

**NEMESIS: Non-inferiority, Individual Patient Meta-analysis of Selective Internal Radiation Therapy with Yttrium-90 Resin Microspheres versus Sorafenib in Advanced Hepatocellular Carcinoma**

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**Running Title:** Meta-analysis: SIRT vs Sorafenib for HCC

## ABSTRACT

In randomized clinical trials (RCTs), no survival benefit has been observed for selective internal radiotherapy (SIRT) over sorafenib in patients with advanced hepatocellular carcinoma (aHCC). This study aimed to assess by means of a meta-analysis whether overall survival (OS) with SIRT, as monotherapy or followed by sorafenib, is non-inferior to sorafenib, and compare safety profiles for patients with aHCC. **Methods.** We searched MEDLINE, EMBASE, and the Cochrane Library up to February 2019 to identify RCTs comparing SIRT as monotherapy, or followed by sorafenib, to sorafenib monotherapy among patients with aHCC. The main outcomes were OS and frequency of treatment-related severe adverse events (AEs grade  $\geq 3$ ). The per-protocol population was the primary analysis population. A non-inferiority margin of 1.08 in terms of hazard ratio (HR) was pre-specified for the upper boundary of 95% confidence interval (CI) for OS. Pre-specified subgroup analyses were performed. **Results.** Three RCTs, involving 1,243 patients, comparing sorafenib with SIRT (SIRveNIB and SARAH) or SIRT followed by sorafenib (SORAMIC), were included. After randomization, 411/635 (64.7%) patients allocated to SIRT and 522/608 (85.8%) allocated to sorafenib completed the studies without major protocol deviations. Median OS with SIRT, whether or not followed by sorafenib, was non-inferior to sorafenib (10.2 and 9.2 months, [HR 0.91, 95% CI 0.78–1.05]). Treatment-related severe adverse events were reported in 149/515 patients (28.9%) who received SIRT and 249/575 (43.3%) who received sorafenib only ( $p < 0.01$ ). **Conclusion.** SIRT as initial therapy for aHCC is non-inferior to sorafenib in terms of OS, and offers a better safety profile.

**Key words:** Meta-analysis, SIRT, sorafenib, hepatocellular carcinoma

## INTRODUCTION

For patients with hepatocellular carcinoma (HCC) that is not amenable to curative therapy, transarterial chemoembolization is the recommended choice when HCC is intermediate stage, liver-confined and inoperable (1-6). The standard of care for patients with HCC with preserved liver function in advanced disease stages, including those with portal vein invasion, lymph node or distant metastases, or altered performance status (Barcelona Clinic Liver Cancer [BCLC]-C) is systemic therapy with sorafenib (1,7). In the subset of patients with advanced HCC but no portal vein invasion, lenvatinib has been shown to be non-inferior to sorafenib (1,7,8).

Case series and small-scale cohort studies (9-13) suggested that the median overall survival (OS) for HCC patients receiving selective internal radiation therapy (SIRT) using yttrium-90 (<sup>90</sup>Y) microspheres was similar to the OS achieved with sorafenib (7,8). Based on these findings, multicenter randomized controlled trials (RCTs) were undertaken in Asia Pacific (SIRveNIB) (14) and European (SARAH) (15) populations of SIRT using <sup>90</sup>Y-resin microspheres (SIR-Spheres<sup>®</sup> Sirtex, North Sydney, Australia) compared with sorafenib 400mg twice daily. In these studies, SIRT with <sup>90</sup>Y-resin microspheres showed similar efficacy to sorafenib, with better tolerability (14,15). A further randomized trial, SORAMIC, showed no difference in OS between patients who received SIRT followed by sorafenib and those who received sorafenib monotherapy (16). However, while these studies did not demonstrate the superiority of SIRT (with or without subsequent sorafenib treatment) to sorafenib with respect to OS, non-inferiority was not tested.

The aim of this study was to assess through meta-analysis of RCTs whether SIRT with <sup>90</sup>Y microspheres, as monotherapy or followed by sorafenib, is non-inferior to sorafenib in OS of patients with advanced HCC, and to compare the safety of both treatment strategies. RCTs of SIRT followed by sorafenib, compared with sorafenib alone, were included on the basis that SIRT was the initial treatment and sorafenib therapy was given sequentially, not simultaneously.

## METHODS

This meta-analysis was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The protocol for this meta-analysis is available in PROSPERO (CRD42019124372).

## **Data Sources and Search Strategy**

Searches were conducted in three databases MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL), and in the abstract books from four congresses (European Society for the study of the Liver [EASL] The International Liver Congress; American Society of Clinical Oncology [ASCO] annual congress and Gastrointestinal symposium [ASCO-GI]; and the European Society for Medical Oncology [ESMO], for 2018) with an end date of 14 February 2019. The filter ‘clinical trials’ was applied to the searches. No other limits were entered for the searches. The following search terms were used (search strategy for PubMed): “yttrium” [All Fields] AND "sorafenib" [All Fields] AND "hepatocellular carcinoma" [All Fields]. The Boolean operator ‘AND’ was used to narrow the search results. In addition, we searched the clinical trial registry ClinicalTrials.gov for unpublished completed trials.

## **Eligibility Criteria**

For inclusion in the meta-analysis, a study had to meet the following criteria: participants aged  $\geq 18$  with histologically or radiologically diagnosed advanced HCC (imaging or biopsy); interventional arm, SIRT with  $^{90}\text{Y}$ -resin microspheres either as a monotherapy or followed by sorafenib; and comparator arm, sorafenib as monotherapy. The studies had to be randomized clinical trials with full information and final study results published, or confirmed by the Principal Investigator, and include analyses of both intention-to-treat (ITT) and per-protocol (PP) populations.

The main outcomes assessed were OS and the frequency of adverse events (AEs). An additional outcome was tumor response assessments (assessed by the Response Evaluation Criteria In Solid Tumors [RECIST 1.1]) (17).

## **Screening and Selection Criteria**

Identified papers and congress abstracts were initially screened by title to remove duplicates and papers not fulfilling inclusion criteria from the review, and then screened in duplicate by two researchers using the abstracts retrieved from congress websites and PubMed, according to the criteria outlined below. The two researchers then reviewed each other’s selection. Full manuscripts of relevant papers from the initial screen were obtained and reviewed in detail for inclusion in this review.

## **Exclusions**

Papers were excluded if they were reviews, did not include outcome data, were case reports or case series, or were an opinion piece or a letter. Congress abstracts were excluded if they did not add information to that obtained in the main RCT publications, reported studies that subsequently appeared as published papers, were encore abstracts, or had insufficient information in the abstract to provide useful data.

## **Assessment of Risk Bias in Included Studies**

The two independent reviewers separately assessed the risk of bias of each included trial according to the recommendations from the Cochrane Handbook for Systematic Reviews of Interventions (18). Risk was assessed for allocation sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessors, incomplete outcome data, selective outcome reporting, for-profit bias and other biases (Supplemental Section 1).

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”. Disagreements were discussed, and the authors of the study were contacted, until consensus was reached. Further details of the risk of bias assessment are given in Supplemental Section 1.

## **Data Extraction**

Using a predefined meta-analysis form, two reviewers, working independently (MV and MP) extracted data from each study. The information collected included the names of the authors, title of the study, the journal in which the study was published or congress at which the study was presented, country and year of the study, treatment regimen, dosage, duration of treatment, testing sample size (with sex differentiation if applicable), the number of patients receiving each regimen, and the number of patients reporting treatment-related adverse events. After completing the data extraction, the two independent reviewers compared the results. Any differences in data extraction were resolved by consensus with a third review author (GL), referring back to the original article. The corresponding authors of the studies were contacted and agreed to contribute to the meta-analysis with individual participant data for protocol relevant analyses.

## Data Synthesis and Analysis

Three data-sets were used. The safety analysis set included all patients that received a study treatment. The per-protocol (PP) set excluded patients with major protocol deviations, such as no or incomplete study treatment. The PP set is regarded as the preferred set for investigating non-inferiority (19) and was therefore used for the primary efficacy analysis, the secondary efficacy analyses, and the subgroup analyses. However, regulatory agencies recommend analysis of both the PP and the ITT population and therefore the ITT set was used in a sensitivity analysis of OS. The ITT set comprised all patients for whom data were available and patients were analyzed according to their randomization group. The SIRT arm, comprised patients randomized to receive SIRT, whether or not followed by sorafenib, the sorafenib arm comprised patients randomized to sorafenib treatment. The proportion of patients in each baseline characteristics category was compared between the treatment arms by a z-test.

The primary endpoint of OS was tested for non-inferiority. The non-inferiority margin was set at 1.08 (corresponding to 60% retention of sorafenib effect vs. placebo, a value recommended in EASL guidelines, and based on previous phase III trials of sorafenib) (7,8,20). The primary outcome of the individual trials was compared between the two groups using a fixed-effect, inverse-variance weighted log hazard ratio (HR) individual participant data meta-analysis approach.

If the one-sided upper 95% confidence interval (CI) for this HR did not cross the non-inferiority boundary of 1.08 then this was interpreted as supporting evidence that the SIRT or SIRT followed by sorafenib was not appreciably worse than sorafenib.

To assess whether the variation in the effects of treatment across trials was greater than might be expected, a statistical evaluation of heterogeneity by  $\chi^2$  test was used. Heterogeneity was considered to be present if the  $\chi^2$  test delivered a  $p < 0.05$ . An  $I^2$  statistic was used to quantify the proportion of variation in the treatment effect in the study that is due to heterogeneity rather than chance. All computations and plots were carried out with STATA 14.0 (StateCorp LP., College Station, TX) with the Leandro's book Metanalysis software (21).

Prespecified subgroup analysis included demographic characteristics, age and gender, ECOG status, presence of liver cirrhosis, etiology of liver disease (hepatitis B, hepatitis C, alcohol), Child-Pugh score, BCLC stage, presence of portal vein invasion, and the absence of distant metastases.

## **RESULTS**

### **Study Selection**

The literature search identified 33 papers and congress abstracts, of which the reports of three trials, SIRveNIB (14), SARAH (15) and SORAMIC (16,22), fulfilled the eligibility criteria and were included in the meta-analysis (Figure 1). At the time of the literature search, two out of the three eligible studies, SIRveNIB (14) and SARAH (15), were fully published, and one study (SORAMIC) was presented at a congress (European Association for the Study of the Liver [EASL] in March 2018) (22). For the SORAMIC trial the presenting author (JR) provided the preliminary proof of the article along with the raw data to allow this meta-analysis. Accordingly, the full publication of SORAMIC is cited in this manuscript.

### **Study Characteristics**

Supplemental Table 1 shows year of study publication, study location, therapy regimens and characteristics of each study. The trials included a total of 1,243 patients with advanced HCC, and the PP population included 933 patients (Supplemental Table 2). There were no significant differences between the studies in the proportions of patients in each category (z-test for proportions).

### **Patient Allocation**

After randomization, 23.3% and 7.1% of patients, in the SIRT and sorafenib arms, respectively, did not receive the allocated treatment. The risk of not receiving the allocated treatment was higher in the SIRT than in the sorafenib arm (odds ratio [OR] 3.3, 95% CI: 2.5–4.4, relative risk [RR] 1.7, 95% CI: 1.5–1.8). Reasons for not receiving the allocated treatment after randomization are shown in Supplemental Table 3.

### **Results of Individual Studies**

OS for the PP and ITT populations in the individual studies are shown in Figure 2. In the PP population, OS in the SIRT arms were 11.0, 9.9 and 14.0 months vs. 10.0, 9.9, and 11.1 months in the sorafenib arm, in SIRveNIB, SARAH and SORAMIC, respectively.

### **Risk of Bias within Studies**

We considered all included trials to be at a low risk of bias. A detailed analysis of the risk of bias within the studies is reported in the Supplemental Section 2.

## Data Synthesis

In the meta-analysis, median OS in the PP population was 10.2 months in the SIRT arm and 9.2 months in the sorafenib arm, (pooled HR 0.91, 95% CI 0.78–1.05; Figures 2 and 3). There was a high degree of similarity (non-heterogeneity) between the study populations ( $\chi^2$  test for heterogeneity: 0.88,  $p=0.666$ ). The  $I^2$  statistic (variation in HR due to heterogeneity) was 0%. Analysis of OS in the ITT population also showed no significant difference between treatments (Figure 2).

The results of the subgroup analyses of the PP population are shown in Figure 4 and Supplemental Table 4. In all subgroups, the HR for OS was  $\leq 1.0$  and non-inferiority of SIRT to sorafenib was demonstrated in most subgroups. Superiority of SIRT to sorafenib was found in non-cirrhotic patients and patients with hepatitis B (Figure 4 and Supplemental Table 4). Patients included in SIRveNIB were younger and more likely to have ECOG 0 and hepatitis B.

Tumor response data by RECIST were not available from SORAMIC, and the combined analysis of SIRveNIB and SARAH is shown in Table 1.

The safety population included 1,090 patients with advanced HCC, 515 received SIRT and 575 received sorafenib as monotherapy (Table 2). In the SIRveNIB and SARAH trials, AEs and SAEs were more numerous in the sorafenib arms than the SIRT arms, and in SORAMIC the addition of SIRT to sorafenib did not increase the AE rate (Table 2). The incidence of treatment-related AEs  $\geq 3$  grade in the SIRveNIB and SARAH trials was lower for SIRT than for sorafenib (30.6% vs. 52.1%, respectively,  $p=0.0002$ , data not shown). In SORAMIC, the incidence of treatment-related  $\geq 3$  grade AEs was slightly higher with SIRT followed by sorafenib, compared with sorafenib monotherapy, without reaching statistical significance.

## DISCUSSION

Our meta-analysis included the results of three RCTs comparing SIRT, as monotherapy (SIRveNIB, SARAH) or followed by sorafenib (SORAMIC) with sorafenib alone. The findings indicate that initial SIRT, whether or not followed by sorafenib, is non-inferior to sorafenib in terms of OS (HR 0.91, 95% CI 0.78–1.05) for patients in whom SIRT proved feasible. Furthermore, the safety profile of SIRT is significantly better than that of sorafenib. The better safety profile of SIRT was confirmed by the pooled analysis of the individual studies, even with the inclusion of the SORAMIC data.

Although the study design of SIRveNIB had more similarities to that of SARAH than to SORAMIC, the HR and 95% CIs for OS reported in SIRveNIB differed from those in SARAH, but

nearly overlapped with those in SORAMIC. The higher total bilirubin levels allowed for inclusion in SARAH ( $\leq 50 \mu\text{mol/l}$ ), compared with SIRveNIB and SORAMIC ( $\leq 32 \mu\text{mol/l}$ ) is a likely explanation for these differences.

Subgroup analyses suggested that non-inferiority of SIRT, whether or not followed by sorafenib, compared with sorafenib alone was consistent across subgroups. Notably, SIRT was superior to sorafenib in terms of OS among patients with HCC etiologically linked to hepatitis B infection and those without liver cirrhosis. These populations may partially overlap as HCC arising in the absence of liver cirrhosis is mostly etiologically linked to hepatitis B infection, hepatitis C infection, or non-alcoholic fatty liver disease (23). The benefit derived from sorafenib therapy appears to be lower in patients with chronic hepatitis B virus (HBV)-related HCC, compared with patients with HCC of other etiologies, however no plausible causal explanation has been given for this clinically relevant observation (24,25). Unlike patients with HCC and liver cirrhosis, where both diseases have prognostic relevance, in non-cirrhotic patients, HCC is the sole life-threatening disease. In the latter patient cohort, the intact liver function may allow consecutive tumor-specific systemic therapies, even in cases of rapid progression after SIRT, and this may account for the better OS in our analysis.

In the pooled analysis of SIRveNIB and SARAH, SIRT leads to a statistically significantly higher percentage of partial responses, whereas there was a higher percentage of stable diseases in the sorafenib arm. Consequently, disease control rates did not differ between the two comparison groups. With respect to sorafenib, our data are in line with the results of the SHARP trial where the percentage of stable diseases mainly accounted for disease control rates whereas partial responses were exceptional and no complete response was observed in patients receiving sorafenib.

According to current recommendations for the design, reporting, and interpretation of non-inferiority trials, the data-set for the full analysis, based on the ITT principle, and the data-set for the PP analysis, should have equal importance, and for a robust interpretation their use should lead to similar conclusions. However, in some instances a PP analysis, which excludes patients who did not receive the randomized per-protocol assignment, may be preferable in a non-inferiority trial (19). In the present meta-analysis, non-inferiority was clearly demonstrated in the PP population, but was not confirmed in the ITT population. The study design and study protocols, of the three studies included in this analysis, with the unusual comparison of a loco-regional therapy with a systemic therapy are the main reasons for this discrepancy. For example, the time interval between randomization and SIRT in the monotherapy trials was 4–5 weeks as could be predicted from the study protocols, whereas patients allocated to sorafenib received the drug within 1 week. During the 4–5 weeks between randomization

and SIRT, deterioration of the patient's general condition, worsening liver function, or progression of HCC precluded a substantial proportion of patients from receiving the allocated SIRT. Furthermore, 11.5% of patients allocated to SIRT had liver-to-lung shunting or were ineligible for SIRT for technical reasons. Thus, for future trials, key prerequisites for more consistent results in the ITT and PP analyses are: ascertaining SIRT eligibility before randomization; and earlier delivery of SIRT. Notably, the increased sites of production for SIR-Spheres microspheres have reduced the shipment times resulting in earlier delivery of SIRT.

A possible drawback of a PP analysis is the low number of participants, and this was the case in each of the three trials included in this meta-analysis. To overcome this drawback, we pooled the individual patient data of the three trials to test the non-inferiority of SIRT to sorafenib. However, heterogeneity between the study populations can make the results difficult to interpret. When combining the PP populations in the present study, heterogeneity tests indicated a high degree of similarity (non-heterogeneity) between the three studies. In addition, a PP analysis that includes fewer participants may introduce post-randomization bias, since baseline characteristics may no longer be balanced between treatment groups. However, this was not the case in our meta-analysis as no significant differences in baseline characteristics were found between the treatment groups of the PP population.

A limitation of this meta-analysis is that only three studies met the selection criteria. A strength of our meta-analysis is the inclusion of individual patient data.

## **CONCLUSION**

Our findings indicate that, whenever feasible, SIRT as initial therapy for advanced HCC is non-inferior to sorafenib in OS and offers a better safety profile.

According to our analysis, SIRT may prove not feasible in roughly 10% of patients with advanced HCC. In these patients, systemic therapy is the standard of care. Early phase trials exploring the efficacy and safety of combining SIRT with check-point inhibitors, modern tyrosine kinase inhibitors and antibodies inhibiting angiogenesis are ongoing or being currently designed.

## **DISCLOSURES**

Marino Venerito: Honoraria: Nordic Pharma, Merck Serono, Bayer Vital, Lilly and Sirtex; Advisory role member: Ipsen, Lilly, Nordic Pharma, BMS, MSD, Eisai and Amgen.

Gilles Chatellier: Research funding: Sirtex.

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Pierce K.H. Chow: Honoraria: Sirtex Medical, QuintilesIMS, Guerbet, Merck Serono; ; Speakers' bureau or advisory role or consulting: Sirtex Medical, Ipsen, Oncosil Medical, Bristol-Myers Squibb, MSD; Research Funding: Sirtex Medical (Inst), New B Innovation (Inst), QuintilesIMS (Inst); Travel, Accommodations, Expenses: Roche.

Valérie Vilgrain: Honoraria: Sirtex.

Peter Malfertheiner: Speakers' bureau or consulting: Biocodex, Biohit, Danone, Mayoly-Spindler.

Jens Ricke: Research funding and speaker's bureau: Bayer and Sirtex.

Maciej Pech, Ali Canbay, Rossella Donghia, Vito Guerra and Gioacchino Leandro: nothing to declare.

No other potential conflicts of interest relevant to this article exist.

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## **AUTHOR CONTRIBUTIONS:**

Guarantors of integrity of entire study: Marino Venerito.

Marino Venerito Gioacchino Leandro and Jens Ricke were responsible for the design of the study, and for conducting the literature searches and literature selection.

Marino Venerito, Maciej Pech and Gioacchino Leandro performed the data extraction, and Marino Venerito, and Gioacchino Leandro conducted the data analysis.

Jens Ricke, Mihir Gandhi, Pierce K.H. Chow, Valérie Vilgrain, Gilles Chatellier, and Helena Pereira provided additional data from the individual trials.

All authors contributed to the data interpretation, and writing, reviewing and revision of the manuscript and all authors gave their final approval for submission.

## **KEY POINTS**

**QUESTION:** Is selective internal radiotherapy (SIRT), as monotherapy or followed by sorafenib, non-inferior to sorafenib in overall survival in patients with advanced hepatocellular carcinoma?

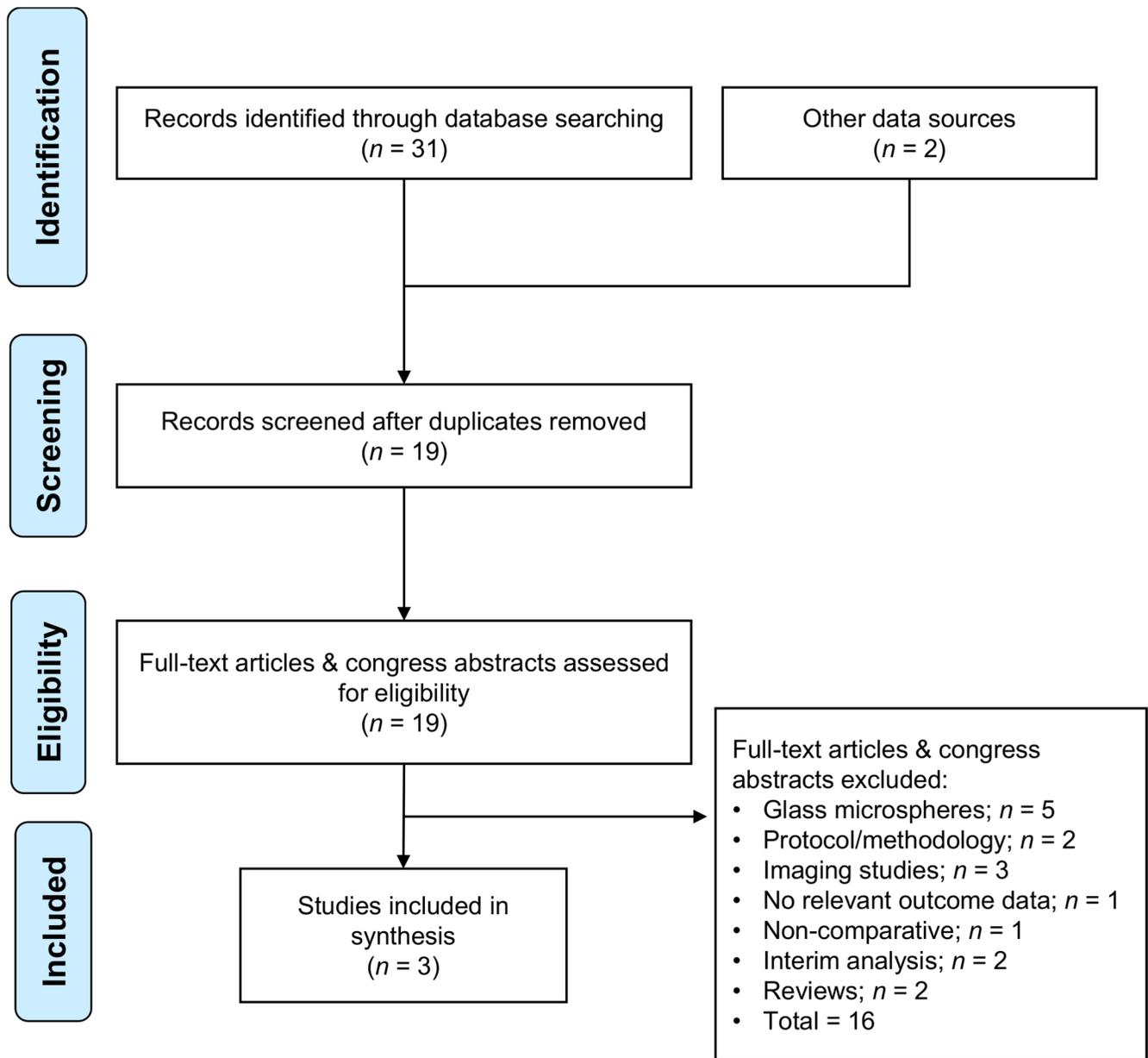
**PERTINENT FINDINGS:** In a non-inferiority, individual patient meta-analysis of SIRT with yttrium-90 resin microspheres versus sorafenib in advanced hepatocellular carcinoma we show that SIRT as initial therapy for advanced HCC is non-inferior to sorafenib in terms of overall survival, and offers a better safety profile.

**IMPLICATIONS FOR PATIENT CARE:** Patients eligible for first-line sorafenib treatment for advanced HCC, could be offered SIRT as an effective, safer therapeutic option.

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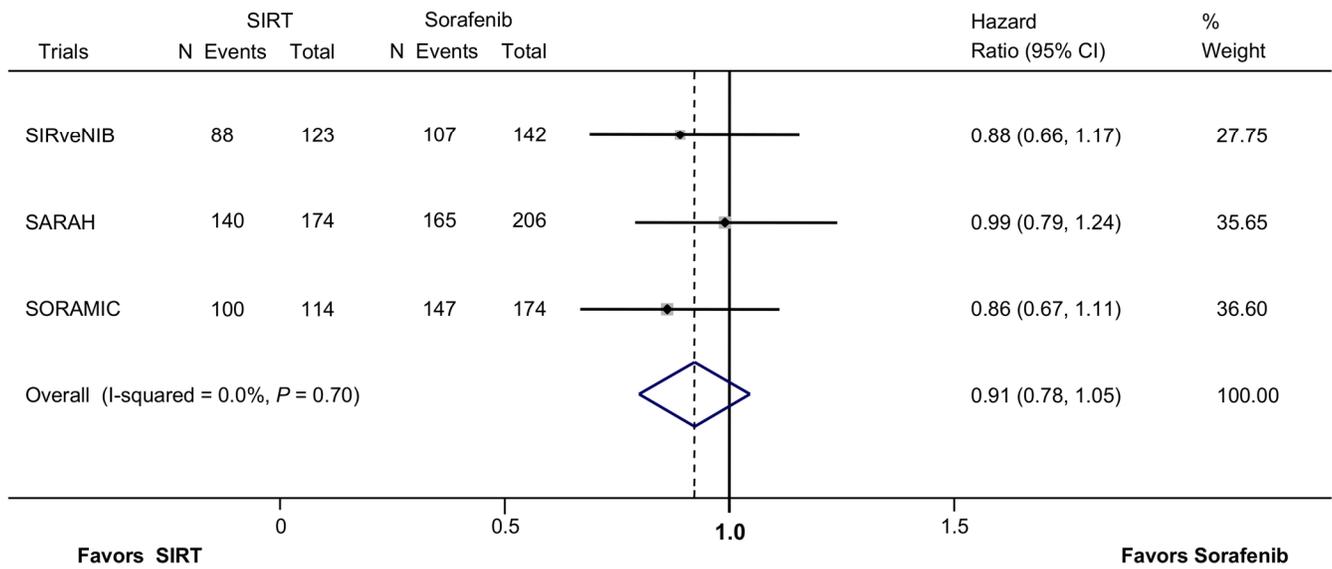
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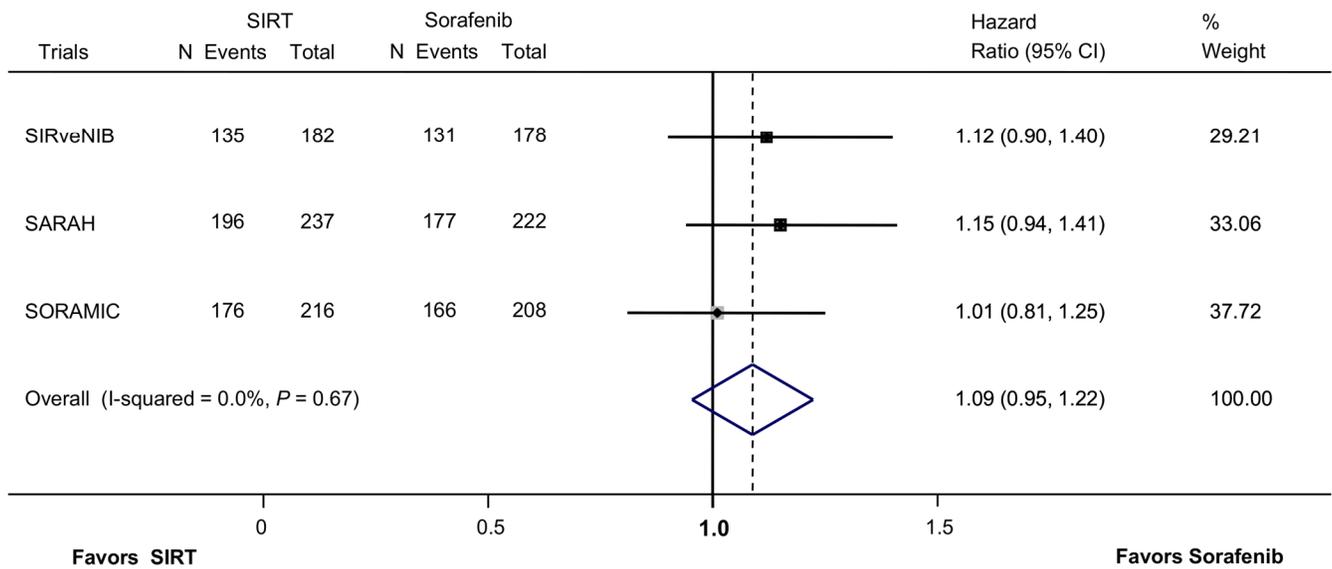


**Figure 1** PRISMA flow diagram for the review

A



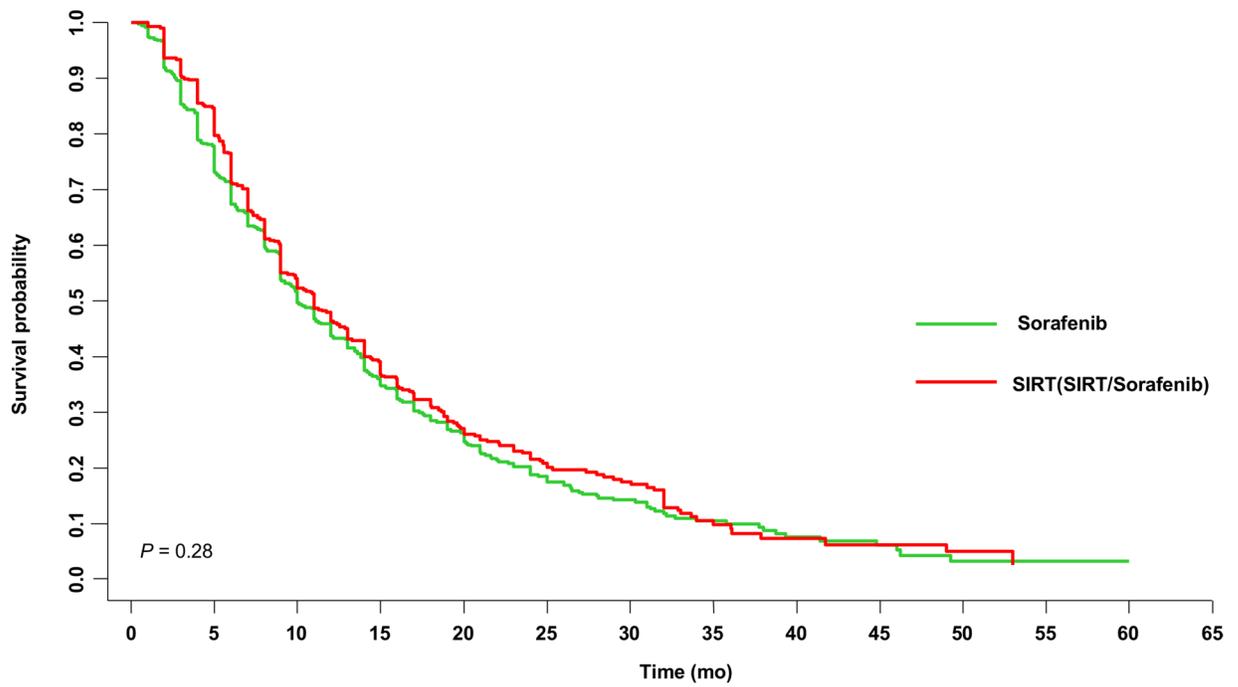
B



**Figure 2** Overall survival for SIRT vs sorafenib in patients with HCC in the individual trials and in the meta-analysis of SIRveNIB, SARAH and SORAMIC A) per-protocol population, B) intention-to-treat-population. Dotted line indicates the overall, pooled estimate.

Dotted line indicates the overall, pooled estimate. Size of shaded grey boxes indicates the relative weight of the study.

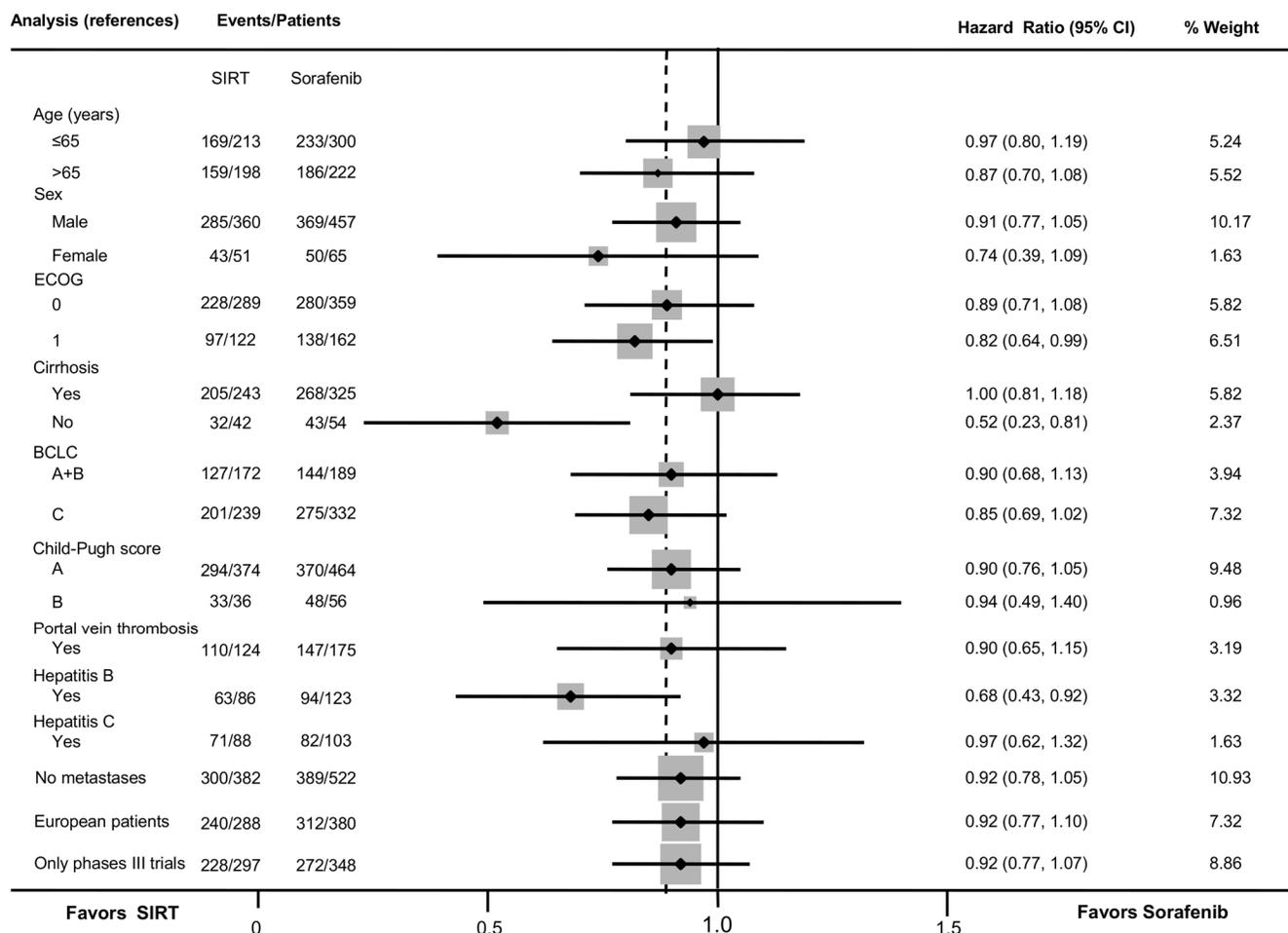
N: number of.



Number at risk (Number failure)

	0	5	10	15	20	25	30	35	40	45	50	55	60
Sorafenib	513 (113)	388 (127)	249 (73)	159 (40)	99(28)	59(13)	39(9)	24(5)	12(2)	8(3)	3(0)	2 (0)	1(0)
SIRT-(SIRT/Sorafenib)	410 (64)	339 (120)	214 (57)	140 (41)	84 (18)	54(8)	37(13)	15(4)	7(1)	6(1)	4(1)	0 (0)	0 (0)

**Figure 3** Kaplan-Meier plot of overall survival for SIRT followed or not by sorafenib vs sorafenib monotherapy in the per-protocol population of patients with HCC.



**Figure 4** Subgroup analyses of overall survival for SIRT, followed or not by sorafenib, vs sorafenib monotherapy in the per-protocol population of patients with HCC (N=933).

Dotted line indicates the overall, pooled estimate. Size of shaded grey boxes indicates the relative weight of the analysis. Cirrhosis: Data available only for SARAH and SORAMIC.

**Table 1** Comparison of tumor responses (RECIST 1.1) in the per-protocol population of the SIRveNIB and SARAH trials<sup>a</sup>

	SIRT			Sorafenib			p-value <sup>b</sup>
	SIRveNIB	SARAH	Combined	SIRveNIB	SARAH	Combined	
	123	174	297	142	206	348	
ORR (CR+PR) (%)	27 (21·9)	32 (18·4)	59 (19·9)	3 (2·1)	23 (11·2)	26 (7·5)	<0·0001
DCR (CR+PR+SDis) (%)	72 (58·5)	115 (66·1)	187 (63·0)	67 (47·2)	148 (71·8)	215 (61·8)	0·81
CR (%)	0 (0·0)	4 (2·3)	4 (1·3)	0 (0·0)	2 (1·0)	2 (0·6)	0·42
PR (%)	27 (21·9)	28 (16·1)	55 (18·5)	3 (2·1)	21 (10·2)	24 (6·9)	<0·0001
SDis (%)	45 (36·6)	83 (47·7)	128 (43·1)	64 (45·1)	125 (60·7)	189 (57·3)	0·005
PD (%)	27 (21·9)	49 (28·2)	76 (25·6)	41 (28·9)	40 (19·4)	81 (23·3)	0·23
Not done/not evaluable	24 (19·5)	10	34 (11·4)	34 (23·9)	18	52 (14·9)	0·20

CR, complete response; PR, partial response; SDis Stable disease; DCR, disease control rate; ORR: objective response rate; PD, progressive disease; SIRT, selective internal radiation therapy.

The numbers (CR+PR+SDis+PD) do not add up to the total N for the SIRveNIB trial due to a small proportion of patients with non-evaluable/missing data.

<sup>a</sup>The SORAMIC trial is not included as tumor response was not an endpoint of the study

<sup>b</sup>SIRT vs Sorafenib

**Table 2 Treatment-related adverse events in the safety population of the SIRveNIB, SARAH and SORAMIC trials**

Arm	SIRT				Sorafenib		
	SIRveNIB	SARAH	SORAMIC <sup>a</sup>	Combined	SIRveNIB	SARAH	SORAMIC
AE (%)	41/130 (31.5)	173/226 (77.0)	113/159 (71.1)	327/515 (63.5)	121/162 (74.7)	203/216 (94.0)	139/197 (70.6)
AE ≥3 (%)	17/130 (13.1)	92/226 (41.0)	40/159 (25.2)	149/515 (28.9)	61/162 (37.7)	136/216 (63.0)	52/197 (26.4)
SAEs (%)	6/130 (4.6)	45/226 (20)	63/159 (39.6)	114/515 (22.1)	15/162 (9.3)	56/216 (26.0)	78/197 (39.6)

AE: adverse events; SAE: serious adverse events;

<sup>a</sup> in the SIRT arm 114/159 patients received sorafenib after SIRT.

## 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).<sup>1</sup> The following definitions in the assessment of risk of bias were used:<sup>2-6</sup>

#### *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

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## **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	<ul style="list-style-type: none"> <li>- aged <math>\geq 18</math> years old;</li> <li>- unequivocal diagnosis of HCC (imaging or biopsy);</li> <li>- Child-Pugh score <math>\leq 7</math>;</li> <li>- BCLC stage B or C without extrahepatic disease with or without PVT;</li> <li>- not amenable to curative treatment modalities;</li> <li>- <b>bilirubin <math>\leq 32 \mu\text{mol/L}</math></b></li> </ul>	<ul style="list-style-type: none"> <li>- aged <math>\geq 18</math> years old;</li> <li>- unequivocal diagnosis of HCC (imaging or biopsy);</li> <li>- Child-Pugh score <math>\leq 7</math>;</li> <li>- BCLC stage B or C without extrahepatic disease with or without PVT;</li> <li>- not amenable to curative treatment modalities;</li> <li>- <b>total bilirubin <math>\leq 50 \mu\text{mol/L}</math>.</b></li> </ul>	<ul style="list-style-type: none"> <li>- aged <math>\geq 18</math> years old;</li> <li>- diagnosis of HCC (imaging or biopsy);</li> <li>- Child Pugh <math>\leq 7</math>;</li> <li>- BCLC stage B or C without TACE per investigator decision) and C;</li> <li>- <b>bilirubin <math>\leq 32 \mu\text{mol/L}</math></b></li> <li>- Prior resection or vascular procedures (PEI, hepatic artery-directed therapy, RFA) permitted; Post hepatic artery-directed therapy: &gt; 3 months interval and revascularization present</li> <li>- <b>Extra-hepatic disease permitted</b></li> </ul>
Exclusion criteria	<ul style="list-style-type: none"> <li>- Received &gt;2 previous administrations of hepatic artery-directed therapy;</li> <li>- hepatic artery-directed treatment &lt; 4 weeks;</li> <li>- previous treatment with Sorafenib</li> <li>- previous VEGF inhibitors,</li> <li>- previous radiotherapy</li> <li>- <b>extrahepatic disease.</b></li> <li>- For patients randomized to receive SIRT: liver-to-lung shunt with &gt; 20 Gy being delivered to the lungs.</li> </ul>	<ul style="list-style-type: none"> <li>- Received &gt;2 previous administrations of hepatic artery-directed therapy;</li> <li>- previous treatment of the current nodule (excluding transarterial chemoembolization);</li> <li>- previous treatment with Sorafenib</li> <li>- <b>extrahepatic metastasis;</b></li> <li>- For patients randomized to receive SIRT: Liver-to-lung shunt greater than 20% / liver-to-lung shunt leading to a lung dose &gt; 25 Gy (amendment).</li> </ul>	<ul style="list-style-type: none"> <li>- Previous external beam radiation therapy to the liver;</li> <li>- Previous therapy with tyrosine kinase inhibitors;</li> <li>- For patients randomized to receive SIRT: liver-to-lung shunt leading to a lung dose &gt;30 Gy;</li> </ul>
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	<b>Within 5 weeks of random assignment.</b>	<b>Within 5 weeks of random assignment.</b>	<b>Within 4 weeks of random assignment.</b>
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	<ul style="list-style-type: none"> <li>- In bilobar tumors, the first treatment was administered in the hemiliver with the greatest tumor burden.</li> <li>- Treatment of the contralateral hemi-liver was scheduled 30–60 days after the first treatment.</li> </ul>	<ul style="list-style-type: none"> <li>- In bilobar tumors, the second SIRT was performed at 4-6 weeks after the first treatment</li> </ul>

<b>Sorafenib therapy</b>	Start with 400 mg bid in the week after random assignment.  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.  Sorafenib administered until the occurrence of radiological progression, unacceptable adverse events, or death.	- In the no-SIRT arm start with sorafenib 400 mg bid; -In the SIRT arm start with sorafenib 3 days after final SIRT, begin with 200 mg bid, escalation to 400mg bid at day 10.
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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**

Study	SIRT				Sorafenib				p <sup>a</sup>
	SIRveNIB	SARAH	SORAMIC	Combined	SIRveNIB	SARAH	SORAMIC	Combined	
<b>Number of patients</b>	123	174	114	411	142	206	174	522	
<b>Age (years) (SD)</b>	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 <sup>b</sup>
<b>Male (%)</b>	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
<b>ECOG 0 (%)</b>	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
<b>ECOG 1 (%)</b>	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
<b>Cirrhosis (%)</b>	NA	154 (88.5)	89 (80.2)	243 (84.0)	NA	187 (90.8)	138 (79.8)	325 (85.5)	0.62
<b>BCLC A (%)</b>	0	7 (4.0)	4 (3.5)	11 (3.8)	1 (0.6)	9 (4.4)	3 (1.7)	13 (2.4)	0.84
<b>BCLC B (%)</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
<b>BCLC C (%)</b>	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
<b>Child Pugh A (%)</b>	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
<b>Child Pugh B 7 (%)</b>	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
<b>(main) PVT (%)</b>	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
<b>Hepatitis B (%)</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
<b>Hepatitis C (%)</b>	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
<b>Alcohol etiology (%)</b>	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

<sup>a</sup>Z-test for proportions of each category for SIRT vs sorafenib.

<sup>b</sup>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 <sup>b</sup> (15.3)	138 (21.3)	16 (9.0)	6 (3.7)	11 <sup>b</sup> (5.3)	33 (5.4)	<0.0001
Liver-to-lung shunting/ Ineligible for SIRT for technical reasons, n (%)	37 (20.3)	26 <sup>a</sup> (11.0)	15 <sup>a</sup> (6.9)	78 (12.3)	0	0	0	0	<0.0001
Other reasons <sup>c</sup> n (%)	15 (8.2)	27 <sup>a</sup> (11.4)	18 (8.3)	60 (9.4)	16 (9.0)	6 (3.7)	11 (5.3)	33 (5.4)	0.007

<sup>a</sup>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.

<sup>b</sup> Did not receive SIRT: 18 received no treatment and 15 received sorafenib only (crossover).

<sup>c</sup>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 <sup>2</sup> (%)
<b>Age (years)</b>						
≤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
<b>Sex</b>						
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
<b>ECOG</b>						
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	-
<b>Cirrhosis<sup>a</sup></b>						
Yes	2	1.00	0.81–1.18	<0.01	0.83	-
No	2	0.52	0.23–0.81	<0.01	0.19	-
<b>BCLC</b>						
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	-
<b>Child Pugh score</b>						
A	3	0.90	0.76–1.05	<0.01	0.60	-
B	3	0.94	0.49–1.40	<0.01	0.92	-
<b>Portal vein thrombosis</b>						
Yes	3	0.90	0.65–1.15	<0.01	0.47	-
<b>Hepatitis B</b>						
Yes	3	0.68	0.43–0.92	<0.01	0.79	-
<b>Hepatitis C</b>						
Yes	3	0.97	0.62–1.32	<0.01	0.25	27.70
<b>No metastases</b>						
	3	0.92	0.78–1.05	<0.01	0.70	-
<b>European patients</b>						
	2	0.92	0.77–1.10	<0.01	0.42	-
<b>Only phase III trials</b>						
	2	0.92	0.77–1.07	<0.01	0.40	-

<sup>a</sup>Data available only for SARAH and SORAMIC