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THE SARAH STUDY IN ADVANCED HCC: IMPLICATIONS FOR CLINICAL PRACTICE

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SARAH TRIAL
SORAFENIB VS. RADIOEMBOLIZATION IN ADVANCED HEPATOCELLULAR CARCINOMA

Vilgrain V, Bouattour M, Sibert A and the SARAH group France

AIMS OF THE SARAH TRIAL

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- Prospective open-label, phase 3, multi-center, investigator-based RCT
  - Locally advanced HCC and inoperable HCC who failed after 2 rounds of TACE
  - Comparison of selective internal radiation therapy (SIRT) to sorafenib

- **Primary objective**
  - Overall survival (OS)
- **Secondary objectives**
  - Progression-free survival
  - Incidence of progression in the liver / outside the liver
  - Tumor response rate
  - Tolerance, Quality of Life

TACE = transcatheter arterial chemoembolization

MAIN RESULTS OF SARAH TRIAL: PRIMARY OBJECTIVE

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- In this study, 459 patients were included, the majority of them with alcoholic cirrhosis

- Two third of patients were BCLC C (with macroscopic vascular invasion, but no extrahepatic metastasis)
- 16% of patients were Child Pugh-B7

- In the **intention-to-treat** analysis, **the primary objective of the study was not reached**: **SIRT was not superior to sorafenib in this setting**. Median OS was of **8.0 months** SIRT group and **9.9 months** in sorafenib groups, P=0.18
- Analysis performed in the **per-protocol population** showed that OS was 9.9 months in both groups

BCLC = Barcelona Clinic Liver Cancer staging

OVERALL SURVIVAL

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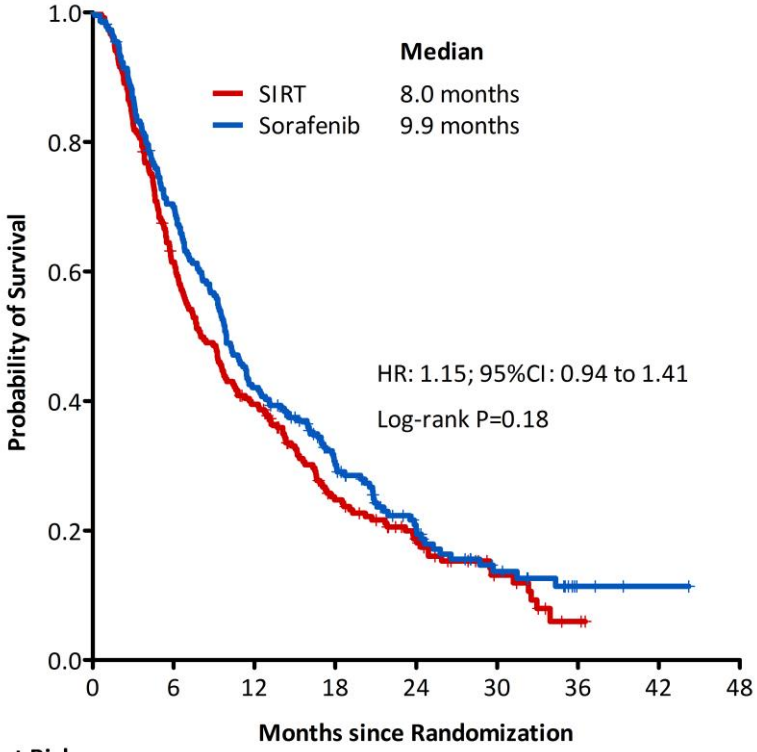
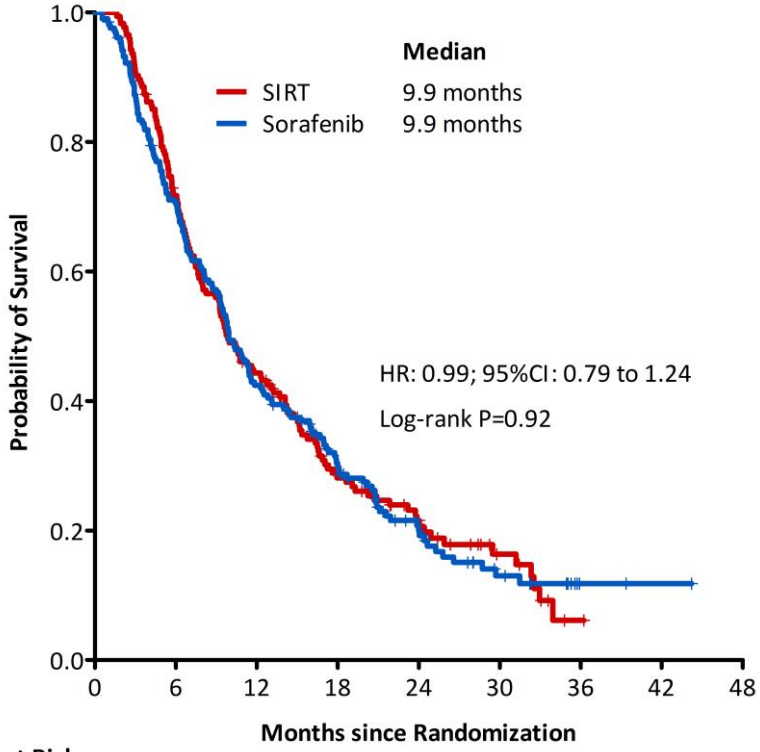
Intention to treat population
N=459



No. at Risk									
SIRT	237	143	90	49	30	11	2	0	
Sorafenib	222	153	92	57	28	14	3	1	0

Per-protocol population
N=380



No. at Risk									
SIRT	174	123	75	41	26	10	1	0	
Sorafenib	206	143	86	54	26	12	2	1	0

MAIN RESULTS OF SARAH TRIAL: SECONDARY OBJECTIVES

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Tumor response

- Patients treated with SIRT compared to those treated with sorafenib had higher overall tumor response rate (19.0% vs. 11.6%; p=0.042) and a significantly reduced risk of first liver progression by 27%
  - This suggests a local effect of radioembolization in the liver
- Higher cumulative incidence of progression outside the liver as first event was observed in the SIRT group
  - This suggests the systemic effect of sorafenib

Safety

- The SIR-Spheres group patients experienced less treatment-related side effects compared to sorafenib group
  - No case of radiation hepatitis in the SIRT group

Quality of life

- Patients who received SIRT maintained a better QoL over time

RADIOLOGIC PROGRESSION

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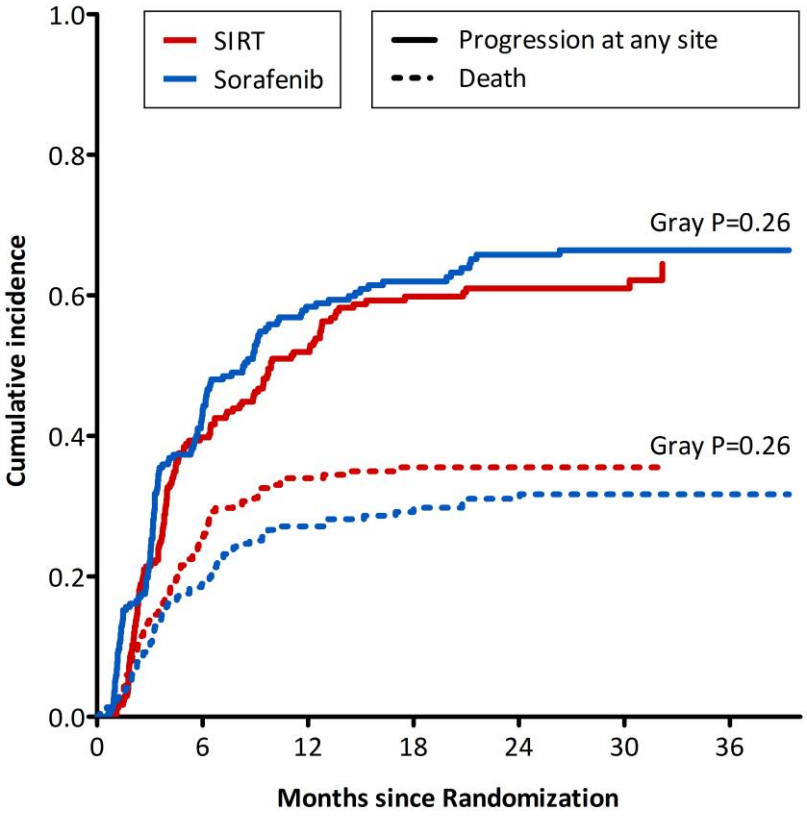
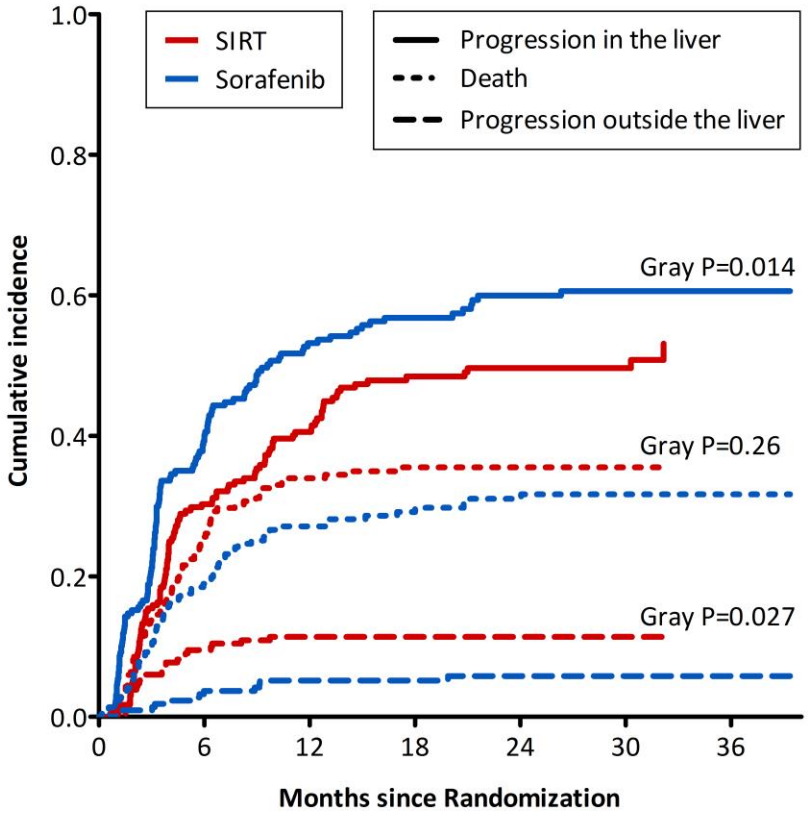
ITT: Progression at any site



ITT: Progression in the liver as first site



TOLERANCE AND SAFETY

Treatment-related AEs	SIRT	Sorafenib
All	1297	2837
⩾ Grade 3	230	411

Treatment-related AEs	SIRT Nb of patients (⩾G 3)	Sorafenib Nb of patients (⩾G 3)
Fatigue	94 (20)	140 (41)
Weight loss	14 (0)	46 (6)
Alopecia	0 (0)	35 (0)
Hand foot skin reaction	1 (1)	45 (12)
Pruritus	7 (1)	19 (1)
Diarrhea	29 (3)	146 (30)
Abdominal pain	46 (6)	63 (14)
Hypertension	6 (0)	28 (5)

QUALITY OF LIFE (QoL)

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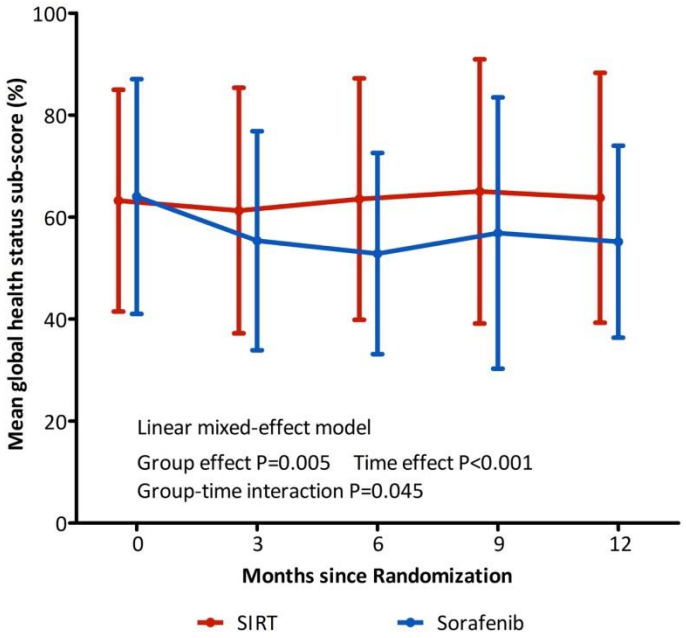
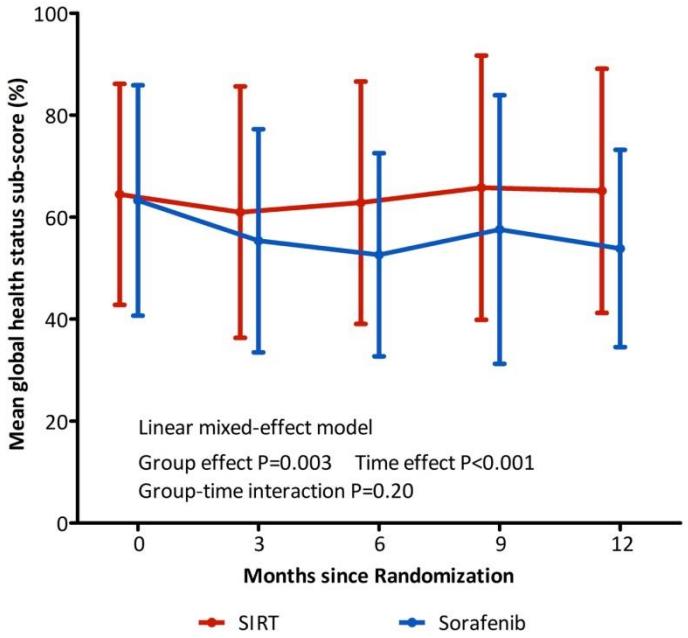
Intention to treat population N=459



No. of completed questionnaires					
SIRT	169	105	69	41	26
Sorafenib	186	118	85	46	29

Per-protocol population N=380



No. of completed questionnaires					
SIRT	128	95	65	37	22
Sorafenib	176	112	80	43	26

Global health subscore EORTC QLQ 30

COMMENTS: STUDY STRENGTHS

- The first reported large multicenter randomized trial including a large cohort of patients with quite homogenous disease
- Implication of 25 centers involved in HCC management with multidisciplinary teams including hepatologist/oncologist, radiologist, nuclear MD investigators
- The primary study endpoint was not reached. SIRT was not superior to sorafenib in patients with locally advanced HCC. Sorafenib remains the standard of care
- Few patients who were assigned to one treatment received the other one
- Safety profile, local disease control, and maintained quality of life seems to be better in the SIRT group

The indication of SIRT as an alternative option to sorafenib for patients with locally advanced HCC should be discussed with the multidisciplinary team

COMMENTS: STUDY LIMITATIONS

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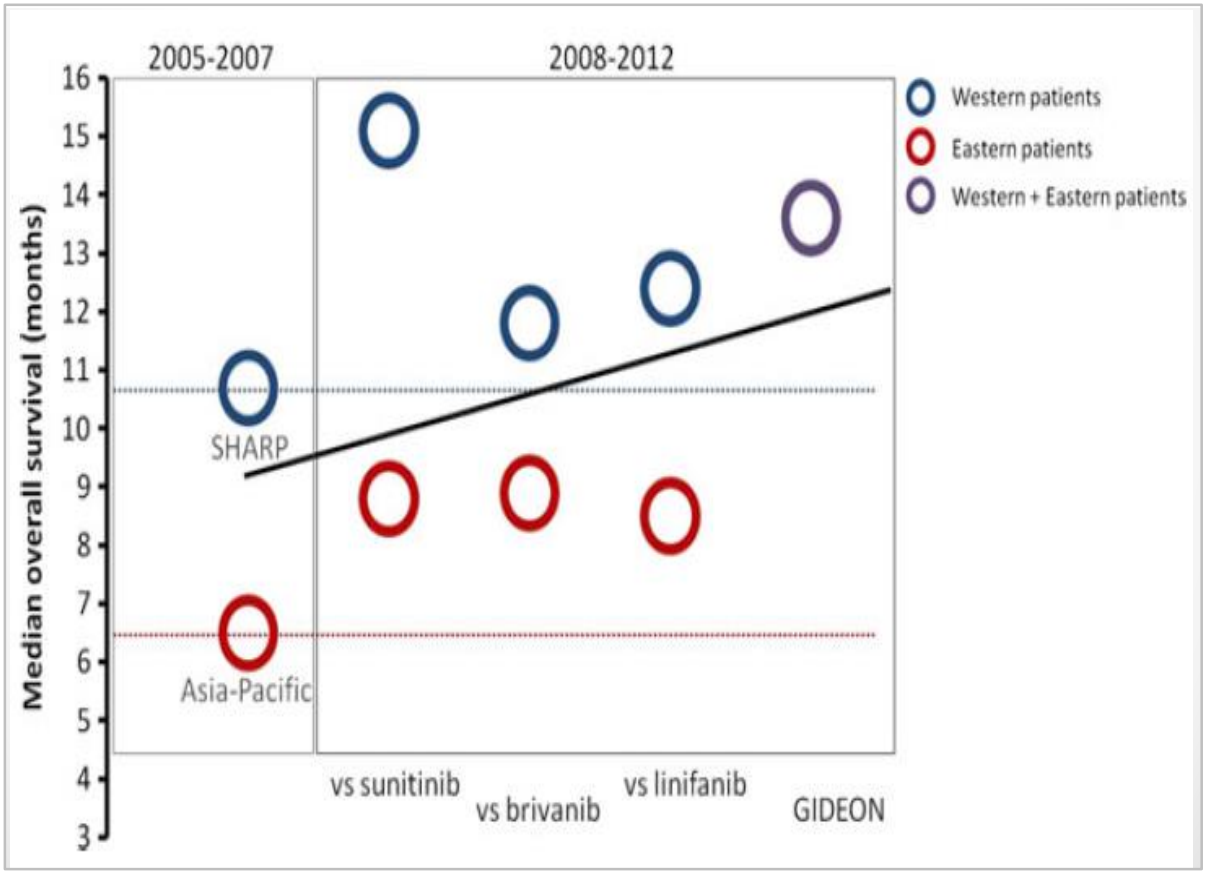
- High rate of patients with Child-Pugh B
- More patients in the SIRT group than in the sorafenib group who did not receive the assigned treatment
- Unlike sorafenib, some delay could be needed to initiate treatment with SIRT (necessity of selective hepatic angiography and scintigraphy followed by microspheres delivery)
  - During the work-up period, some patients could worsen their liver disease and would not be eligible for treatment
- Experience with SIRT is center-dependent and needs a learning curve

LEARNING FROM 7 YEARS OF EXPERIENCE WITH SORAFENIB IN ADVANCED HCC: SORAFENIB BETTER THAN SORAFENIB?



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