reduced dose without the appearance of rash or hand foot syndrome ≥grade 1.

All other grade 3 toxicities related to the study drug will result in a permanent dose reduction.

4.6.4. Prior and Concomitant Therapy

All medication (i.e., best supportive care) that is considered necessary for the patient's welfare and is not expected to interfere with the evaluation of the study drug may be given at the discretion of the Investigator. All concomitant medications (including start/stop dates, total daily dose and indication) must be recorded in the patient's source documentation, as well as in the appropriate pages of the CRF.

Permissible Concomitant Medication/Therapies

The following concomitant treatments and supportive care may be provided if necessary.

1) Patients may receive nontargeted therapy for the primary disease (e.g.,

acupuncture) or eat foods fortified with vitamins/minerals if the investigator or investigator determines the treatment or food will not interfere with or influence the evaluation of the study results.

2) Palliative care or supportive care may be provided for the primary disease as long as prohibited drugs are not used.

3) All recruited patients with HBV-related HCC will receive preemptive antiviral therapy.

4) Symptomatic treatment drugs, such as analgesics, antiemetics

5) Drugs for hypertension, diabetes and other chronic diseases

Nonpermissible Concomitant Medication/Therapies:

Patients are forbidden to receive the following treatments during the protocol treatment period. After protocol treatment, patients are allowed to receive the following treatments.

1) Immunotherapy including programmed cell death protein-1 inhibitor treatment

2) Antitumor drugs treatments, such as radiotherapy, ablation, TACE, systemic chemotherapy and surgery

3) Other molecular targeted agents, such as regorafenib and lenvatinib

4.6.5. Subsequent treatment

Treatments for HCC not described in this protocol will not be performed until the criteria for discontinuation of the protocol treatment are met. Subsequent treatments

include HAIC, resection, ablation, sorafenib, systemic chemotherapy, immunotherapy, TACE, radiotherapy, regorafenib, lenvatinib and other treatments. The choice of the subsequent treatment will be determined according to the patient's request and the results of discussions by our multidisciplinary team after the protocol treatment is discontinued. For patients in whom all residual tumors can be safely removed by surgery or ablated by RF ablation, the corresponding treatment will be recommended.

The protocol treatment should generally be discontinued if the patient shows PD according to the RECIST criteria during the protocol treatment period. However, continuation of HAIC or sorafenib or both treatments is allowed if the investigator determines that the patient is clinically responding to the protocol treatment. Continuation of these treatments in this situation will also be considered subsequent treatment.

If the tumors are completely devascularized after HAIC, patients will receive sorafenib monotherapy and will be followed up by contrast CT/MRI every 6 weeks (± 1 week). HAIC will be repeated if new tumor enhancement is depicted on follow-up CT imaging. If the tumor progresses but still meets the eligibility criteria for HAIC, HAIC will be allowed. Continuation of these HAIC treatments in this situation will also be considered subsequent treatment.

Treatment crossover is permitted after the protocol treatment is discontinued during the initially assigned treatment.

4.7. Study Variables

4.7.1. Primary endpoint

Overall survival (OS)

The length of time from the date of randomization until death from any cause. The date survival was last confirmed will be used to censor surviving patients. In the absence of confirmation of death, the survival time will be censored at the last date the patient was known to be alive or at the cutoff date, whichever comes first. Unfollowable patients will be censored by the date survival was last confirmed before they became unfollowable.

4.7.2. Secondary endpoints

Progression-free survival (PFS)

The length of time from the date of randomization until progression of intrahepatic and extrahepatic lesions or death from any cause, whichever is sooner.

Intrahepatic progression-free survival (ITPFS)

The length of time from the date of randomization until progression of intrahepatic lesions or death from any cause, whichever is sooner.

Tumor response

The disease control rate (DCR) is defined as the rate of complete response (CR) plus partial response (PR) plus stable disease (SD). The objective response rate (ORR) is defined as the rate of CR plus PR. ORR and DCR will be determined using the RECIST criteria and modified RECIST criteria. Tumor response includes assessment

of target lesions, nontarget lesions and new lesions. All objective responses will be confirmed at least 4 weeks after the first observation.

Intrahepatic response

Intrahepatic ORR and DCR only including assessment of the change in tumor burden inside the liver will be also assessed by the RECIST and mRECIST criteria, respectively.

OS by Vp

OS will be compared by Vp stage.

Safety

Adverse events will be graded based on CTCAE v4.03. All observations pertinent to the safety of the study medication will be recorded on the CRF and included in the final report.

Safety variables are as follows: adverse events; laboratory changes (hematology and clinical chemistry); and changes in vital signs (blood pressure, heart rate, respiratory rate, and temperature), electrocardiogram (ECG) and, in some instances, chest X-ray.

All adverse events, whether considered treatment-related or not, will be reported on the CRF with diagnosis, start/stop dates, action taken, whether treatment was discontinued, any corrective measures taken, outcome and other possible causes. For all events, the relationship to the treatment and the severity of the event will be determined by the Investigator using the terms and definitions given in **Section 7.**

4.8. Parameters Assessed, Clinical Tests, and Assessment Schedule

4.8.1. Parameters Assessed Before Enrollment

Data on the following parameters will be collected within 3 weeks before enrollment for pre-enrollment evaluation.

1) Patient characteristics: Sex, height, pathological diagnosis, treatment history, disease stage (using the General Rules for the Clinical and Pathological Study of Primary Liver Cancer, see Section 21.3), ECOG-PS (see Section 21.2), allergies, and concomitant diseases
2) Signs and symptoms and blood pressure
3) Body weight
4) Chest enhanced CT to evaluate potential lung metastasis
5) Electrocardiogram
6) Target lesion measurements (dynamic CT is preferred, but dynamic MRI is also acceptable)
7) Hematology parameters: hemoglobin, white blood cell count, neutrophil count, red blood cell count, platelet count
8) Blood biochemistry: AST, ALT, total bilirubin, direct bilirubin, ALP, γ-GTP, albumin, creatinine, Na, K, Cl, amylase, lipase, blood glucose
9) Urinalysis: urine protein, urine erythrocytes, urine leukocytes
10) Coagulation: PT (INR)
11) Ultrasound-guided percutaneous tumor biopsy
12) Tumor markers: AFP, PIVKA-II, CA199

13) Hepatitis virus: HBs antigen/HBs antibody/Hbc antibody, HCV antibody

4.8.2. Tests and Evaluations before Discontinuation of the Protocol Treatment

The following parameters will be collected every 3 weeks:

1) Signs and symptoms and blood pressure
2) Hematology parameters: hemoglobin, white blood cell count, neutrophil count, red blood cell count, platelet count
3) Blood biochemistry: AST, ALT, total bilirubin, direct bilirubin, ALP, γ-GTP, albumin, creatinine, Na, K, Cl, amylase, lipase, blood glucose
4) Urinalysis: urine protein, urine erythrocytes, urine leukocytes
5) Coagulation: PT (INR)
6) Tumor markers: AFP, PIVKA-II, CA199

Upper abdomen-enhanced CT (MRI is also acceptable) and chest-enhanced CT will be performed every 6 weeks (± 1 week).

4.8.3. Tests and Evaluations after Discontinuation of the Protocol Treatment

When a patient is to be taken off treatment, the following assessment should be done within 30 days after study treatment has stopped:

1) Signs and symptoms and blood pressure
2) Hematology parameters: hemoglobin, white blood cell count, neutrophil count, red blood cell count, platelet count
3) Blood biochemistry: AST, ALT, total bilirubin, direct bilirubin, ALP, γ-GTP, albumin, creatinine, Na, K, Cl, amylase, lipase, blood glucose

4) Urinalysis: urine protein, urine erythrocytes, urine leukocytes

5) Coagulation: PT (INR)

6) Tumor markers: AFP, PIVKA-II, CA199

7) Upper abdomen-enhanced CT (MRI is also acceptable) and chest-enhanced CT

4.8.4. Follow-up

After study treatment ends, patients will be contacted every 3 months. The following items will be monitored to the greatest extent possible until the end of the entire study. Tests will be performed at the investigator's discretion depending on the patient's condition and will not be defined as part of this study.

1) Survival: Date survival was last confirmed or date of death; if dead, cause of death

2) Disease progression: Whether the disease has progressed, date of last follow-up regarding progression or date progression was confirmed, site of progression

3) Subsequent treatment: If the patient has received any diagnostic and therapeutic procedures or subsequent anti-tumoral/anti-cancer therapy, the name of the drug(s) in the first regimen following end of treatment should be collected.

4) Adverse event: AEs that were still ongoing at discontinuation of the protocol treatment should be followed up till resolution.

4.9. Data Quality and Documentation

Monitoring and auditing procedures defined/agreed by the primary Investigator will

be followed to comply with Good Clinical Practice (GCP) guidelines. Each center will be visited at regular intervals by a monitor to ensure compliance with the study protocol, GCP and legal aspects. This will include on-site checking of the CRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters.

Entries made in the CRF must be either verifiable against source documents or have been directly entered into the CRF, in which case the entry in the CRF will be considered as the source data. The source data parameter to be verified and the identification of the source document must be documented. The study file and all source data should be retained until notification is given by the primary Investigator for destruction.

5. ETHICAL CONSIDERATIONS

5.1. Protection of Patients' Rights

All researchers involved in this study will conduct the study in accordance with the Declaration of Helsinki and the Ethical Guidelines of each participating institution for clinical studies.

5.2. Informed Consent

5.2.1. Informed consent discussion

Prior to enrollment, investigators will give an Informed Consent Form approved by

the participating institution directly to the patient along with a thorough verbal explanation of the following items. In this protocol, “approval by the participating institution” means that the matter was reviewed by the advisory body of the institution (institutional review board or ethics committee) and a written letter of approval was sent to the applicant by the director of the participating institution or the chair of the reviewing committee.

1) Explanation of the diagnosis, stage, and expected prognosis
2) Notification that this study is a clinical trial
   The difference between a clinical trial and clinical practice
3) Study design and rationale (e.g., significance, number of enrolled patients, need for the study, objective, and treatment assignment)
4) Protocol treatments
   Drug names, routes of administration, dose, treatment schedule, duration of the entire protocol treatment, etc.
5) Anticipated effects of the protocol treatment
   Prolongation of survival, tumor shrinkage, symptom alleviation, etc.
6) Expected adverse events, complications, and sequelae and measures to be taken if they occur
   Explanation of the severity and incidence of expected adverse events (including complications, sequelae, and treatment-related death) and measures to be taken if an event occurs
7) Study-related costs and compensation

Explanation that the study will be similar to routine care in that treatment costs (both for the protocol treatment and treatment for any adverse events) will be covered by health insurance and compensation for illness or injury will be consistent with that awarded in normal clinical practice

8) Alternative treatments

Current typical treatments (including palliative care) and the procedures, effectiveness, and toxicity of standard therapies

Advantages and disadvantages of selecting alternative treatment

9) Potential benefits and potential risks

Explanation of potential benefits and risks of participating in the study

10) Direct access to medical history

Explanation that medical records may be reviewed, for example, healthcare providers from another institution may directly access medical history records and other such records with the permission of the institution's director to ensure accuracy

11) Declining to consent and withdrawal of consent

Explanation that patients are free to decline to participate in this study before participating and are also free to withdraw consent even after providing consent and that these decisions will not adversely impact their care

12) Protection of patients' rights

That the utmost efforts will be made to keep names and other personal information confidential

13) Freedom to ask questions

Written notification of the contact information of not only their assigned investigator but also the site investigator and the study chair (or study coordinator) and explanation that patients are free to ask questions about the study or treatment

5.2.2. Informed consent

A patient's participation in the study will be requested after they are given an explanation of the study, sufficient time to consider the decision, and their firm understanding of what the study entails has been confirmed. If the patient personally consents to participate in the study, the name of the doctor who conducted the informed consent discussion, the name of the patient giving informed consent, and the date of informed consent will be confirmed and recorded on the appended Informed Consent Form or an informed consent form in a format chosen by the study site.

The informed consent form will be copied two times. One copy will be given to the patient directly, and one copy will be retained by the site coordinator. The original will be stored with medical records.

5.3. Protection of Personal Information and Identification of Patients

To protect the privacy of individual patients, enrollment numbers issued on enrollment will be used to identify or refer to enrolled patients. All researchers will

make the utmost effort to protect personal information.

5.4. Adherence to the Protocol

Researchers participating in this study will adhere to this protocol as long as it does not infringe on the safety or rights of patients.

5.5. Conflicts of Interest

The researchers declare that they have no conflict of interest. The study has no commercial affiliations with any company.

5.6. Funding

This work was supported by National Key R&D Program of China (2017YFA0505803), and the National Natural Science Foundation of China (No. 81625017，No.81572385), and the Fundamental Research Funds for the Central Universities of China (No. 16ykjc36).

5.7. Approval by Institutional Review Boards or Ethics Committees

Documented approval from appropriate ECs/IRBs will be obtained for all participating centers/countries according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the EC approval must be obtained and forwarded to the primary investigator. The ECs must supply to the primary investigator, upon request, a list of the EC members involved in the vote and a statement to confirm that the EC is organized and operates according to

GCP and applicable laws and regulations.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1. Sample Size

Planned number of patients: 244 patients (122 in each group)

The sample size is based on the assumptions that the median overall survival in patients receiving sorafenib monotherapy would be 6.5 months and that adding HAIC would improve median overall survival to 10 months. To detect this difference with a power of 80% and a one-sided α of 0.05, we calculated that the required number of events would be observed if 218 patients were enrolled with an enrollment period of 18 months and a follow-up period of 10 months. Based on an estimated dropout rate of 10%, target enrollment was set at 244 patients (122 per group).

6.2. Enrollment Period and Follow-up Period

Enrollment period: 18 months (from May 1, 2016, to November 1, 2017)

Follow-up period: 10 months

Overall study period: 28 months (from May 1, 2016, to September 1, 2018)

6.3. Intent-to-treat (ITT)

The ITT population includes all randomized patients, i.e., patients assigned to a treatment group by the randomization process, regardless of whether the patient

753 received any study treatment or received a different study treatment from which they
754 were randomized.

755 **6.4. Interim analyses**

756 There were no interim analyses in this study.

757

758 **7. ADVERSE EVENTS**

759 **7.1. Definition of Adverse Events**

760 An adverse event (AE) is defined as any undesirable medical event that occurs in a
761 patient receiving the study treatment (excluding worsening of the primary disease).
762 These events may or may not have a clear causal relationship with the study treatment.
763 Essentially, an adverse event is any undesirable or unintended sign (including
764 abnormal laboratory test values), symptom, or condition that arises in a patient
765 receiving the study treatment, regardless of whether the event has a causal
766 relationship with the study treatment. In this study, adverse events that satisfy the
767 above definition will be identified and recorded on case report forms.

768 **7.2. Assessment of Adverse Events**

769 All AEs and severe adverse events (SAEs) occurring after initiation of clinical trial
770 and until the end of follow-up/final visit should be recorded in the case report form
771 (CRF). Investigators will look out for adverse events throughout the entire study

period. The following items must be recorded.

1) Date of occurrence
2) Grade (According to CTCAE v4.03)
3) Causal relationship of adverse event with each study drug (causality definitions from **7.3. Causal Relationship of AE**)
4) Assessment of the adverse event as serious or nonserious
5) Outcome of the adverse event (resolved/not resolved)

The principle investigator and subinvestigators must notify the IRB of all SAEs during the study regardless of causal relationship. They must fax or email the SAE form to the principal investigator and Asan Medical Center IRB within 24 hours of the investigator's acknowledgement of the event.

All information about SAEs should be reported to the principal investigator and IRB until they are completely resolved.

7.3. Causal Relationship of AE

The following categories and definitions of causal relationships to the study drug should be used for any AE:

7.3.1. Definitely related

1) Event or laboratory test abnormality, with plausible temporal relationship to drug intake or intervention
2) Cannot be explained by the disease or other drugs

3) Response upon withdrawal of the study drug (pharmacologically, pathologically)
4) Event definitive pharmacologically or clinically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon)

7.3.2. Probably related

1) Event or laboratory test abnormality with reasonable time relationship to drug intake or intervention
2) Unlikely to be attributed to the disease or other drugs
3) Response to withdrawal clinically reasonable

7.3.3. Possibly related

1) Event or laboratory test abnormality with reasonable time relationship to drug intake or intervention
2) Could also be explained by disease or other drugs
3) Response to withdrawal clinically reasonable

7.3.4. Probably not related

1) Event or laboratory test abnormality that could be explained by the disease or drugs others than the study drug intake or intervention
2) Response to withdrawal unsatisfactory or vague

7.3.5. Definitely not related

1) Event or laboratory test abnormality with a temporal relationship to drug intake or intervention unlikely
2) The disease or other drugs provide plausible explanations

7.3.6. Unknown

1) Cannot be judged because information is insufficient or contradictory
2) Data cannot be supplemented or verified

7.4. Intensity of AE

All AEs will be graded according to the Common Terminology Criteria of Adverse Event (CTCAE), version 4.03 grading scale.

Table 7-1. Grade refers to the severity of the AE.

Grade		Description
1	Mild	Symptoms causing no or minimal inference with usual social & functional activities
2	Moderate	Symptoms causing greater than minimal interference with usual social & functional activities
3	Severe	Symptoms causing inability to perform usual social & functional activities
4	Life-threatening	Symptoms causing inability to perform basic self-care functions or

		medical or operative intervention indicated to prevent permanent impairment, persistent disability
5	Death	Death

7.5. Severe Adverse Events (SAEs)

Events that meet the following criteria are defined as serious:

1) Death
2) Disability (dysfunction severe enough to interfere with ADL)
3) Life-threatening
4) Risk of disability
5) Requiring hospitalization or prolongation of existing hospitalization for treatment is indicated
6) Congenital anomaly or birth defect

Investigators will properly diagnose and treat events to minimize patient risks. They will also perform appropriate diagnostic tests to collect evidence that clarifies the causality of serious adverse events.

Life-threatening: The term “life-threatening” in the definition of “serious” refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event that hypothetically might have caused death if it were more severe.

Hospitalization: Any adverse event leading to hospitalization or prolongation of

hospitalization will be considered as serious UNLESS at least one of the following exceptions are met:

1) The admission results in a hospital stay of less than 12 hours.
2) The admission is preplanned (i.e., elective or scheduled surgery arranged prior to the start of the study).
3) The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care).

However, notably, invasive treatment during any hospitalization may fulfill the criteria of 'medically important' and as such may be reportable as an SAE dependent on clinical judgement. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability: A substantial disruption of a person's ability to conduct normal life functions.

8. DATA COLLECTION

8.1. Types of Case Report Forms (CRFs) and Submission Deadlines

The types of CRFs used in this study and their submission deadlines are as follows.

1) Enrollment Eligibility Form: Fax to data center at enrollment
2) Patient Characteristics Report: Fax to data center within 2 weeks before the start of the study
3) Progress Report (each cycle): Fax to data center within 1 week after eligibility

to start next cycle is confirmed

4) SAE Report (Expedited Primary Report): Fax to study coordinator within 72 hours of SAE onset

5) SAE Report (Expedited Secondary Report): Fax to study coordinator within 7 days of learning of the event

6) Adverse Event Report (Normal Report): Fax to study coordinator within 15 days of learning of the event

7) Treatment Response Report: Fax to data center within 4 weeks after the end of the protocol treatment

8) Treatment Completion Report: Fax to data center within 4 weeks after the end of the protocol treatment

9) Follow-up Form: Fax to data center within 2 weeks after receiving a request*

10) Treatment Suspension Report: Fax to the study chair when considering discontinuation for a patient who does not clearly meet the specified criteria for discontinuation of the protocol treatment

*Will be requested every 4 months following the monitoring schedule of the data center after the end of the study treatment.

8.2. Submission of Imaging Data

When submitting imaging data (CT or MRI) for interim analysis, each study site will mask personal information (e.g., ID number, name, date of birth) on data from enrollment and after discontinuation of the protocol treatment, write in the patient's

enrollment number for this study, and send the data to the study coordinator. DICOM data recorded on CD-R or DVD-R is generally preferred, but films are also acceptable. These should be submitted after discontinuation of the protocol treatment. Imaging data from enrollment will be collected for patients who did not start the protocol treatment.

8.3. Where to Direct Inquiries

1) Eligibility criteria, criteria for adjusting treatments, or imaging assessment, and inquiries requiring clinical judgment: Primary Investigator
2) Enrollment procedures or completion of CRFs: Data Center
3) Serious Adverse Event Reports: Primary Investigator

8.4. Data Management

Data sent to the data center will be anonymized in a linkable fashion at each study site. These data will be strictly managed in accordance with institutional standards. The data center will notify each participating institution of the serial numbers assigned to each enrolled patient. Data collected by the data center will be kept under strict control using these serial numbers.

When study results are presented at academic conferences or published in academic journals, measures will be taken to ensure study subjects cannot be identified. Patient data will be deleted if they withdraw their consent. However, results of analysis will not be deleted if study results have already been published.

If data from this study are used for secondary purposes, such as meta-analysis,

personal information will be kept strictly confidential, and measures will be taken to ensure study subjects cannot be identified.

9. APPENDICES

9.1. Tumor Assessment

Overall response, including assessment of the change in tumor burden inside and outside the liver, will be assessed by investigators by using the Response Evaluation Criteria in Solid Tumors (RECIST)[37]. Assessments will be made based on changes in the diameter of tumors that are observed by contrast CT or MRI until completion or discontinuation of the protocol treatment. The disease control rate (DCR) is defined as the rate of complete response (CR) plus partial response (PR) plus stable disease (SD). The objective response rate (ORR) is defined as the rate of CR plus PR. Tumor response includes assessment of target lesions, nontarget lesions and new lesions. All objective responses will be confirmed at least 4 weeks after the first observation.

In a post hoc analysis, the overall response will be assessed according to the modified RECIST (mRECIST) guidelines[38]. Assessments will be made based on changes in the diameter of surviving tumors deemed viable by contrast CT or MRI. Intrahepatic response, only including assessment of the change in tumor burden inside the liver, will be assessed by RECIST and mRECIST criteria, respectively.

Table 9-1. Assessment of Target Lesion Response: Conventional RECIST and mRECIST Assessment for HCC Following the AASLD-JNCI Guideline

RECIST	mRECIST
CR=Disappearance of all target lesions	CR=Disappearance of any intratumoral arterial enhancement in all target lesions
PR=At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	PR=At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
SD=Any cases that do not qualify for either partial response or progressive disease	SD=Any cases that do not qualify for either partial response or progressive disease
PD=An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	PD=An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started

925 AASLD, American Association for the Study of Liver Diseases; JNCI, Journal of the National
926 Cancer Institute; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation
927 Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD,
928 progressive disease.

929

930 Table 9-2. Overall Response Assessment in mRECIST: Responses for All Possible Combinations

of Tumor Responses in Target and Nontarget Lesions with or without the Appearance of New Lesions

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	IR/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; IR, incomplete response; SD, stable disease; PD, progressive disease.

9.2. Definitions of Eastern Cooperative Oncology Group Performance Status

Table 9-3

Grade	Performance Status
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking

	hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

9.3. Child–Pugh Score*

Table 9-4

Measure	1 point	2 points	3 points
Total bilirubin, μmol/L (mg/dL)	<34 (<2)	34–50 (2–3)	>50 (>3)
Serum albumin, g/dL	>3.5	2.8–3.5	<2.8
Prothrombin time, prolongation (s) or INR	<4.0 <1.7	4.0–6.0 1.7-2.3	> 6.0 >2.3
Ascites	None	Mild (or suppressed with medication)	Moderate to severe (or refractory)
Hepatic encephalopathy†	None	Grade I–II	Grade III–IV

* Child–Pugh A: 5 or 6 points; Child–Pugh B: 7–9 points; Child–Pugh C: >9 points

†Grade of encephalopathy:

Grade 0: Lucid, normal personality, normal neurological test results, normal electroencephalogram

Grade 1: Restlessness, sleep disorder, irritability/agitation, tremors, dysgraphia, 5 cps waves

Grade 2: Lethargy, disorientation (temporal), inappropriateness, difficulty maintaining stable posture, ataxia, slow triphasic waves

Grade 3: Somnolence, confused state, disorientation (spatial), hyperreflexia, rigidity, slow waves

Grade 4: Coma, no personality/unresponsive, cessation of cerebral activity, slow 2–3 cps delta activity

9.4. BCLC Staging System

Table 9-5

	Very early stage (0)	**Early stage (A)**	**Intermediate stage (B)**	**Advanced stage (C)**	**Terminal stage (D)**
Child–Pugh	A	A-B	A-B	A-B	C
Performance status	0	0	0	1-2	>2
Tumor Features	1 HCC <2cm Carcinoma in situ	1 HCC or 3 Nodules <3cm	Multinodular	Portal invasion, N1, M1	Any

N1, lymph node metastasis. M1, extrahepatic spread.

9.5. Functional Assessment of Cancer Therapy–Hepatobiliary Symptom Index 8 questionnaire

Below is a list of statements that other people with your illness have said are important. By circling one number per line, please indicate how true each statement

959 has been for you during the past 7 days.

960 Table 9-6

		Not at all	A little bit	Somewhat	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
CNS7	I have pain in my back	0	1	2	3	4
HI7	I am fatigued	0	1	2	3	4
Hep2	I am bothered by jaundice or yellow color to my skin	0	1	2	3	4
Hep8	I have discomfort or pain in my stomach	0	1	2	3	4

961 ## 9.6. Degree of Portal Vein Tumor Thrombus

962 Table 9-7.

Grade	
Vp1	Portal invasion at the 3rd or more peripheral portal branch
Vp2	Portal invasion at the 2nd portal branch
Vp3	Portal invasion at the 1st portal branch

Vp4	Portal invasion at the main portal branch

The degree of PVTT is according to Clinical Practice Guidelines proposed by the Liver Cancer Study Group of Japan[39].

10. REFERENCES

1. Global Burden of Disease Cancer C, Fitzmaurice C, Allen C, et al: Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol 3:524-548, 2017
2. Park JW, Chen M, Colombo M, et al: Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. Liver Int 35:2155-66, 2015
3. Yu MC, Yuan JM, Govindarajan S, et al: Epidemiology of hepatocellular carcinoma. Can J Gastroenterol 14:703-9, 2000
4. Hung H: Treatment modalities for hepatocellular carcinoma. Curr Cancer Drug Targets 5:131-8, 2005
5. Chan SL, Johnson PJ, Mo F, et al: International validation of the Chinese university prognostic index for staging of hepatocellular carcinoma: a joint United Kingdom and Hong Kong study. Chin J Cancer 33:481-91, 2014
6. Ikai I, Kudo M, Arii S, et al: Report of the 18th follow-up survey of primary liver cancer in Japan. Hepatology Research 40:1043-1059, 2010
7. Llovet JM, Bustamante J, Castells A, et al: Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. Hepatology 29:62-7, 1999
8. Villa E, Moles A, Ferretti I, et al: Natural history of inoperable hepatocellular carcinoma: estrogen receptors' status in the tumor is the strongest prognostic factor for survival. Hepatology 32:233-8, 2000
9. Bruix J, Sherman M: Management of hepatocellular carcinoma: an update. Hepatology 53:1020-2, 2011
10. European Association For The Study Of The L, European Organisation For R, Treatment Of C: EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 56:908-43, 2012
11. Wilhelm SM, Carter C, Tang L, et al: BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res 64:7099-109, 2004
12. Cheng AL, Kang YK, Chen Z, 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 10:25-34, 2009

13. Llovet JM, Ricci S, Mazzaferro V, et al: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359:378-90, 2008

14. Song do S, Song MJ, Bae SH, et al: A comparative study between sorafenib and hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis. J Gastroenterol 50:445-54, 2015

15. Zhang Y, Fan W, Wang Y, et al: Sorafenib With and Without Transarterial Chemoembolization for Advanced Hepatocellular Carcinoma With Main Portal Vein Tumor Thrombosis: A Retrospective Analysis. Oncologist 20:1417-24, 2015

16. Choi JH, Chung WJ, Bae SH, et al: Randomized, prospective, comparative study on the effects and safety of sorafenib vs. hepatic arterial infusion chemotherapy in patients with advanced hepatocellular carcinoma with portal vein tumor thrombosis. Cancer Chemother Pharmacol, 2018

17. Guthoff I, Lotspeich E, Fester C, et al: Hepatic artery infusion using oxaliplatin in combination with 5-fluorouracil, folinic acid and mitomycin C: oxaliplatin pharmacokinetics and feasibility. Anticancer Res 23:5203-8, 2003

18. Ensminger WD, Rosowsky A, Raso V, et al: A Clinical-Pharmacological Evaluation of Hepatic Arterial Infusions of 5-Fluoro-2′-deoxyuridine and 5-Fluorouracil. Cancer Research 38:3784, 1978

19. Ando E, Tanaka M, Yamashita F, et al: Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis: analysis of 48 cases. Cancer 95:588-95, 2002

20. Park JY, Ahn SH, Yoon YJ, et al: Repetitive short-course hepatic arterial infusion chemotherapy with high-dose 5-fluorouracil and cisplatin in patients with advanced hepatocellular carcinoma. Cancer 110:129-37, 2007

21. Ikeda M, Shimizu S, Sato T, et al: Sorafenib plus hepatic arterial infusion chemotherapy with cisplatin versus sorafenib for advanced hepatocellular carcinoma: randomized phase II trial. Ann Oncol 27:2090-2096, 2016

22. Kudo M, Ueshima K, Yokosuka O, et al: Sorafenib plus low-dose cisplatin and fluorouracil hepatic arterial infusion chemotherapy versus sorafenib alone in patients with advanced hepatocellular carcinoma (SILIUS): a randomised, open label, phase 3 trial. Lancet Gastroenterol Hepatol, 2018

23. Bruno PM, Liu Y, Park GY, et al: A subset of platinum-containing chemotherapeutic agents kills cells by inducing ribosome biogenesis stress. Nat Med 23:461-471, 2017

24. Dzodic R, Gomez-Abuin G, Rougier P, et al: Pharmacokinetic advantage of intra-arterial hepatic oxaliplatin administration: comparative results with cisplatin using a rabbit VX2 tumor model. Anticancer Drugs 15:647-50, 2004

25. Tesniere A, Schlemmer F, Boige V, et al: Immunogenic death of colon cancer cells treated with oxaliplatin. Oncogene 29:482-91, 2010

26. Apetoh L, Ghiringhelli F, Tesniere A, et al: Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nat Med 13:1050-9, 2007

27. Groot Koerkamp B, Sadot E, Kemeny NE, et al: Perioperative Hepatic Arterial Infusion Pump Chemotherapy Is Associated With Longer Survival After Resection of Colorectal Liver Metastases: A Propensity Score Analysis. J Clin Oncol 35:1938-1944, 2017

28. Allard MA, Sebagh M, Baillie G, et al: Comparison of complete pathologic response and hepatic injuries between hepatic arterial infusion and systemic administration of oxaliplatin in patients with colorectal liver metastases. Ann Surg Oncol 22:1925-32, 2015

29. Qin S, Bai Y, Lim HY, et al: Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. J Clin Oncol 31:3501-8, 2013

30. Lyu N, Kong Y, Mu L, et al: Hepatic arterial infusion of oxaliplatin plus fluorouracil/leucovorin vs. sorafenib for advanced hepatocellular carcinoma. J Hepatol 69:60-69, 2018

31. He MK, Zou RH, Li QJ, et al: Phase II Study of Sorafenib Combined with Concurrent Hepatic Arterial Infusion of Oxaliplatin, 5-Fluorouracil and Leucovorin for Unresectable Hepatocellular Carcinoma with Major Portal Vein Thrombosis. Cardiovasc Intervent Radiol, 2018

32. Ma SQ, Cao BR, Zhang H, et al: The lack of Raf-1 kinase feedback regulation enhances antiapoptosis in cancer cells. Oncogene, 2016

33. Malofeeva EV, Domanitskaya N, Gudima M, et al: Modulation of the ATPase and transport activities of broad-acting multidrug resistance factor ABCC10 (MRP7). Cancer Res 72:6457-67, 2012

34. Lewin M, Fartoux L, Vignaud A, et al: The diffusion-weighted imaging perfusion fraction f is a potential marker of sorafenib treatment in advanced hepatocellular carcinoma: a pilot study. Eur Radiol 21:281-90, 2011

35. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228-47, 2009

36. Yount S, Cella D, Webster K, et al: Assessment of patient-reported clinical outcome in pancreatic and other hepatobiliary cancers: the FACT Hepatobiliary Symptom Index. J Pain Symptom Manage 24:32-44, 2002

37. Tsuchida Y, Therasse P: Response evaluation criteria in solid tumors (RECIST): new guidelines. Med Pediatr Oncol 37:1-3, 2001

38. Lencioni R, Llovet JM: Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 30:52-60, 2010

39. Kudo M, Matsui O, Izumi N, 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 3:458-68, 2014

Statistical analysis plan

The primary dataset for efficacy analyses is defined as all randomized patients (intention-to-treat analysis). The safety analysis comprised all randomized patients who received at least one dose of study treatment. There were no interim analyses in this study.

For baseline data, means and standard deviations were used for normally distributed data, and medians and interquartile ranges were used for data that are not normally distributed. The baseline characteristics were compared by Student's t-tests or chi-square tests. Survival outcomes of overall survival, overall survival stratified by portal vein invasion grade, progression-free survival, and intrahepatic progression-free survival were calculated with the Kaplan-Meier method and compared by log-rank tests. The response rates will be compared using Chi-square test or Fisher's exact test, as appropriate. Any factors that were statistically significant at P less than 0.10 in the univariate analysis were candidates for entry into a multivariable Cox proportional hazards model. Hazard ratio and 95% confidence interval will be calculated for the SoraHAIC group relative to the sorafenib group using a Cox proportional-hazards model. All P values were two-sided, with P values less than 0.05 considered significant. The statistical package used to perform analyses was SAS, version 9.0 (SAS Institute, Cary, NC, USA).