## Supplemental Section 1. Risk of bias assessment

***Assessment of risk bias in included studies***

The two authors will independently assess the risk of bias of each included trial according to the recommendations from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).[1] The following definitions in the assessment of risk of bias were used:[2–6]

***Allocation sequence generation:***

- low risk of bias (sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice are adequate if performed by an independent person not otherwise involved in the trial);
- uncertain risk of bias (the method of sequence generation was not specified);
- high risk of bias (the sequence generation method was not random).

***Allocation concealment:***

- low risk of bias (the participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomization unit. The allocation sequence was unknown to the investigators (for example, if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes)).
- uncertain risk of bias (the method used to conceal the allocation was not described so that intervention allocations may have been foreseen in advance of, or during, enrolment);
- high risk of bias (the allocation sequence was likely to be known to the investigators who assigned the participants).

***Blinding of participants, personnel, and outcome assessors:***

- low risk of bias (blinding was performed adequately, or the assessment of outcomes was not likely to be influenced by lack of blinding);
- uncertain risk of bias (there was insufficient information to assess whether blinding was likely to induce bias on the results);
- high risk of bias (no blinding or incomplete blinding, and the assessment of outcomes were likely to be influenced by lack of blinding).

***Incomplete outcome data:***

- low risk of bias (missing data were unlikely to make treatment effects depart from plausible values. Sufficient methods, such as multiple imputation, have been employed to handle missing data);
- uncertain risk of bias (there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results);
- high risk of bias (the results were likely to be biased due to missing data).

***Selective outcome reporting:***

- low risk of bias (all pre-defined, or clinically relevant and reasonably expected, outcomes are reported on. If the original trial protocol is available, the outcomes should be those called for in that protocol) (Note: If the trial protocol is obtained from a trial registry, the outcomes to be sought are those enumerated in the original protocol if the trial protocol was registered before or at the time that the trial was begun; if the trial protocol was registered after the trial was begun, those outcomes will not be considered to be reliable in representing the outcomes initially being sought. If the trial protocol is not available or if the protocol was registered after the trial was begun, we will assess this domain following the outcomes presented earlier in our review protocol);
- unclear risk of bias (not all pre-defined, or clinically relevant and reasonably expected, outcomes are reported fully, or it is unclear whether data on these outcomes were recorded or not);
- high risk of bias (one or more predefined or clinically relevant and reasonably expected outcomes were not reported, despite the fact that data on these outcomes should have been likely to have been available and even recorded).

***For-profit bias:***

- low risk of bias (the trial appears to be free of industry sponsorship or other kind of for-profit support that may manipulate the trial design, conductance, or results of the trial);

- uncertain risk of bias (the trial may or may not be free of for-profit bias as no information on clinical trial support or sponsorship is provided);
- high risk of bias (the trial is sponsored by the industry or has received other kind of for-profit support).

***Other biases:***

- low risk of bias (the trial appears to be free of other sources of bias);
- uncertain risk of bias (there is insufficient information to assess whether other sources of bias are present);
- high risk of bias (it is likely that potential sources of bias related to the specific trial design used, or other bias risks are present).

Trials assessed as having 'low risk of bias' in all of the specified individual domains will be considered 'trials with low risk of bias'. Trials assessed as having 'uncertain risk of bias' or 'high risk of bias' in one or more of the specified individual domains will be considered as trials with 'high risk of bias'. Any disagreements will be discussed and the authors of the study contact until consensus is reached

**References**


1. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0, Higgins JPT, & Green S, March 2011]
2. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995; 273 (5):408–12.
3. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998; 352 (9128):609–13.
4. Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Ann Intern Med* 2001; 135: 982–9.
5. Wood L, Egger M, Gluud LL, Schulz K, Jüni P, Altman DG, *et al*. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 2008; 336: 601–5.
6. Savović J1, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. *Ann Intern Med* 2012; 157 (6):429-38

**Supplemental Section 2. Risk of Bias within Studies**

In all included trials sequence generation was achieved using computer random number generation. The participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomization unit. The allocation sequence was unknown to the investigators. None of the included RCTs was blinded due to the nature of the treatments, but the primary outcome was unlikely to have been influenced by the lack of blinding. Missing data were considered unlikely to make treatment effects depart from plausible values.

With respect to the selective outcome reporting, all trials are registered with ClinicalTrials.gov, numbers NCT01135056 (SIRveNIB), NCT01482442 (SARAH) and NCT01126645 (SORAMIC). All pre-defined outcomes enumerated in the original protocols are reported on. All trial publications declared industry funding but all were investigator-led and free from influence that manipulated the trial design, conduct, or results. The trials appeared to be free of other sources of bias. We resolved any queries and verified the final database entries by discussion with the responsible trial investigator or statistician. We received individual patient data for all outcomes of interest, therefore we considered reporting bias to be low for all RCTs. We considered all included trials to be at a low risk of bias.

**Supplemental Table 1 Study characteristics**

| Study | SIRveNIB | SARAH | SORAMIC |
|---|---|---|---|
| **Author/year** | Chow et al. 2018 | Vilgrain et al. 2018 | Ricke et al. 2019( |
| **Location** | Singapore, Myanmar, Philippines, Mongolia, Thailand, Indonesia, Malaysia, South Korea, Taiwan, New Zealand, Brunei | France | Germany, France, Netherlands, Poland, Italy, UK, Austria, Spain, Slovenia, Switzerland, Turkey, Belgium |
| **Test arm** | SIRT | SIRT | SIRT plus sorafenib |
| **Control arm** | Sorafenib | Sorafenib | Sorafenib |
| **Primary endpoint** | Overall survival | Overall survival | Overall survival |
| **Secondary endpoints** | TRR, DCR, PFS, TTP at any site and in the liver, safety; QOL. | TRR, DCR, PFS, TTP at any site and in the liver, safety; QOL. | Safety |
| **Visits** | monthly | monthly | every 2 months |
| **Follow-up by imaging** | CT or MRI scan every 3 months from the date of random assignment to disease progression | CT or MRI scan at screening, 1 month, and every 3 months thereafter for at least 1 year after randomization or until death | no imaging required |
| **Length of follow-up** | Median follow-up was 26.6 months (IQR 42.0) in the SIRT group and 36.3 months (IQR 58.6) in the sorafenib group. | Median follow-up was 27·9 months (IQR 21.9–33.6) in the SIRT group and 28·1 months (IQR 20.0–35.3) in the sorafenib group. | NA |
| **Evaluation of CT and MRI** | RECIST 1.1 | RECIST 1.1 | NA |
| **Inclusion criteria** | - aged ≥18 years old;<br>- unequivocal diagnosis of HCC (imaging or biopsy);<br>-Child-Pugh score ≤7;<br>- BCLC stage B or C without extrahepatic disease with or without PVT;<br>- not amenable to curative treatment modalities;<br>**- bilirubin ≤ 32 µmol/L** | - aged ≥18 years old;<br>- unequivocal diagnosis of HCC (imaging or biopsy);<br>-Child-Pugh score ≤7;<br>- BCLC stage B or C without extrahepatic disease with or without PVT;<br>- not amenable to curative treatment modalities;<br>**- total bilirubin ≤50 µmol/L.** | - aged ≥18 years old;<br>- diagnosis of HCC (imaging or biopsy);<br>- Child Pugh ≤7;<br>- BCLC stage B not eligible for TACE per investigator decision) and C;<br>**- bilirubin ≤ 32 µmol/L**<br>- Prior resection or vascular procedures (PEI, hepatic artery–directed therapy, RFA) permitted; Post hepatic artery–directed therapy: > 3 months interval and revascularization present<br>**- Extra-hepatic disease permitted** |
| **Exclusion criteria** | - Received >2 previous administrations of hepatic artery–directed therapy;<br>- hepatic artery–directed treatment < 4 weeks;<br>- previous treatment with Sorafenib<br>- previous VEGF inhibitors,<br>- previous radiotherapy<br>**- extrahepatic disease.**<br>- For patients randomized to receive SIRT: liver-to-lung shunt with > 20 Gy being delivered to the lungs. | - Received >2 previous administrations of hepatic artery–directed therapy;<br>- previous treatment of the current nodule (excluding transarterial chemoembolization);<br>- previous treatment with Sorafenib<br>**- extrahepatic metastasis;**<br>- For patients randomized to receive SIRT: Liver-to-lung shunt greater than 20% / liver-to-lung shunt leading to a lung dose > 25 Gy (amendment). | - Previous external beam radiation therapy to the liver;<br>- Previous therapy with tyrosine kinase inhibitors;<br>- For patients randomized to receive SIRT: liver-to-lung shunt leading to a lung dose >30 Gy; |
| **Randomization** | SIRT vs. sorafenib, randomization in a 1:1 ratio | SIRT vs. sorafenib, randomization in a 1:1 ratio | SIRT followed by sorafenib vs. sorafenib, randomization in a 11:10 ratio |
| **Time interval between randomization and SIRT** | **Within 5 weeks of random assignment.** | **Within 5 weeks of random assignment.** | **Within 4 weeks of random assignment.** |
| **SIRT delivery in patients with bilobar disease** | Single delivery | Lobar delivery | Lobar delivery |
| **Time to delivery of the second SIRT in patients with bilobar disease** | Single delivery also in patients with bilobar disease | -In bilobar tumors, the first treatment was administered in the hemiliver with the greatest tumor burden.<br>-Treatment of the contralateral hemi-liver was scheduled 30–60 days after the first treatment. | - In bilobar tumors, the second SIRT was performed at 4-6 weeks after the first treatment |

| | | | |
|---|---|---|---|
| **Sorafenib therapy** | Start with 400 mg bid in the week after random assignment.<br><br>Sorafenib administered until the occurrence of radiological progression, complete response, the initiation of other HCC therapies, unacceptable adverse events, patient request to stop treatment, or death. | Start with 400 mg bid in the week after random assignment.<br><br>Sorafenib administered until the occurrence of radiological progression, unacceptable adverse events, or death. | - In the no-SIRT arm start with sorafenib 400 mg bid;<br>-In the SIRT arm start with sorafenib 3 days after final SIRT, begin with 200 mg bid, escalation to 400mg bid at day 10. |

TRR: tumor response rate; DCR: disease control rate; PFS: progression-free survival; TTP: time to tumor progression; NA: not available; RECIST: Response Evaluation Criteria in Solid Tumors 1.1; QOL: quality of life; BCLC: Barcelona Clinic Liver Cancer stage; IQR: interquartile range; PVT: portal vein thrombosis; TACE: transarterial chemoembolization VEGF: vascular endothelial growth factor. Differences in inclusion and exclusion criteria among studies are highlighted in bold.

**Supplemental Table 2 Baseline characteristics of the per-protocol population in the SIRveNIB, SARAH and SORAMIC trials**

| | SIRT | | | | Sorafenib | | | | p [a] |
|---|---|---|---|---|---|---|---|---|---|
| **Study** | **SIRveNIB** | **SARAH** | **SORAMIC** | **Combined** | **SIRveNIB** | **SARAH** | **SORAMIC** | **Combined** | |
| **Number of patients** | 123 | 174 | 114 | 411 | 142 | 206 | 174 | 522 | |
| **Age (years) (SD)** | 60.9 (11.5) | 66.3 (9.4) | 66.7 (7.8) | 64.7 (10.0) | 57.5 (10.6) | 64.6 (9.5) | 65.8 (8.9) | 62.8 (10.2) | <0.01[b] |
| **Male (%)** | 102 (82.9) | 158 (90.8) | 100 (87.7) | 360 (87.6) | 120 (84.3) | 186 (90.3) | 151 (86.8) | 457 (87.5) | 0.98 |
| **ECOG 0 (%)** | 100 (81.3) | 109 (62.6) | 77 (67.5) | 286 (69.6) | 111 (78.2) | 127 (61.7) | 121 (69.5) | 359 (68.8) | 0.64 |
| **ECOG 1 (%)** | 23 (18.7) | 65 (37.4) | 34 (29.8) | 122 (29.7) | 31 (21.8) | 79 (38.3) | 52 (29.9) | 162 (31.0) | 0.76 |
| **Cirrhosis (%)** | NA | 154 (88.5) | 89 (80.2) | 243 (84.0) | NA | 187 (90.8) | 138 (79.8) | 325 (85.5) | 0.62 |
| **BCLC A (%)** | 0 | 7 (4.0) | 4 (3.5) | 11 (3.8) | 1 (0.6) | 9 (4.4) | 3 (1.7) | 13 (2.4) | 0.84 |
| **BCLC B (%)** | 76 (61.8) | 53 (30.5) | 32 (28.1) | 161 (39.2) | 75 (52.8) | 54 (26.2) | 48 (27.7) | 177 (33.9) | 0.41 |
| **BCLC C (%)** | 47 (38.2) | 114 (65.5) | 78 (68.4) | 239 (58.2) | 67 (47.2) | 143 (69.4) | 122 (70.5) | 332 (63.6) | 0.27 |
| **Child Pugh A (%)** | 113 (91.9) | 153 (87.9) | 107 (93.9) | 373 (90.8) | 129 (90.8) | 176 (85.4) | 159 (91.4) | 464 (88.9) | 0.54 |
| **Child Pugh B 7 (%)** | 10 (8.1) | 20 (11.5) | 7 (6.1) | 37 (8.8) | 13 (9.2) | 30 (14.6) | 14 (8.0) | 57 (10.9) | 0.74 |
| **(main) PVT (%)** | 28 (22.8) | 29 (29.0) | 44 (38.6) | 101 (24.6) | 46 (32.4) | 37 (32.7) | 76 (43.7) | 159 (30.6) | 0.37 |
| **Hepatitis B (%)** | 66 (53.7) | 8 (5.1) | 12 (10.5) | 86 (20.9) | 88 (62.0) | 14 (7.4) | 21 (12.1) | 123 (23.6) | 0.64 |
| **Hepatitis C (%)** | 22 (17.9) | 38 (24.4) | 28 (24.6) | 88 (21.4) | 20 (14.1) | 46 (24.5) | 37 (21.3) | 103 (19.7) | 0.76 |
| **Alcohol etiology (%)** | NA | 108 (69.2) | 50 (43.9) | 158 (54.9) | NA | 114 (60.6) | 73 (42.0) | 187 (49.2) | 0.29 |

BCLC: Barcelona Clinic Liver Cancer; PVT: portal vein thrombosis; ECOG: Eastern Cooperative Oncology Group

[a]Z-test for proportions of each category for SIRT vs sorafenib.

[b] Wilcoxon rank-sum (Mann-Whitney) test.

**Supplemental Table 3 Reasons for not receiving allocated treatment after randomization in the SIRveNIB, SARAH and SORAMIC trials.**

| | Randomly assigned to SIRT | | | | Randomly assigned to sorafenib | | | | p |
|---|---|---|---|---|---|---|---|---|---|
| | SIRveNIB | SARAH | SORAMIC | Combined | SIRveNIB | SARAH | SORAMIC | Combined | |
| Total assigned | 182 | 237 | 216 | 635 | 178 | 222 | 208 | 608 | - |
| Did not receive allocated treatment, n (%) | 52 (28.6) | 53 (22.4) | 33[b] (15.3) | 138 (21.3) | 16 (9.0) | 6 (3.7) | 11[b] (5.3) | 33 (5.4) | <0.0001 |
| Liver-to-lung shunting/ Ineligible for SIRT for technical reasons, n (%) | 37 (20.3) | 26[a] (11.0) | 15 [a] (6.9) | 78 (12.3) | 0 | 0 | 0 | 0 | <0.0001 |
| Other reasons[c] n (%) | 15 (8.2) | 27[a] (11.4) | 18 (8.3) | 60 (9.4) | 16 (9.0) | 6 (3.7) | 11 (5.3) | 33 (5.4) | 0.007 |

[a]Crossover: in the SARAH trial 26 patients received sorafenib instead of SIRT (21 patients did not receive SIRT for technical reasons and 5 had worsening disease). In the SORAMIC trial 15 patients did not receive SIRT for technical reasons.
[b] Did not receive SIRT: 18 received no treatment and 15 received sorafenib only (crossover).
[c]Did not meet inclusion criteria/received another anticancer therapy before progression/ major protocol deviations, patient withdrew consent/worsening disease/worsening medical condition/medical decision/early deaths.
The two-tailed p-values were calculated by Fisher´s exact test

**Supplemental Table 4** Treatment effect on overall survival by subgroup in the per-protocol population (N=933 participants)

| Analysis (references) | Studies (n) | Pooled HR | (95% CI) | p-value | Heterogeneity p-value | $I^2$ (%) |
|---|---|---|---|---|---|---|
| **Age (years)** | | | | | | |
| ≤65 | 3 | 0.97 | 0.80–1.19 | <0.01 | 0.22 | 34.80 |
| >65 | 3 | 0.87 | 0.70–1.08 | <0.01 | 0.22 | 33.20 |
| **Sex** | | | | | | |
| Male | 3 | 0.91 | 0.77–1.05 | <0.01 | 0.44 | 0.00 |
| Female | 3 | 0.74 | 0.39–1.09 | <0.01 | 0.57 | 0.00 |
| **ECOG** | | | | | | |
| 0 | 3 | 0.89 | 0.71–1.08 | <0.01 | 0.06 | 64.00 |
| 1 | 3 | 0.82 | 0.64–0.99 | <0.01 | 0.55 | - |
| **Cirrhosis**[a] | | | | | | |
| Yes | 2 | 1.00 | 0.81–1.18 | <0.01 | 0.83 | - |
| No | 2 | 0.52 | 0.23–0.81 | <0.01 | 0.19 | - |
| **BCLC** | | | | | | |
| A+B | 3 | 0.90 | 0.68–1.13 | <0.01 | 0.79 | - |
| C | 3 | 0.85 | 0.69–1.02 | <0.001 | 0.18 | - |
| **Child Pugh score** | | | | | | |
| A | 3 | 0.90 | 0.76–1.05 | <0.01 | 0.60 | - |
| B | 3 | 0.94 | 0.49–1.40 | <0.01 | 0.92 | - |
| **Portal vein thrombosis** | | | | | | |
| Yes | 3 | 0.90 | 0.65–1.15 | <0.01 | 0.47 | - |
| **Hepatitis B** | | | | | | |
| Yes | 3 | 0.68 | 0.43–0.92 | <0.01 | 0.79 | - |
| **Hepatitis C** | | | | | | |
| Yes | 3 | 0.97 | 0.62–1.32 | <0.01 | 0.25 | 27.70 |
| **No metastases** | 3 | 0.92 | 0.78–1.05 | <0.01 | 0.70 | - |
| **European patients** | 2 | 0.92 | 0.77–1.10 | <0.01 | 0.42 | - |
| **Only phase III trials** | 2 | 0.92 | 0.77–1.07 | <0.01 | 0.40 | - |

[a]Data available only for SARAH and SORAMIC