

Study title

Randomized phase 2/3 trial comparing **S**orafenib versus **T**rans**A**rterial chemoembolization plus external beam **R**adio**T**herapy in patients with hepatocellular carcinoma showing major vascular invasion (**START**)

Protocol Version	3.4
Clinical Study Type	Investigator-sponsored randomized controlled trial
Principal Investigator	Young-Suk Lim, M.D., Ph.D. Professor, Department of Gastroenterology & Liver Center Asan Medical Center, University of Ulsan College of Medicine
Clinical phase	Phase 2/3 (Definition by US National Cancer Institute)

Confidentiality

The information contained in this document is provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an applicable Institutional Review Board or Independent Ethics Committee. The information is only to be used by you in connection with authorized clinical studies described in the protocol. You should not disclose any of the information to others without written authorization from the investigator, except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

Protocol Synopsis

Study Title	Randomized phase 2/3 trial comparing <u>S</u> orafenib versus <u>T</u> rans <u>A</u> rterial chemoembolization plus external beam <u>R</u> adio <u>T</u> herapy in patients with hepatocellular carcinoma showing major vascular invasion (START)
Trial sites and investigators-	Professor Young-Suk Lim, Department of Gastroenterology, Asan Medical Center
Clinical phase	Phase 2/3
Study design	An investigator-sponsored, prospective randomized controlled trial
Number of Subjects planned	90 subjects in total - 45 subjects in sorafenib arm - 45 subjects in transarterial chemoembolization (TACE) plus radiotherapy (RT) arm
Target population	Patients with hepatocellular carcinoma (HCC) showing major vascular invasion (including, portal vein, hepatic vein, and/or inferior vena cava)
Objectives	Primary Study Objective : To compare the progression-free survival rate at 12 weeks between the subjects treated with sorafenib and those with TACE+RT Secondary Study Objectives 1) progression-free survival at 24 weeks 2) radiologic response rates at 12- and 24-weeks 3) treatment-crossover rates at 12 and 24 weeks 4) time to disease progression during up to 4-years of follow-up 5) time to treatment-crossover during up to 4-years of follow-up 6) overall patient survival during up to 4-years of follow-up
Duration of study planned	From the date of IRB approval to 31 DEC 2017
Study procedures	1) Diagnosis of HCC according to the AASLD practice guideline (published in 2011) 2) Selection of the subjects according to the eligibility criteria 3) Examination of the required and optional medical tests 4) Allocation into each treatment arm (sorafenib or TACE plus radiotherapy) by randomization 5) After the treatment, the clinical results that correspond to the above-mentioned study objectives are evaluated and analyzed through the follow-up method
Eligibility criteria (Inclusion /Exclusion)	# Inclusion criteria: Patients with HCC meeting all of following criteria; 1) Older than 20 years of age 2) Child-Pugh A hepatic function 3) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1 4) The first diagnosis of HCC with major vascular invasion 5) The major vascular invasion - an intraluminal filling defect adjacent to HCC in portal vein, hepatic vein, or inferior vena cava (IVC) - an enhanced filling defect on arterial phase and a washout on portal/delayed phase - reserved unilateral portal blood flow at least in partial 6) HCC > 1 cm and the extent of tumor < 50% of liver volume 7) Adequate hematologic function - hemoglobin \geq 8.5 g/dL - absolute neutrophil count \geq 750/mm ³ - platelet \geq 30,000/mm ³ - prothrombin time international normalized ratio \leq 1.5

	<p>8) Adequate hepatic and renal function</p> <ul style="list-style-type: none">- aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 10 x upper limit of normal (ULN)- albumin \geq 2.8 g/dL- total bilirubin \leq 3 mg/dL- serum creatinine < 1.5 mg/dL <p>6) Patient understand the clinical trial protocol and is willing to provide written informed consent to participate in the study</p> <p># Exclusion criteria:</p> <p>Patients will be excluded from the study for any of the following reasons:</p> <ol style="list-style-type: none">1) Treatment history of prior TACE, radiotherapy, or sorafenib2) Extrahepatic metastasis3) A complete obstruction of portal flow or hepatic outflow4) Extent of tumor > 50% of liver volume5) Uncontrolled ascites and hepatic encephalopathy6) History of liver or other organ transplantation7) Active gastric or duodenal ulcer within 3 months8) Uncontrolled severe medical comorbidity9) Infection with human immunodeficiency virus10) Pregnant or breastfeeding women11) Women of childbearing ages unless using effective contraception12) Double primary malignancy (a history of treated malignancy (other than HCC) is allowable if the patient's malignancy has been in complete remission, off chemotherapy and without additional surgical intervention, during the preceding two years.)13) Any other condition which, in the opinion of the Investigator, would make the patient unsuitable for enrollment or could interfere with the completing the study.
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Statistical Analyses	Sample Size Justification Sample size required for this study was estimated with following assumptions, - Estimated progression-free survival (PFS) rates at 12 weeks for sorafenib group = 50% - Estimated PFS rates at 12 weeks for TACE+RT group = 80% - Power (1-beta) = 0.8 - Alpha error = 0.05 - Drop-out rate = 10% - The primary endpoint is PFS rates at 12 weeks in all randomized subjects. For estimating the difference in PFS rates between arms, the sample size was 90 subjects in total and 45 subjects per arm, based on a test for equality of proportions. Statistical Analytic Plan The primary dataset for efficacy analyses is defined as all randomized patients (intention-to-treat [ITT] analysis). Progression is defined as progressive disease (PD) by independent radiologic review according to RECIST criteria (version 1.1) or death from any cause. Patients who discontinue the initially-assigned treatment without PD or death will be censored at the time of discontinuation. Efficacy analyses will be performed comparing the originally randomized treatment groups, sorafenib and TACE+RT. Safety profiles will be evaluated in the modified ITT population including the patients who received at least one dose of sorafenib or at least one session of TACE treatment. Interim analysis is not planned. Survival curves for time-to-event variables, such as PFS rate, time to radiologic progression, time to treatment-crossover, and overall survival rate, will be determined by the Kaplan-Meier estimation, and the log-rank test will be used for treatment comparisons. The response rates at 12- and 24-weeks in the treatment groups will be compared using Chi-square test or Fisher's exact test, as appropriate. An exploratory Cox proportional-hazards model will be used to evaluate the interaction between important baseline characteristics and the effect of treatments on overall survival. Hazard ratio (HR) and 95% confidence interval (CI) will be calculated for the TACE+RT group relative to the sorafenib group using a Cox proportional-hazards model. The tests performed will be 2-sided, and <i>P</i> values <0.05 will be considered statistically significant. All statistical analyses will be performed using SPSS Statistics version 21 (IBM, Armonk, NY).
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Time & Event Table

Assessment / Procedure	Screening	Randomization	Day1	Evaluation		End of Treatment	Overall survival
	Random ≤1 week	W0	Day1 (Random ≤1 week)	W6 ±7d	W12 ±14d	W24 ± 14d	Every 3 M ± 1 M
Informed Consent	X						
Medical History	X		X	X	X	X	X
Inclusion/Exclusion Criteria	X	X					
Physical Examination ¹	X		X	X	X	X	X
Randomization		X ⁹					
Sorafenib vs TACE+RT ¹¹			X	X	X	X ⁸	X
Vital signs ²	X		X	X	X	X	X
Hematology ³	X		X	X	X	X	X
Chemistry ⁴	X		X	X	X	X	X
Prothrombin Time	X		X	X	X	X	X
HBsAg/Anti-HCV ¹⁰	X						
Alpha-fetoprotein/PIVKA-II			X	X	X	X	X
Liver dynamic CT/MRI ⁵	X			X	X	X	X
Chest X-ray	X			X ⁷	X ⁷	X ⁷	X
Serum for storage			X	X	X	X	X
Genomic DNA sample storage ⁶			X				
Compliance check				X	X	X	X
Concomitant medications	X		X	X	X	X	X
Adverse event				X	X	X	X

1. Physical examination: to check the performance status, other significant signs
2. Vital signs: blood pressure, pulse rate, body weight, and height (The height is scheduled to be measured once at the screening)
3. Hematology: hemoglobin, red blood cell (RBC), white blood cell and differential white blood cell count, and platelet count
4. Chemistry: Sodium, potassium, BUN, creatinine, total protein, albumin, AST, ALT, ALP, total/direct bilirubin, amylase, phosphorus, calcium, and creatinine phospho-kinase (CPK)

5. If there are standard dynamic 4-phase multidetector computed tomography (CT) or magnetic resonance images (MRI) that was performed within 2 weeks before screening, it is applicable
6. Either peripheral blood mononuclear cell (PBMC) or genomic DNA extract
7. This test is carried out according to the judgement of the investigator or the symptoms of the patient after screening
8. Curative surgical resection is allowed after 24 weeks for patients with partial response.
9. Screening and randomization can be done on the same day.
10. Available if the test results are within 2 weeks of screening.
11. In the case of disease progression (target lesions or non-target lesions), the assigned treatment can be switched over to the other treatment for a chance of salvage treatment at the discretion of the investigator

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1. Study Title and Phase

1.1. Study Title

Randomized phase 2/3 trial comparing Sorafenib versus TransArterial chemoembolization plus external beam RadioTherapy in patients with hepatocellular carcinoma with major vascular invasion (START)

1.2. Study Phase

Phase 2/3 (Definition by US National Cancer Institute)

2. Study Site and Investigator

	Investigator	Address
Asan Medical Center	Young-Suk Lim	88, Olympic-ro 43-gil, Songpa-gu, Seoul, Korea

3. Study Objectives and Background

3.1. Study Objectives

The objective of this study is to compare the efficacy and safety of the combined treatment of transarterial chemoembolization (TACE) plus radiotherapy (RT) compared with sorafenib treatment for hepatocellular carcinoma (HCC) with major vascular invasion.

3.1.1. Primary Endpoint

- progression-free survival rate at 12 weeks

3.1.2. Secondary Endpoints

- 1) progression-free survival at 24 weeks
- 2) radiologic response rates at 12- and 24-weeks
- 3) treatment-crossover rates at 12 and 24 weeks
- 4) time to disease progression during up to 4-years of follow-up
- 5) time to treatment-crossover during up to 4-years of follow-up
- 6) overall patient survival during up to 4-years of follow-up

3.2. Background

HCC is the sixth most common cancer worldwide and the second most common cause of cancer-related death (1). The greatest burden of HCC comes from developing countries, with 80% of occurrences originating in Asia and Africa. However, HCC has been the fastest-rising cause of cancer-related deaths in Western countries during the past two decades and is expected to increase further in the next decade (2-4).

Approximately 50% of the patients with HCC are already diagnosed as locally advanced HCC with major vascular invasion at the time of diagnosis. Portal vein, hepatic vein, or inferior vena cava tumor thrombus often cause extensive intrahepatic dissemination of the tumor through these vessels, can decrease blood supply to the normal liver, and finally cause portal hypertension resulting in the rupture of collateral vessels, ascites, hepatic encephalopathy, and deteriorating liver function (5,6). This, in turn, may limit further treatment options in patients with HCC. The only evidence-based treatment option for these patients is sorafenib in many guidelines for HCC, including that of the American Association for the Study of Liver Disease (AASLD) (Figure 1) (7).

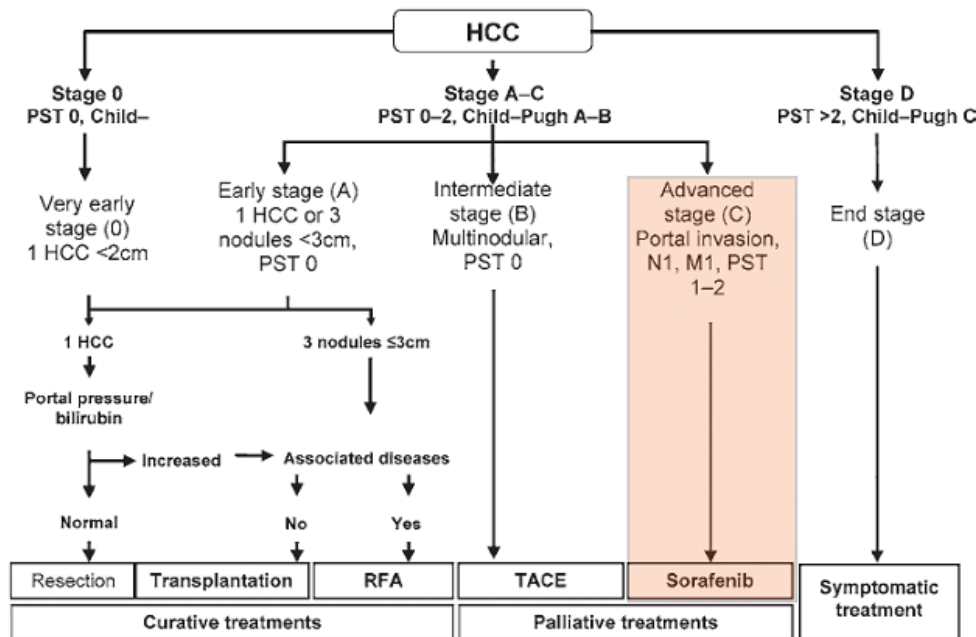


Figure 1. Treatment allocation for HCC according to AASLD practice guideline

Although sorafenib has been approved as a standard systemic therapy for patients with advanced HCC, the objective response rate is somewhat disappointing at 2-5% (8,9). Furthermore, median time to progression was only 2.8 months and the prolongation of patients' survival was 2.5 months in a study of the Asia-Pacific region (9). Therefore, even after the introduction of sorafenib in Korea in 2009, the frequency of the use of this agent as a first-line therapy for advanced HCC has not been high.

Recent improvement in radiotherapy techniques, including 3-dimensional conformal radiotherapy (3D-CRT) and image-guided radiotherapy, as well as information on partial volume liver tolerance, has allowed the delivery of radiation doses to these tumors that are higher than previously thought possible, allowing radiotherapy to be used as an alternative treatment option for HCC (10,11). One of the primary indications for radiotherapy has been the major vascular invasion of HCC; and good responses and promising outcomes have been obtained usually combined with TACE (12-15). Because major vascular invasion is a major obstacle to performing TACE, focal field radiotherapy targeting the vascular invasion, may be a good treatment option. The rationale for this combined approach is that focused on vascular invasion may decrease intravascular tumor growth and maintain portal blood flow, allowing the maintenance of normal liver function, limiting intrahepatic tumor spread, and thereby allowing additional TACE (13,16). However, evidence level to support combined treatment with TACE plus radiotherapy in the patients is low, and there have been no randomized trials.

Thus, we conduct a randomized phase 2 trial comparing combined TACE plus external beam radiotherapy with sorafenib with HCC and major vascular invasion.

4. Study Design

Prospective randomized, active-controlled, open-label, single-center trial

5. Projected Duration of the Study

From the date of IRB approval to 31 DEC 2017

Initial assessment period: 24 weeks from randomization

Follow-up assessment period: up to 4 years from randomization

The duration of the study could be extended according to the enrollment rate.

6. Target Disease

- * Patients with HCC showing major vascular invasion
 - The confirmation of HCC is based on the following criteria (1 or 2+3)
 - (1) histologic confirmation
 - (2) a typical image finding of HCC in 4-phase multi-detector computed tomography (CT) or dynamic contrast enhanced magnetic resonance imaging (MRI) (nodule >1 cm with arterial hypervascularity and portal/delayed-phase washout)
 - (3) the presence of risk factors including hepatitis B virus (HBV), hepatitis C virus (HCV), and cirrhosis
 - The presence of vascular invasion is assessed by dynamic CT or MRI using the following criteria (1+2):
 - (1) an intraluminal filling defect adjacent to the primary tumor in portal vein, hepatic vein, and/or inferior vena cava
 - (2) an enhancement of the filling defect on arterial phase and a washout on portal/delayed phases.

7. Study Subjects Criteria (Inclusion/Exclusion)

7.1. Inclusion criteria

- * Patients with HCC meeting all of following criteria;
 - (1) Older than 20 years of age
 - (2) Child-Pugh A hepatic function (See Appendix 2)
 - (3) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1 (See Appendix 1)
 - (4) The first diagnosis of HCC with major vascular invasion
 - main portal vein thrombus with maintaining adequate blood flow
 - (5) HCC > 1 cm and the extent of tumor < 50% of liver volume
 - (6) Adequate hematologic function
 - hemoglobin \geq 8.5 g/dL
 - absolute neutrophil count \geq 750/mm³
 - platelet \geq 30,000/mm³
 - prothrombin time international normalized ratio \leq 1.5
 - (7) Adequate hepatic and renal function
 - aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 10 x upper limit of normal (ULN)
 - albumin \geq 2.8 g/dL
 - total bilirubin \leq 3 mg/dL
 - serum creatinine < 1.5 mg/dL
 - (8) Patient understand the clinical trial protocol and is willing to provide written informed consent to participate in the study

7.2. Exclusion criteria

- * Patients will be excluded from the study for any of the following reasons:
 - (1) Treatment history of prior TACE, radiotherapy, or sorafenib
 - (2) Extrahepatic metastasis
 - (3) A complete obstruction of portal flow or hepatic outflow
 - (4) Extent of tumor > 50% of liver volume
 - (5) Uncontrolled ascites and hepatic encephalopathy
 - (6) History of liver transplantation
 - (7) Active gastric or duodenal ulcer within 3 months
 - (8) Uncontrolled sever medical comorbidity

- (9) Infection with human immunodeficiency virus
- (10) Pregnant or breastfeeding women
- (11) Women of childbearing ages unless using effective contraception
- (12) Double primary malignancy (a history of treated malignancy (other than HCC) is allowable if the patient's malignancy has been in complete remission, off chemotherapy and without additional surgical intervention, during the preceding two years)
- (13) Any other condition which, in the opinion of the Investigator, would make the patient unsuitable for enrollment or could interfere with the completing the study

8. Study Procedures and Methods

8.1. Assignment of subjects

All eligible patients are randomly assigned to receive 400 mg twice a day of sorafenib or combined TACE plus RT during the study period.

8.2. Method of assigning patients to treatment groups and randomization

- (1) Sorafenib group: sorafenib (800 mg/day)
- (2) TACE plus RT group
- (3) The randomization process
 - After making the four blocks-sized randomization list, we will make it be connected with the electronic Case Report Form (eCRF). Eligible subjects for the study will be randomized in a 1:1 ratio to each group, using the Interactive Web Response System (IWRS). The IWRS will be integrated with the electronic data capture (EDC) system (Medrio, Inc, San Francisco, CA, eClinical & Electronic Data Capture in the Cloud. Available at <http://medrio.com/>). Site personnel (Principal Investigator, Sub-Investigator or Study Coordinator) will access the IWRS through the EDC system. Patient randomization number and assignment to treatment arm will be provided by this IWRS/EDC system.
- (4) Allocated patients
 - Number of total population – 90 (sorafenib: 45, TACE+radiotherapy: 45)
- (5) Randomization method
 - As an open-label trial, all the doctors and patients know assigned treatments.
- (6) Stratification
 - Stratification will not be performed during randomization process.

8.3 Treatment

8.3.1. Sorafenib

1) Medication of sorafenib

- Sorafenib is administered orally as a standard 400 mg dose twice daily (800 mg/day) as a continuous dose.
- Sorafenib will be taken 1 hour before meals or at least 2 hours after meals.
- Sorafenib medication is continued until disease progression unacceptable toxicity, death, withdrawal of consent, or decision by the investigator.

2) Dose modification and treatment interruptions

- Treatment interruptions and dose reductions (first 200 mg twice daily, then 200 mg once daily) are allowed for drug-related toxicity.
- The reduced dose can be re-escalated to the standard dose according to the investigator's discretion.

- The treatment can be suspended in the case of complete response at the discretion of the investigator.

8.3.2. Transarterial chemoembolization

1) TACE procedure

- Selective catheterization of the feeding artery will be performed using a 2.0 to 2.8 F microcatheter.
- 2 mg/kg cisplatin (Dong-A Pharmaceutical, Korea) will be infused as the chemotherapeutic agent.
- The feeder arteries will be then subsequently embolized by using an emulsion of 5 to 10 mL of cisplatin and iodized oil (Lipiodol Ultra-Fluide; Laboratoire Guerbet, Aulnay-sous-Bois, France) mixture, and finally by absorbable gelatin sponge (Gelfoam; Upjohn, Kalamazoo, MI).
- The feeder arteries will be embolized until arterial flow stasis is achieved.
- To minimize the risk of post-TACE hepatic decompensation, gelatin sponge particle embolization will not be performed according to the severity of portal blood flow impairment at the discretion of the investigator.
- TACE will be repeated every 6 weeks for the first 24 weeks, and every 6 to 8 weeks thereafter.
- TACE can be suspended if there is no longer residual viable HCC at the discretion of the investigator.

8.3.3. External beam radiotherapy

1) Simulation process

- Patients are immobilized with a vacuum cushion in the supine position before CT simulation.
- Free-breathing 4-dimensional (4D) CT scanning is performed using a 16-slice CT system.
- To analyze the patients' breathing patterns, a Real-time Position Management respiratory gating system is used.
- All CT datasets are sorted into 10-phase bins that corresponded to the respiratory phase, using 4D imaging software.

2) Delineation of the target volume and organs at risk

- Every contouring is delineated on end-expiratory phase (phase 50%) CT images.
- The gross tumor volume (GTV) includes vascular invasion and a 2-cm margin into the contiguous HCC. The GTV can consist of the entire HCC and vascular invasion at the discretion of the investigator.
- The clinical target volume (CTV), which is an additional margin for the subclinical tumor extension, is not considered as a target volume in this study.
- The internal target volume (ITV) is delineated as the sum of the individual GTVs, as defined within the gated phases of respiration (usually 30-70% phase).
- The planning target volume (PTV) is expanded to include a 0.7-cm margin from the ITV.
- Organs at risk (OARs): the whole and normal liver, both kidneys, spinal cord, duodenum, and stomach are delineated and 3-dimensionally reconstructed.

3) Treatment planning

- 3D-conformal radiotherapy technique is used to determine target volumes, radiation ports, and dose prescriptions by using a 3D radiotherapy planning system.
- Dose-volume histogram (DVH) is used to define the tumor dose and dose for normal organs.
- Either 6 MV, 10 MV, or 15 MV photon energies can be used for treatment planning.

- Static radiation beams are primarily used for treatment. (Intensity modulated radiotherapy is not a primary treatment method in this study.)
- The dose per fraction to the PVT is 2.5 to 3 Gy at 5 fractions per week.
- The target dose is 45 Gy, however, the total dose can be reduced as low as 30 Gy according to the liver function, liver volumes, or the maximum dose to the stomach/duodenum during the planning process.
- The general prescription guideline is as follows:
 - the normal liver treated with more than 50% of prescribed dose should be less than 50% of the normal liver volume ($V_{50\%} < 50\%$).
 - the volume of the normal liver that was damaged by irradiation is defined as the fraction volume of normal liver that received more than 30 Gy ($V_{30\text{ Gy}}$), with no more than 30% of the normal liver exposed to more than 30 Gy ($V_{30\text{ Gy}} \leq 30\%$).
 - the maximum dose for the stomach or duodenal walls are 30 Gy.

4) Radiation therapy in treatment room

- Radiation beams are delivered by a linear accelerator.
- Actual beam delivery is performed with a respiratory-gated beam delivery technique.
- Image guidance is performed in two stages before administering each fraction of radiotherapy using On-Board Imager.
 - First, cone-beam CT is done and 3D matching is performed.
 - Second, gated fluoroscopy is performed in the anterior-posterior and lateral directions to confirm the internal surrogate positions at the end-exhale phase.
- During radiation beam delivery, respiratory patterns is monitored by the Real-time Position Management system.

5) Prophylactic anti-viral therapy

- Patients, who have HBV infection and do not use antiviral drugs, are prescribed preventive antiviral therapies at the discretion of the investigator to prevent the HBV reactivations after TACE and radiotherapy.

8.4 Evaluation Assessments

8.4.1. Time table of the study

Assessment / Procedure	Screening	Randomization	Day1	Evaluation		End of Treatment	Overall survival
	Random ≤1 week	W0	Day1 (Random ≤1 week)	W6 ±7d	W12 ±14d	W24 ± 14d	Every 3 M ± 1 M
Informed Consent	X						
Medical History	X		X	X	X	X	X
Inclusion/Exclusion Criteria	X	X					
Physical Examination ¹	X		X	X	X	X	X
Randomization		X ⁹					
Sorafenib vs TACE+RT ¹¹			X	X	X	X ⁸	X
Vital signs ²	X		X	X	X	X	X
Hematology ³	X		X	X	X	X	X
Chemistry ⁴	X		X	X	X	X	X
Prothrombin Time	X		X	X	X	X	X
HBsAg/Anti-HCV ¹⁰	X						
Alpha-fetoprotein/PIVKA-II			X	X	X	X	X
Liver dynamic CT/MRI ⁵	X			X	X	X	X
Chest X-ray	X			X ⁷	X ⁷	X ⁷	X
Serum for storage			X	X	X	X	X
Genomic DNA sample storage ⁶			X				
Compliance check				X	X	X	X
Concomitant medications	X		X	X	X	X	X
Adverse event				X	X	X	X

1. Physical examination: to check the performance status, other significant signs

2. Vital signs: blood pressure, pulse rate, body weight, and height (The height is scheduled to be measured once at the screening)

3. Hematology: hemoglobin, red blood cell (RBC), white blood cell and differential white blood cell count, and platelet count

4. Chemistry: Sodium, potassium, BUN, creatinine, total protein, albumin, AST, ALT, ALP, total/direct bilirubin, amylase, phosphorus, calcium, and creatinine phospho-kinase (CPK)
5. If there are standard dynamic 4-phase multidetector computed tomography (CT) or magnetic resonance images (MRI) that was performed within 2 weeks before screening, it is applicable
6. Either peripheral blood mononuclear cell (PBMC) or genomic DNA extract
7. This test is carried out according to the judgement of the investigator or the symptoms of the patient after screening
8. Curative surgical resection is allowed after 24 weeks for patients with partial response.
9. Screening and randomization can be done on the same day.
10. Available if the test results are within 2 weeks of screening.
11. In the case of disease progression (target lesions or non-target lesions), the assigned treatment can be switched over to the other treatment for a chance of salvage treatment at the discretion of the investigator

8.4.2. Study procedures

1) Screening (Randomization \leq 1 week)

- Review of inclusion/exclusion criteria
- Obtain written informed consent
- Basic information, Medical history
- Complete physical examination and vital signs
- Evaluate concomitant medications
- Evaluate clinical imaging (Liver dynamic- and pelvic-CT, chest CT, whole body bone scan)
- Laboratory assessments (Hematology, Chemistry, Prothrombin Time, HBsAg/Anti-HCV, U/A)

2) Randomization (Week 0)

- Confirmation of inclusion/exclusion criteria
- Allocation to treatment group

3) Day 1 (Randomization \leq 1 week)

- Complete physical examination and vital signs
- Confirm the treatment allocation
- Laboratory assessments (Hematology, Chemistry, PT, serum for storage, Alpha-fetoprotein/PIVKA-II Genomic DNA sample for storage)
- Evaluate concomitant medications
- Treatment start by allocation (sorafenib medication or TACE procedure)

4) Week 6 (\pm 7 days)

- Complete physical examination and vital signs
- Liver dynamic CT/MRI, Chest X-ray
- Laboratory assessments (Hematology, Chemistry, PT, Alpha-fetoprotein/PIVKA-II, serum for storage)
- Evaluate concomitant medications
- Assessment of adverse events
- Study drugs dispensing and assessment of medication adherence

5) Week 12 (\pm 14 days)

- Complete physical examination and vital signs
- Liver dynamic CT/MRI, Chest X-ray
- Laboratory assessments (Hematology, Chemistry, PT, Alpha-fetoprotein/PIVKA-II, serum for

storage)

- Evaluate concomitant medications
- Assessment of adverse events
- Study drugs dispensing and assessment of medication adherence

6) Week 18 (± 14 days)

- Complete physical examination and vital signs
- Liver dynamic CT/MRI, Chest X-ray
- Laboratory assessments (Hematology, Chemistry, PT, Alpha-fetoprotein/PIVKA-II, serum for storage)
- Evaluate concomitant medications
- Assessment of adverse events
- Study drugs dispensing and assessment of medication adherence

7) Week 24 (± 14 days)

- Complete physical examination and vital signs
- Liver dynamic CT/MRI, Chest X-ray
- Laboratory assessments (Hematology, Chemistry, PT, Alpha-fetoprotein/PIVKA-II, serum for storage)
- Evaluate concomitant medications
- Assessment of adverse events
- Study drugs dispensing and assessment of medication adherence
- Assessment of treatment summary (sorafenib or TACE or radiotherapy or other additional treatments)

8) Follow-up, q 6-8 weeks, up to 4 years

- Complete physical examination and vital signs
- Liver dynamic CT/MRI, Chest X-ray
- Laboratory assessments (Hematology, Chemistry, PT, Alpha-fetoprotein/PIVKA-II, serum for storage)
- Evaluate concomitant medications
- Assessment of adverse events
- Study drugs dispensing and assessment of medication adherence
- Assessment of treatment summary (sorafenib or TACE or radiotherapy or other additional treatments)

8.4.3. Evaluation of the subjects

1) Regular evaluation

- All patients undergo regular laboratory assessments according to the protocol.
- For response evaluation, dynamic liver CT is checked in every 6 weeks after treatment start.
- Dynamic liver MRI can be optionally used for further response evaluation.
- In case of tumor progression or recurrence, the timing of the examination may be frequently checked at the discretion of the investigator.
- More examinations (e.g. chest x-ray, chest CT, whole body bone scan, abdominal ultrasonography, PET scan, etc.) can be performed if needed.

2) Response evaluation

- The standard images for response evaluation is dynamic liver CT.
- Tumor measurements and response evaluation will be conducted by an independent radiologist

based on liver dynamic CT images at screening and every 6 weeks after randomization.

- If it is difficult to evaluate the response with liver CT, dynamic liver MRI can be performed for more accurate judgment.
- Evaluation of tumor response by dynamic CT or MRI is performed based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (See Appendix 3) at an evaluation point in the study protocol.
- If the patient is not diagnosed as tumor progression and died unrelated to treatment toxicity, it is defined as progressive disease separately from RECIST by protocol-defined criteria.

9. Safety Evaluation

As sorafenib, TACE, and radiotherapy are ones of the standard treatment of HCC, their side effects and adverse events have been known well. Therefore, investigators will individually evaluate the well-known side effect, common side effects and unpredictable side effects that have not been reported yet.

9.1. Definition of Adverse Events

All adverse events will be assessed and recorded on the AE CRF page by the investigator. An adverse event (AE) is any untoward medical occurrence in a study patient, regardless of the potential relation with the use of a study drugs.

9.2. Assessment of AEs

All AEs and SAEs occurring after initiation of clinical trial and until the end of follow-up/final visit should be recorded in the CRF.

9.3. Severe Adverse Events (SAEs)

A serious adverse event is any untoward medical occurrence that, at any dose:

- Death or life-threatening events
- Requiring hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Development of fetal anomalies

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered a SAE

9.4. Reporting Procedure

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

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

9.5. Intensity of AE

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

Grade	Score	
Mild	1	Symptoms causing no or minimal interference with usual social & functional activities.
Moderate	2	Symptoms causing greater than minimal interference with usual social & functional activities
Severe	3	Symptoms causing inability to perform usual social & functional activities
Life-threatening	4	Symptoms causing inability to perform basic self-care functions OR Medical OR operative intervention indicated to prevent permanent impairment, persistent disability, or death

9.6 Causal Relationship of AE

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

1) Definitely related

- Event or laboratory test abnormality, with plausible temporal relationship to the drug intake or intervention
- Cannot be explained by the disease or other drugs
- Response by the withdrawal of the study drug (pharmacologically, pathologically)
- Event definitive pharmacologically or clinically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon)

2) Probably related

- Event or laboratory test abnormality, with reasonable time relationship to drug intake or intervention
- Unlikely to be attributed by the disease or other drugs
- Response to withdrawal clinically reasonable

3) Possibly related

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

4) Probably not related

- Event or laboratory test abnormality, could be explained by the disease or other drugs than the study drug intake or intervention
- Response to withdrawal unsatisfactory or vague

5) Definitely not related

- Event or laboratory test abnormality, with a temporal relationship to the drug intake or intervention unlikely
- The disease or other drugs provide plausible explanations

6) Unknown

- Cannot be judged because information is insufficient or contradictory
- Data cannot be supplemented or verified

10. Statistical Considerations

10.1. Sample Size Justification

* Sample size required for this study was estimated with following assumptions,

- Estimated PFS rates at 12 weeks for sorafenib group according to the Asia-Pacific sorafenib trial (9)

= 50%

- Estimated PFS rates at 12 weeks for TACE plus radiotherapy group according to our previous observational study (15) = 80%
- Power (1-beta) = 0.8
- Alpha error = 0.05
- Drop-out rate = 10%

* The primary endpoint is PFS rates at 12 weeks in all randomized subjects. For estimating the difference in PFS rates between arms, the sample size was 90 subjects in total and 45 subjects per arm, based on a test for equality of proportions.

Two Independent Proportions (Null Case) Power Analysis Numeric Results of Tests Based on the Difference: P1 - P2
H0: P1-P2=0. H1: P1-P2=D1<>0. Test Statistic: Z test with pooled variance

	Sample Size Grp 1	Sample Size Grp 2	Prop H1 Grp 1 or Trtmnt P1	Prop Grp 2 or Control P2	Diff if H0 D0	Diff if H1 D1	Target Alpha	Actual Alpha	Beta
Power	45	45	0.7500	0.5000	0.0000	0.2500	0.1000	0.1133	0.1951

Note: exact results based on the binomial were only calculated when both N1 and N2 were less than 100.

Report Definitions

'Power' is the probability of rejecting a false null hypothesis. It should be close to one. 'N1 and N2' are the sizes of the samples drawn from the corresponding populations.

'P1' is the proportion for group one under H1. This is the treatment or experimental group. 'P2' is the proportion for group two. This is the standard, reference, or control group

'D1: Diff. if H1' is the difference P1 - P2 assuming the alternative hypothesis. 'Target Alpha' is the probability of rejecting a true null hypothesis that was desired. 'Actual Alpha' is the value of alpha that is actually achieved.

'Beta' is the probability of accepting a false null hypothesis.

Summary Statements

Group sample sizes of 45 in group one and 45 in group two achieve 80% power to detect a difference between the group proportions of 0.2500. The proportion in group one (the treatment group) is assumed to be 0.5000 under the null hypothesis and 0.7500 under the alternative hypothesis. The proportion in group two (the control group) is 0.5000. The test statistic used is the two-sided Z test with pooled variance. The significance level of the test was targeted at 0.0500. The significance level actually achieved by this design is 0.0528.

10.2. Statistical Analytic Plan

The primary dataset for efficacy analyses is defined as all randomized patients (intention-to-treat [ITT] analysis). Progression is defined as progressive disease (PD) by independent radiologic review according to RECIST criteria (version 1.1) or death from any cause. Patients who discontinue the initially-assigned treatment without PD or death will be censored at the time of discontinuation. Efficacy analyses will be performed comparing the originally randomized treatment groups, sorafenib and TACE+RT. Safety profiles will be evaluated in the modified ITT population including the patients who received at least one dose of sorafenib or at least one session of TACE treatment. Interim analysis is not planned.

Survival curves for time-to-event variables, such as PFS rate, time to radiologic progression, time to treatment-crossover, and overall survival rate, will be determined by the Kaplan-Meier estimation, and the log-rank test will be used for treatment comparisons. The response rates at 12- and 24-weeks in the treatment groups will be compared using Chi-square test or Fisher's exact test, as appropriate. An exploratory Cox proportional-hazards model will be used to evaluate the interaction between important baseline characteristics and the effect of treatments on overall survival. Hazard ratio (HR) and 95% confidence interval (CI) will be calculated for the TACE+RT group relative to the sorafenib group using a Cox proportional-hazards model. The tests performed will be 2-sided, and *P* values <0.05 will be considered statistically significant. All statistical analyses will be performed using SPSS Statistics version 21 (IBM, Armonk, NY).

11. Measurement of Compliance

The importance of compliance with the sorafenib will be emphasized at each visit. Adherence to sorafenib will be assessed by returned pill counts and patient survey. A record of this reconciliation must be maintained using the accountability forms, and any issues of non-compliance discussed with the subject.

_____ x

12. Discontinuation and Withdrawal

Subjects may be withdrawn from the study at the investigator's discretion in any of the following instances:

- Development of a toxicity or adverse event which warrants discontinuation of the drug or intervention
- Vital violations of the clinical trial protocol
- The subjects refuse the administration of the study drugs/intervention or safety tests
- The subjects withdraw the agreement of participation of the trial

Treatment after discontinuation or withdrawal will be determined by the investigator. In case of discontinuation or withdrawal due to adverse events or safety issue, subjects should be followed until full recovery and the events should be recorded in CRFs.

13. Protection of the Subjects

The investigational institutions should make sure that the necessary personnel and facilities to conduct the study are appropriately provided. The investigators should do their best for the safety of the study subjects. If serious adverse events occur during the trial, the investigators should notify IRB after taking adequate therapeutic measures.

The responsible conduct of the study will be regularly monitored by the Human Research Protection Center of each participating sites.

14. Informed Consent, Agreement of Compensation, Post-Study Treatment

14.1 Patient Information and Informed Consent

The investigator is responsible for obtaining written informed consent from each participant after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the IRB-approved consent form for the written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining the consent.

A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative. If the subject or representative cannot read, an impartial witness is needed.

14.2. Compensation Available to the Patients in the Event of Trial Related Injury

In the event of health injury associated with this trial, the sponsor is responsible for compensation based on the contract.

14.3. Treatment of the Subjects after the End of the Clinical Trial

The subjects who have fulfilled the study would follow the standard treatment of liver cirrhosis. The subjects who are terminated in the middle of the study should receive other appropriate surveillance of HCC. After detection of HCC, treatment will be determined by the subjects' clinical status and at the physician's discretion.

15. Additional Considerations for the Study

15.1. Compliance and modification of the clinical trial protocol

This study must be conducted according to the clinical trial protocol, including written informed consent approved by the IRB. All protocol modifications should be upfront discussed between the investigators. All protocol modifications, except those intended to reduce immediate risk to subjects, should be submitted to and approved by the IRB. Approvals must be obtained before changes can be implemented. In the event that modification applied to prevent immediate damage to the subjects before the IRB approval, they should be reported to the IRB as soon as possible.

15.2. Monitoring

Assigning the Data Safety and Monitoring Committee (DSMB) in charge of this trial, the DSMB will regularly visit and monitor the study sites before starting the study and during the whole study period. The monitor is responsible for routine review of the CRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

15.3. Storage of the Documents and Data

The investigator must maintain all the documents and records of this study to be adequate and accurate, and should subsequently verify them. The investigator is responsible for maintaining and providing of the essential documents. The essential documents mean ones that allow evaluating conduct of the clinical trial. The clinical trial essential document will contain the protocol/amendments, CRF and query forms, IRB approval with correspondence, informed consent, and monitoring records and other appropriate documents and correspondence.

Subject clinical source documents contain all the observed data, the records of clinical trial activities and all the reports and records for assessment and reconstruction of the clinical trial. Therefore subject clinical source documents should include the records of all the procedures conducted by the clinical trial protocol.

All clinical study documents must be retained by the investigator until at least 3 years after the end of the study.

15.4. Confidentiality of the Data and Records of the Subjects

The investigator must assure that subjects' anonymity will be strictly maintained. The subjects should be accessed by only subject initials or an identification code. Their identities have to be protected from unauthorized parties. Only the investigators, study coordinators, those who conduct inspections, IRB, the director of KFDA can review the data of the subjects to verify the reliability and the study process within the range prescribed by the relevant provisions and without violating the confidentiality of research subjects.

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Appendix. 1

Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease 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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix. 2

Child-Pugh score

Measures	Points			
	1	2	3	
Total bilirubin	< 2 (<34)	2-3 (34-50)	> 3 (>50)	mg/dL (μmol/L)
Serum Albumin	> 35 (>3.5)	28-35 (2.8-3.5)	< 28 (<2.8)	g/L (g/dL)
PT (INR)	< 3 (< 1.70)	4-6 (1.71-2.20)	> 6 (>2.20)	sec
Ascites	None	Mild	Moderate to Severe	
Hepatic encephalopathy	None	Grade I-II	Grade III-IV	
Interpretation – class A : 5-6, B : 7-9, C : 10-15 points				

Appendix. 3

Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

Target lesions	
CR	Disappearance of any intratumoral arterial enhancement in all target lesions
PR	At least a 30% decrease in the sum of the 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 PR or PD
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
Non-target lesions	
CR	Disappearance of any intratumoral arterial enhancement in all non-target lesions
IR/SD	Persistence of intratumoral arterial enhancement in one or more non-target lesions
PD	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Appendix. 4

Study Outline

