Supplementary Online Content

He MK, Li QJ, Zou RH, et al. Sorafenib plus hepatic arterial infusion of oxaliplatin, fluorouracil, and leucovorin vs sorafenib alone for hepatocellular carcinoma with portal vein invasion: a randomized clinical trial [published online May 9, 2019]. *JAMA Oncol*. doi:10.1001/jamaoncol.2019.0250

This supplementary material has been provided by the authors to give readers additional information about their work.

Supplementary 1 Online Content

eTable 1. Study institutes

Study Institute	Principal Investigators	Planned Number (n=244)	Actual Number (n=247)
Sun Yat-sen University Cancer Center	Ming Shi	80	114
First Affiliated Hospital, Sun Yat-sen University	Guo-Sheng Tan	52	49
Guangzhou No.12 People's Hospital	Yuan-Min Zhou	52	45
Kaiping Central Hospital	Wan-Qiang Fang	30	24
The First Affiliated Hospital of the University of South China	Xiao-Ping Wu	30	12

eTable 2. Baseline characteristics of the intention-to-treat population

	SoraHAIC group(n=125)	Sorafenib group (n=122)
Age, median (IQR), y	49 (41-55)	49 (40-56)
Sex		
Male	111 (88.8%)	112 (91.8%)
Female	14 (11.2 %)	10 (8.2%)
ECOG score		
0	12 (9.6%)	9 (7.4%)
1	79 (63.2%)	83 (68.0%)
2	34 (27.2%)	30 (24.6%)
Tumor size, maximum, Median (IQR), cm	10.1 (7.7-13.2)	10.1 (8.3-12.1)
Tumor number		
Single	30 (24.0%)	33 (27.0%)
Multiple	95 (76.0%)	89 (73.0%)
Neutrophil: lymphocyte ratio		
≤3	56 (44.8%)	67 (54.9%)
>3	69 (55.2%)	55 (45.1%)
Etiology		
HBV infection	100 (80.0%)	99 (81.1%)
HCV infection	6 (4.8%)	7 (5.7%)
Others	19 (15.2%)	16 (13.1%)
AFP, median (IQR), ng/mL	5922 (142.6-56200.5)	6666.5 (86.8-49609.8)
ALB, median (IQR), g/dL	40.8 (37.9-43.5)	39.7 (36.6-42.3)
TBil, median (IQR), μmol/L	16.7 (12.3-22.8)	16.9 (12.4-22.9)
Portal vein invasion		
Vp1-2	24 (19.2%)	24 (19.6%)
Vp3	54 (43.2%)	53 (43.4%)
Vp4	47 (37.6%)	45 (36.9%)
Extrahepatic sites, n (%)		
Absent	87 (69.6%)	80 (65.6%)
Present	38 (30.4%)	42 (34.4%)
Lymph node	24 (19.2%)	21 (17.2%)
Lung	20 (16%)	24 (19.7%)

Abbreviations: SD, standard deviation; IQR, interquartile range; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; Alb, albumin; Tbil, total bilirubin; Vp4, main portal vein invasion; Vp3, first branch portal vein invasion; Vp2, second branch portal vein invasion; Vp1, third branch portal vein invasion.

SoraHAIC group=sorafenib plus hepatic arterial infusion chemotherapy group. Sorafenib group=Sorafenib monotherapy group.

eTable 3. Univariable analysis for all recruited patients

	Baseline characteristics analysis				Univariable analysis	
	SoraHAIC group (n=125) (%)	Sorfenib group (n=122) (%)	*P1*	No.	OS, months	*P2*
Age，y			0.61			0.07
≤50	72 (57.6%)	66 (54.1%)		138	8.23	
>50	53 (42.4%)	56 (45.9%)		109	8.53	
Sex			0.52			0.2
Male	111 (88.8%)	112 (91.8%)		223	8.3	
Female	14 (11.2 %)	10 (8.2%)		24	11.33	
ECOG score			0.69			0.09
0	12 (9.6%)	9 (7.4%)		21	10.77	
1	79 (63.2%)	83 (68.0%)		162	8.47	
2	34 (27.2%)	30 (24.6%)		64	7.13	
Maximum tumor diameter, cm			0.8			0.06
≤10	60 (48.0%)	61 (50.0%)		121	9.47	
>10	65 (52.0%)	61 (50.0%)		126	7.9	
Tumor number			0.66			0.63
Single	30 (24.0%)	33 (27.0%)		63	8.37	
Multiple	95 (76.0%)	89 (73.0%)		184	8.33	
Neutrophil: lymphocyte ratio			0.13			0.009
≤3	56 (44.8%)	67 (54.9%)		123	9.53	
>3	69 (55.2%)	55 (45.1%)		124	7.23	
Etiology			0.86			0.99
HBV infection	100 (80.0%)	99 (81.1%)		199	8.33	

HCV infection	6 (4.8%)	7 (5.7%)		13	9.47	

eTable 3. Univariable analysis for all recruited patients (continued)

	Baseline characteristics analysis				Univariable analysis	
	SoraHAIC group (n=125) (%)	Sorfenib group (n=122) (%)	*P1*	No.	OS, months	*P2*
Others	19 (15.2%)	16 (13.1%)		35	8.47	
AFP, ng/ml			0.9			0.02
≤1000	49 (39.2%)	46 (37.7%)		95	9.53	
>1000	76 (60.8%)	76 (62.3%)		152	8	
ALB, g/dL			0.2			0.21
<4	53 (42.4%)	62 (50.8%)		115	8.1	
≥4	72 (57.6%)	60 (49.2%)		132	9.43	
TBil, μmol/L			0.89			0.01
≤20.5	85 (68.0%)	81 (66.4%)		166	9.43	
>20.5	40 (32.0%)	41 (33.6%)		81	7.13	
Portal vein invasion			0.99			0.007
Vp1-2	24 (19.2%)	24 (19.6%)		48	12.13	
Vp3	54 (43.2%)	53 (43.4%)		107	8.23	
Vp4	47 (37.6%)	45 (36.9%)		92	7	
Extrahepatic sites, n (%)			0.59			0.001
Absent	87 (69.6%)	80 (65.6%)		167	9	
Present	38 (30.4%)	42 (34.4%)		80	7.37	
Lymph node	24 (19.2%)	21 (17.2%)				
Lung	20 (16%)	24 (19.7%)				

Abbreviations: OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; Alb, albumin; Tbil, total bilirubin; Vp4, main portal vein invasion; Vp3, first branch portal vein invasion; Vp2, second branch portal vein invasion; Vp1, third branch portal vein invasion.

SoraHAIC group=sorafenib plus hepatic arterial infusion chemotherapy group. Sorafenib group=Sorafenib monotherapy group.

P1 value was calculated by a two-sided Chi-square test.

P2 value was calculated with two-sided log-rank test.

eTable 4. HAIC administration

	HAIC (n=124)
HAIC cycle	485
Mean (SD)	3.91 (1.78)
Median (IQR)	4 (2-5)
Reasons for HAIC discontinuation	
Disease progression	35 (28.23%)
Hepatic resection	13 (10.48%)
Technical difficulty	10 (8.06%)
Disappearance of any intratumoral arterial enhancement in all intrahepatic lesion	14 (11.29%)
Unacceptable AEs	32 (25.81%)
Patient's decision	15 (12.1%)
Other reasons	5 (4.03%)
HAIC reduction related to AEs	43 (34.68%)
HAIC delay related to AEs	22 (17.74%)

Data are n (%), mean (SD), or median (IQR). HAIC=hepatic arterial infusion chemotherapy. AE=adverse event. SD=standard deviation. IQR=interquartile range

eTable 5. Sorafenib administration

	SoraHAIC group (n=124)	Sorafenib group (n=121)	*P*
Duration of sorafenib treatment, days			
Mean±SD	173.81±145.86	80.73±76.88	<0.001
Median (IQR)	137.5(63.75-227.25)	57(39-92)	
Sorafenib daily dose, mg			
Mean±SD	650.15±149.43	679.19±143.85	0.12
Median (IQR)	638.54(507.98-800)	800(530.46-800)	
Sorafenib dose administration due to AEs			
Reductions, n (%)	67(54.03)	54(44.63)	0.16
Interruptions, n (%)	51(41.13）	56(46.28)	0.44
Discontinuations, n (%)	38(30.65)	34(28.1)	0.68

SoraHAIC=sorafenib plus hepatic arterial infusion chemotherapy. Sorafenib=Sorafenib monotherapy. SD=standard deviation. IQR=interquartile range. AE=adverse event.

P value was calculated by a two-sided chi-square test.

eTable 6. Number of patients who received subsequent treatments after discontinuation of study treatment.

	SoraHAIC group (n=125)		Sorafenib group (n=122)
HAIC	30		39
Resection	16		1
Ablation	3		1
Sorafenib	31		42
Systemic chemotherapy	1		3
Programmed cell death protein-1 inhibitor treatment	2		4
TACE	13		11
Radiotherapy	6		3

SoraHAIC group=sorafenib plus hepatic arterial infusion chemotherapy group. Sorafenib group=sorafenib monotherapy group. HAIC=hepatic artery infusion chemotherapy. TACE=transarterial chemoembolization.

eTable 7. Treatment Related Adverse Events*

Adverse event	SoraHAIC group (n=124)			Sorafenib group (n=121)			*P* value	
	Any grade (%)	Grade 3-4 (%)		Any grade (%)	Grade 3-4 (%)		Any grade	Grade 3-4
Overall incidence	118(95.16)	66(53.23)		109(90.08)	51(42.15)		0.15	0.1
Blood/bone marrow suppression								
Neutropenia	55 (44.35)	12(9.68)		37(30.58)	3(2.48)		0.04	0.03
Thrombocytopenia	69 (55.65)	16 (12.9)		51(42.15)	6(4.96)		0.04	0.04
Anemia	85 (68.55)	6(4.84)		76(62.81)	4(3.31)		0.35	0.75
Cardiovascular system								
Hypertension	34(27.42)	3(2.42)		38(31.4)	4(3.31)		0.58	0.72
Edema	21 (16.94)	5(4.03)		10(8.26)	2(1.65)		0.05	0.45
Constitutional symptoms								
Fatigue	95 (76.61)	8(6.45)		45(37.19)	4(3.31)		＜0.001	0.38
Fever	16(12.9)	2(1.61)		6(4.96)	0		0.04	0.5
Weight loss	44(35.48)	1(0.81)		39(32.23)	2(1.65)		0.69	0.62
Dermatologic events								
Hand–foot skin reaction	51 (41.13)	13 (10.48)		55(45.45)	17(14.05)		0.52	0.44
Alopecia	12(9.68)	0		30(24.79)	0		0.002	-
Rash	15(12.1)	0		20(16.53)	1(0.83)		0.36	0.49
Gastrointestinal events								
Nausea	99(79.84)	9(7.26)		35(28.93)	2(1.65)		＜0.001	0.06
Vomiting	74 (59.68)	8(6.45)		17(14.05)	1(0.83)		＜0.001	0.04
Diarrhea	36 (29.03)	11(8.87)		51(42.15)	15(12.4)		0.03	0.41
Abdominal pain	44 (35.48)	8(6.45)		12(9.92)	2(1.65)		＜0.001	0.1
Neurotoxicity								

Sensory neuropathy	40 (32.26)	0		4(3.31)	0		＜0.001	-
eTable 7. Treatment Related Adverse Events* (continued)								
Adverse event	SoraHAIC group (n=124)			Sorafenib group (n=121)			*P* value	
	Any grade (%)	Grade 3-4 (%)		Any grade (%)	Grade 3-4 (%)		Any grade	Grade 3-4
Hepatic function								
Elevated ALT	86(69.35)	14(11.29)		80(66.12)	11(9.09)		0.68	0.67
Elevated AST	100(80.65)	36 (29.03)		103(85.12)	30(24.79)		0.4	0.47
Hyperbilirubinemia	91(73.39)	6(4.84)		79(65.29)	4(3.31)		0.21	0.75
Hypoalbuminemia	101 (81.45)	6(4.84)		49(40.5)	1(0.83)		＜0.001	0.12

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

SoraHAIC group=sorafenib plus hepatic arterial infusion chemotherapy group. Sorafenib group=sorafenib monotherapy group.

The safety population comprised all randomised patients who received at least one dose of study treatment.

P value was calculated by a two-sided chi-square test.

*Listed are adverse events, as defined by the National Cancer Institute Common Terminology Criteria (version 4.03), that occurred in at least 10% of patients in either study group.

eTable 8. Incidence of serious treatment-emergent adverse events

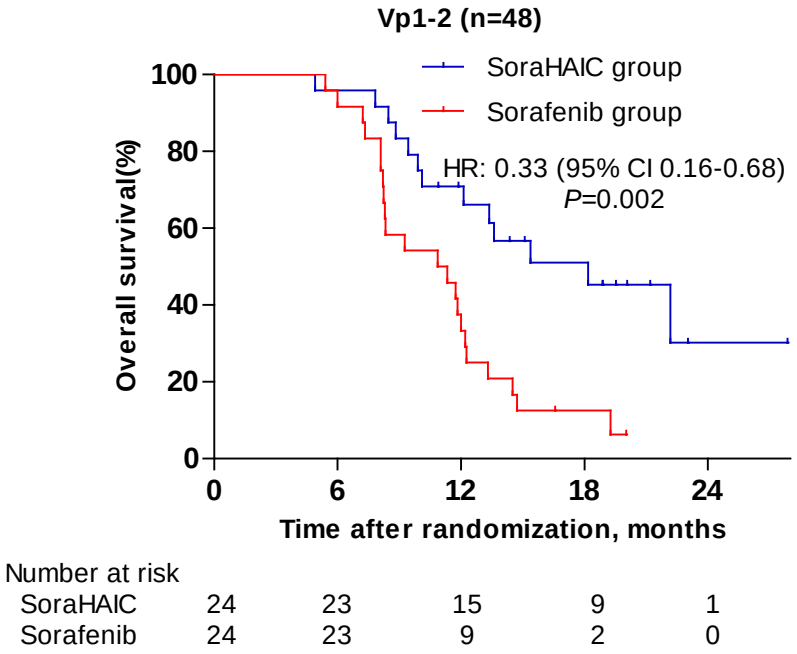
Serious adverse event *	SoraHAIC group (n=124) (%)	Sorafenib group (n=121) (%)	*P* value
Overall incidence	40(32.26)	42(34.71)	0.69
Blood/bone marrow			
Thrombocytopenia	6(4.84)	4(3.31)	
Constitutional symptoms			
Fatigue	8(6.45)	4(3.31)	
Gastrointestinal events			
Upper gastrointestinal bleeding	5(4.03)	8(6.61)	
Diarrhea	6(4.84)	8(6.61)	
Gastric ulcer	4(3.23)	1(0.83)	
Dehydration	3(2.42)	7(5.79)	
Hepatobiliary			
Hepatic encephalopathy	2(1.61)	0	
Hyperbilirubinemia	2(1.61)	4(3.31)	
Ascites	6(4.84)	9(7.44)	
Renal			
Creatinine >3.0 x ULN	3(2.42)	0	

*Adverse events that resulted in death, were life threatening, required hospitalization or prolongation of existing hospitalization, resulted in a persistent or significant disability or incapacity, or a congenital anomaly or birth defect, required medical or surgical intervention to prevent any of these outcomes, or were determined by the investigator to be medically important event, reported for at least 1% of patients in either treatment group.

SoraHAIC group=sorafenib plus hepatic arterial infusion chemotherapy group; Sorafenib=sorafenib monotherapy group.ULN=Upper limit of normal.

P value was calculated by a two-sided chi-square test.

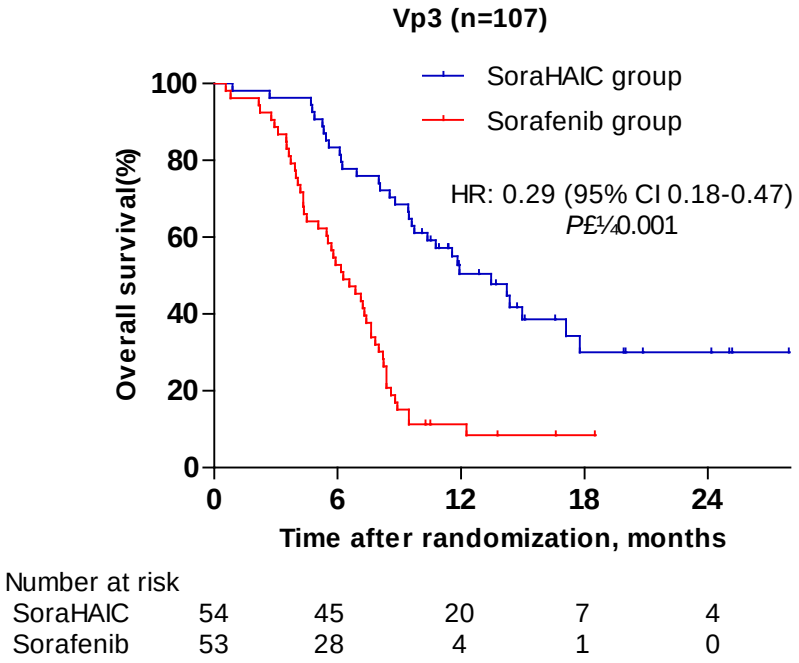
eFigure 1. Kaplan-Meier analysis of overall survival in patients with Vp1-2



Number at risk					
SoraHAIC	24	23	15	9	1
Sorafenib	24	23	9	2	0

SoraHAIC group=sorafenib plus hepatic arterial infusion chemotherapy group. Sorafenib group=Sorafenib monotherapy group. HR=hazard ratio. CI=confidence interval. Vp2=second branch portal vein invasion. Vp1=third branch portal vein invasion.

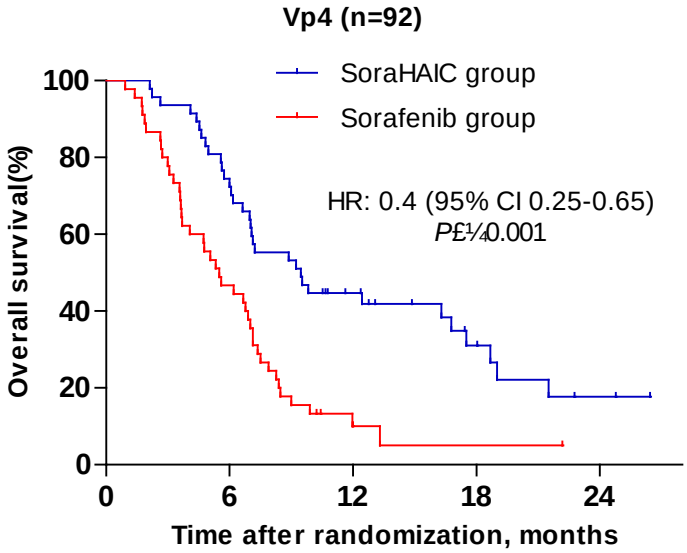
eFigure 2. Kaplan-Meier analysis of overall survival in patients with Vp3



Number at risk					
SoraHAIC	54	45	20	7	4
Sorafenib	53	28	4	1	0

SoraHAIC group=sorafenib plus hepatic arterial infusion chemotherapy group. Sorafenib group=Sorafenib monotherapy group. HR=hazard ratio. CI=confidence interval. Vp3=first branch portal vein invasion.

eFigure 3. Kaplan-Meier analysis of overall survival in patients with Vp4



Number at risk					
SoraHAIC	47	35	17	8	3
Sorafenib	45	21	3	1	0

SoraHAIC group=sorafenib plus hepatic arterial infusion chemotherapy group. Sorafenib group=Sorafenib monotherapy group. HR=hazard ratio. CI=confidence interval. Vp4=main portal vein invasion.

eMethods. Additional Methods

Pretreatment evaluation

Pretreatment evaluation included a complete medical history, physical examination, blood test, and α-fetoprotein measurement as well as liver function tests. For potentially eligible patients, tumors were assessed by abdominal contrast magnetic resonance imaging/contrast-enhanced ultrasonography and dynamic contrast computed tomography of the abdomen and thorax. Thrombus enhancement on image study was considered diagnostic for malignant or benign portal venous thrombosis. Ultrasound-guided percutaneous tumor biopsy was performed with a gauge needle. Further investigations were performed only when there was clinical suspicion of extrahepatic metastases. Resectable disease was defined as the complete removal of all macroscopic tumor tissue and an expected remnant liver volume no less than 250 ml/m^2.[1] All patients were assessed by the same surgery team from the Department of Hepatobiliary Oncology, Cancer Center, Sun Yat-sen University (Guangzhou, China).

Catheterization

A 3.5 French catheter was 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 was performed routinely. Then, a 2.7 French microcatheter was super selectively placed into the feeding arteries of the tumor and the tumor thrombus. If the tumor simultaneously accepts blood supply from the celiac trunk and superior mesenteric artery, the microcatheter was placed into the largest tumor feeding arteries. The peripheral end of the microcatheter was 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 that was exposed to the outside of the body was covered with sterile medical gauze and fastened on the skin of thigh using medical rubberized fabric and bandage. Then, the patient was transferred to the ward and confined to bed for 48 hours. After confirming the location of the tips of the microcatheter by bed side X-ray radiography, the microcatheter was marked in vitro and connected to the artery infusion pump to administer the chemotherapy agent. When the mark changed, bedside X-ray radiography was also conducted to confirm the location of the catheter tip. If dislocation of the catheter tip was confirmed, the patient was transferred to the digital subtraction angiography room to correct the location of the catheter tip.

Dose reduction and delay

Patients were assessed before starting each 3-week cycle using the National Cancer Institute common toxicity criteria. hepatic arterial infusion chemotherapy (HAIC) was delayed until recovery if neutrophil count less than 1200 cells/μL, platelet count less than 60 000 platelets/μL, a total bilirubin level exceeding 30 mmol/L, an albumin level less than 3.0 mg/dL, or serum creatinine up to 1.5 times the institutional upper limit of normal. The 5-fluorouracil dose was decreased to 300 mg/m^2 bolus and 1800 mg/m^2/cycle continuous infusion in cases of grade 3 or 4 diarrhea or stomatitis, skin toxicity or other grade 3 major organ drug-related toxicity. The oxaliplatin dose was decreased to 65 mg/m^2/cycle in cases of grade 3 or 4 neutropenia or thrombocytopenia, any other grade 3 major organ drug-related toxicity, or paresthesia associated with pain. It was not permitted to re-escalate HAIC doses that had been reduced because of toxicity.

HAIC was continued until tumor progression, unacceptable toxicity, the next cycle was delayed for 30 days or longer, technical difficulties in repeating the HAIC (stenosis or occlusion of tumor feeding artery or supplied only by extrahepatic collateral arteries), disappearance of any intratumoral arterial enhancement in all intrahepatic lesions, or patient choice. In the SoraHAIC group, patients were allowed to have sorafenib as a single agent and were still considered in the study when the HAIC was

delayed or discontinued in the absence of disease progression.

Sorafenib doses were adjusted by interruption or reduction in patients who had clinically significant dermatological or nondermatological toxicities attributed to sorafenib. As defined in the previous protocol, oral doses of sorafenib were reduced stepwise from 400 mg twice daily to 400 mg once daily to 400 mg every other day.[2] Stepwise increases of sorafenib were allowed after resolution of the adverse event.

Termination of treatment

The study treatment was stopped in cases of tumor progression (both radiological progression, as defined by Response Evaluation Criteria in Solid Tumors (RECIST),[3] and symptomatic progression, as defined by the Functional Assessment of Cancer Therapy–Hepatobiliary Symptom Index 8 questionnaire[4]), intolerable toxicity, sorafenib interruption exceeding 30 days, the need for another anticancer treatment (such as surgery) at the physician's discretion, or at the patient's request. The choice of the subsequent treatment was determined according to the patient's request and the results of discussions by our multidisciplinary team. For patients whose residual tumors could be safely removed by surgery or ablated by radiofrequency ablation, the corresponding treatment was recommended**.** If the tumors were completely devascularized after HAIC, patients were to be followed up by contrast computed tomography/ magnetic resonance imaging every 6 weeks, and HAIC was repeated if new tumor enhancement was depicted on follow-up computed tomography imaging. In both groups, if the tumor progressed after study treatment but still met the eligibility criteria of HAIC, HAIC was allowed for subsequent treatment. Otherwise, only conservative treatment was recommended.

Definition of endpoint

Overall survival was defined as the date of randomization to death from any cause. For patients still alive and not lost to follow-up by the cutoff date, data were censored at the cutoff date. Patients who were lost to follow-up will be censored at the last date on which patients were confirmed to be alive. Progression-free survival was defined as the length of time from the date of randomization until progression of intrahepatic and extrahepatic lesions or tumor recurrence after completely surgical resection or death from any cause, whichever is sooner. Patients who did not progress until the end of follow-up of this study were censored by the cutoff date. Overall response rate was the proportion of patients with a best response of complete response or partial response according to RECIST version 1.1. (the detail of complete response and partial response was described in the supplement 2-protocol).

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