

## SARAH AND SIRveNIB: TWO RECENT STUDIES IN HEPATOCELLULAR CARCINOMA (HCC)

### What are the SARAH and SIRveNIB studies?

The SARAH and SIRveNIB studies are two large multi-centre Randomised Controlled Trials (RCT) that compared the efficacy and safety of SIR-Spheres® Y-90 resin microspheres versus sorafenib in European and Asian patient populations respectively. The two studies combined enrolled more than 800 patients.

Sorafenib is the standard systemic therapy for patients with unresectable locally advanced HCC and well-preserved liver function. It was first approved in 2007, based on a pivotal study that demonstrated an increase in median survival from 7.9 months to 10.7 months in patients with advanced disease.<sup>1</sup>

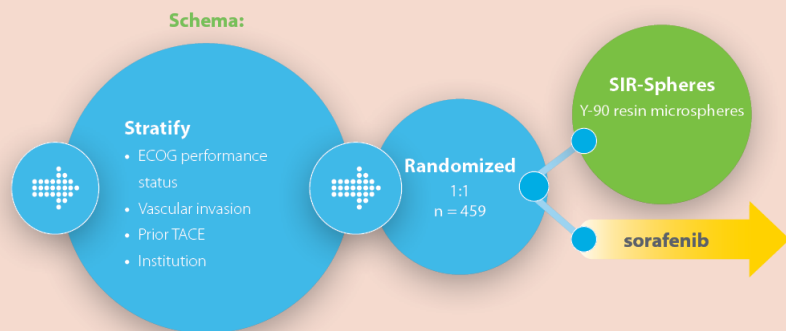
The SARAH Study (Sorafenib versus Radioembolisation in Advanced Hepatocellular Carcinoma) was a French multi-centre prospective randomised open-label study, and the first randomised head-to-head study to compare Selective Internal Radiation Therapy (SIRT) with sorafenib in advanced HCC in a Caucasian population.

The SARAH study was initiated in December 2011 and completed enrolment of 467 patients in March 2015.

### The SARAH Study

#### Eligible Patients:

- Unresectable HCC
- BCLC stage C or
- BCLC stage A/B:
  - New lesions post-radical therapy and unsuitable for further radical therapy or
  - No objective response after ≤2 TACE sessions
- Child-Pugh class A or B ≤7 points
- ECOG performance status 0-1
- Fit for sorafenib and SIRT
- Limited extrahepatic disease (e.g. non-specific pulmonary tumours <1 cm and abdominal lymph nodes <2 cm)



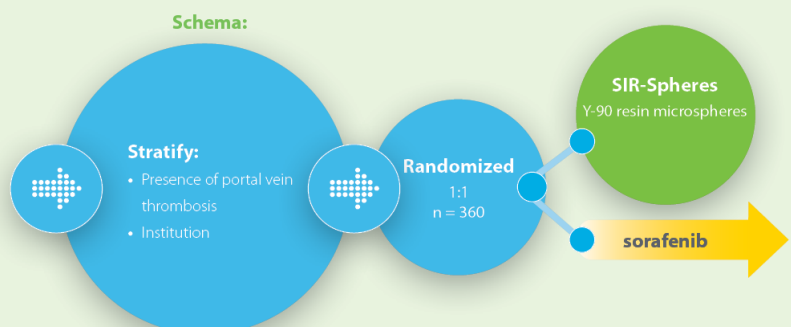
SIRveNIB (SIR-Spheres versus sorafenib) was a multi-centre prospective randomised open-label study to compare the efficacy and safety of SIR-Spheres Y-90 resin microspheres versus sorafenib conducted in sites in Asia and New Zealand.

The study began in 2010 and completed its planned enrolment of 360 patients in May 2016.

### The SIRveNIB Study

#### Eligible Patients:

- Unresectable HCC
- BCLC stage B or C
- Child-Pugh class A or B ≤7 points
- ECOG performance status 0-1
- Fit for sorafenib and SIRT
- Limited extrahepatic disease (e.g. lung nodules <1 cm or local-regional lymph nodes <2 cm)



## What is the significance of these studies?

Since 2007, sorafenib has been the first-line treatment of choice in advanced HCC. The SARAH and SIRveNIB studies examined whether radioembolisation using SIR-Spheres Y-90 resin microspheres was more effective than a long-standing standard of care that has been the subject of unsuccessful comparative studies for a decade.

The researchers did not find a statistically significant difference in overall survival (OS) between the local treatment group with SIR-Spheres Y-90 resin microspheres and the group treated with sorafenib, which was the primary objective of both the SARAH and SIRveNIB studies.

However, the difference in the frequency and severity of side effects of patients treated with SIR-Spheres Y-90 resin microspheres versus sorafenib was striking, in both European and Asian populations. Significantly fewer patients experienced adverse events, of any grade and of grade  $\geq 3$ , in the SIRT arm. There were also few SIRT-associated treatment-related complications and, importantly, radioembolization-induced liver disease (radiation hepatitis) affected no patients in the SARAH study and only two patients in the SIRveNIB study.

Moreover, patient Quality of Life according to the global health status sub-score of the QLQ-C30 questionnaire reported in the SARAH study was significantly better in the SIRT arm.

The authors of the SARAH publication stated, “Quality of life and tolerance might help when choosing between the two treatments”.

## Which outcomes were measured in these studies?

The primary endpoint of both the SARAH and SIRveNIB studies was OS and the primary objective was to demonstrate a significant increase in overall survival with SIR-Spheres Y-90 resin microspheres compared with sorafenib.

The secondary endpoints were:

- for the SARAH study:
  - Progression-free survival (PFS)
  - Progression at any site
  - Progression in the liver as the first event
  - Tumour response (RECIST 1.1)
  - Disease control
  - Safety and toxicity
  - Health-Related Quality of Life (global health status sub-score, QLQ-C30)

Secondary endpoints of non-tumour liver and tumour dosimetry, cost analysis and QLQ-HCC18 and the remaining sub-scores of QLQ-C30 will be reported in a separate paper.

- for the SIRveNIB study
  - Safety and toxicity
  - PFS overall and in the liver
  - Time to disease progression (overall and in liver)
  - Tumour response (RECIST 1.1)
  - Disease control rate
  - Health-related quality of life assessed by EQ-5D-3L utility index

## Where were SARAH and SIRveNIB conducted?

The European SARAH study enrolled patients in 25 centres throughout France. The Asian SIRveNIB study was conducted in 27 specialist centres in 11 Asia-Pacific countries including Singapore, Myanmar, Philippines, Mongolia, Thailand, Indonesia, Malaysia, South Korea, Taiwan, New Zealand and Brunei Darussalam.

## Which types of patients were included in these studies?

Both studies included patients with:

- Unresectable HCC
- ECOG performance status 0-1
- Child-Pugh class A or B  $\leq 7$  points

In the SARAH study, the following additional inclusion criteria were used:

- BCLC stage C or
- BCLC stage A/B:
  - with recurrence of HCC after surgical or loco-regional treatment not eligible for surgical resection, liver transplantation nor RFA or
  - who have not achieved an objective response after  $\leq 2$  sessions of TACE in the target lesions
- No extra-hepatic disease (pulmonary nodules  $< 1$  cm and lymph nodes  $< 2$  cm were permitted)

In the SIRveNIB study, the additional following inclusion criteria were used:

- BCLC stage C or B (branch portal vein thrombosis allowed)
- No extra-hepatic disease (lung nodules  $< 1$  cm and local-regional lymph nodes  $< 2$  cm were permitted)

## Which types of patients were excluded from the SARAH and SIRveNIB studies?

In the SARAH study, patients were excluded if, for example, their advanced HCC had been treated previously with systemic therapy. Patients who had previously received TACE or other loco-regional/radical therapies were eligible for the study.

Patients were excluded from the SIRveNIB study if they had received  $> 2$  administrations of hepatic arterial-directed therapy or hepatic arterial-directed therapy  $< 4$  weeks prior to study entry; complete portal vein thrombosis; prior systemic chemotherapy or hepatic radiation therapy for HCC.

Patients were also excluded if they were pregnant or breast feeding at the time of the study.

## What were the results of the SARAH and SIRveNIB studies?

The study results did not show a significant difference in overall survival for the use of SIR-Spheres Y-90 resin microspheres compared to standard chemotherapy in patients with advanced HCC, which was the primary endpoint, but significantly reduced the number and severity of treatment-related adverse effects.

In the intention-to-treat population, the overall survival was not significantly different between the two arms for both the SARAH (median 8.0 vs. 9.9 months for the sorafenib group; HR= 1.15;  $p= 0.18$ ) and the SIRveNIB studies (median 8.84 vs. 10.02 months, respectively; HR= 1.12;  $p= 0.360$ ) despite 22% and 28,6% of patients in the SIRT arm not receiving SIR-Spheres Y-90 resin microspheres in SARAH and SIRveNIB, respectively.

Looking at the patients who actually received SIR-Spheres Y-90 resin microspheres or sorafenib per the study's protocol, median OS was identical in the SARAH study (9.9 vs. 9.9 months; HR= 0.99;  $p= 0.92$ ) and a modest but not statistically significant trend in favour of SIRT was shown in the SIRveNIB study (median OS 11.27 vs. 10.41 months, HR= 0.86;  $p= 0.273$ ).

In terms of safety, significantly fewer patients treated with SIR-Spheres Y-90 resin microspheres in the SARAH study had any treatment-related side effects at all (77% vs. 94% for sorafenib;  $p < 0.001$ ), and these were also less severe ( $\geq$  grade 3; 41% vs. 63%, respectively;  $p < 0.001$ ). Moreover, those patients treated with SIR-Spheres Y-90 resin microspheres who reported treatment-related side effects experienced a median of only 5 such events over the course of the SARAH study, compared to a median of 10 events in those who received sorafenib ( $p < 0.001$ ).

The comparative data on side effects reported in the SIRveNIB study unequivocally favoured SIR-Spheres Y-90 resin microspheres over sorafenib. In addition to two-fold fewer severe adverse events, about one fourth as many adverse events (60.0% vs. 84.6%  $p < 0.0001$ ) as well as fewer serious adverse events (20.8% vs. 35.2%;  $p= 0.009$ ) were observed.

In both studies, patients treated with SIR-Spheres Y-90 resin microspheres reported substantially less debilitating side effects such as fatigue (45% vs 76% (SARAH) and 4% vs 15% (SIRveNIB)), diarrhoea (13% vs 77% (SARAH) and 2% vs 30% (SIRveNIB)), hypertension (3% vs 15% (SARAH) and 0% vs 15% (SIRveNIB)) or hand-foot skin reaction ( $< 1\%$  vs 23% (SARAH) and 1% vs 55% (SIRveNIB)) and only few SIRT-associated treatment-related complications.

Finally, the results of Quality of Life (QoL) surveys filled out by SARAH participants at three month intervals after their initial treatment underscored the benefit of SIR-Spheres Y-90 resin microspheres. Patients treated with SIR-Spheres Y-90 resin microspheres maintained their global health status over the duration of the study, whereas patients receiving sorafenib reported a significant and sustained decline in QoL (group effect:  $p= 0.005$ ; time effect:  $p< 0.0001$ ; group-time interaction:  $p= 0.045$ ).



SIR-Spheres Y-90 resin microspheres are tiny radioactive resin beads that emit radiation and possess unique physical characteristics and biological effects.<sup>4</sup> They are only about one third the width of a human hair and have about the same specific gravity as a red blood cell. This enables the microspheres to flow easily in the blood and become lodged in the small blood vessels around the liver tumour where they destroy it while sparing the surrounding healthy tissue.

SARAH and SIRveNIB were direct head-to-head comparisons between SIR-Spheres Y-90 resin microspheres and sorafenib. A third study that is soon to be reported, SORAMIC (see separate backgrounder) has studied the effect of treatment with SIRT prior to sorafenib, versus treatment with sorafenib alone in patients with advanced HCC.

---

*For more information please visit:*

[www.sirtex.com/HCC](http://www.sirtex.com/HCC)

[www.sirtex.com](http://www.sirtex.com)

---

1. Llovet JM *et al. N Engl J Med* 2008; **359**: 378–90.
2. Vilgrain V *et al. Lancet Oncol* 2017; **18**: 1624–36.
3. Chow PKH *et al. J Clin Oncol* 2017; **35** (Suppl): Abs 4002.
4. Walrand S *et al. J Nucl Med* 2014; **55**: 1317–22.