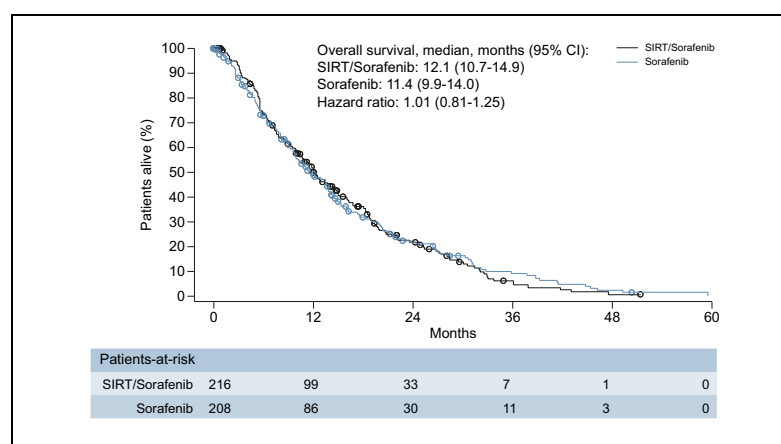


Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma

Graphical abstract



Highlights

- Sorafenib given orally is the recommended treatment for patients with advanced hepatocellular carcinoma.
- Addition of selective internal radiation therapy did not significantly improve overall survival compared to sorafenib alone.
- Subgroup analyses provided results that will guide future clinical trial designs for this combination therapy.

Authors

Jens Ricke, Heinz Josef Klümper, Holger Amthauer, ..., Chris Verslype, Bruno Sangro, Peter Malfertheiner

Correspondence

jens.ricke@med.uni-muenchen.de
(J. Ricke)

Lay summary

Sorafenib given orally is the recommended treatment for patients with advanced hepatocellular carcinoma (HCC). In selective internal radiation therapy (SIRT), also known as radioembolisation, microscopic, radioactive resin or glass spheres are introduced into the blood vessels that feed the tumours in the liver. This study found that the addition of SIRT with ⁹⁰yttrium-loaded resin microspheres to sorafenib treatment in people with advanced HCC did not significantly improve overall survival compared with sorafenib treatment alone. However, the results give an indication of how future studies using this combination therapy in people with advanced HCC could be designed.



Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma

Jens Ricke^{1,*}, Heinz Josef Klumpen², Holger Amthauer³, Irene Bargellini⁴, Peter Bartenstein⁵, Enrico N. de Toni⁶, Antonio Gasbarrini⁷, Maciej Pech⁸, Markus Peck-Radosavljevic⁹, Peter Popović¹⁰, Olivier Rosmorduc¹¹, Eckart Schott¹², Max Seidensticker¹³, Chris Verslype¹⁴, Bruno Sangro^{15,#}, Peter Malfertheiner^{16,#}

¹Department of Radiology, University Hospital, LMU Munich, Munich, Germany; ²Department of Medical Oncology, Amsterdam University Medical Centers, University of Amsterdam, Meibergdreef 9, Amsterdam, the Netherlands; ³Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin, Germany; ⁴Department of Interventional Radiology, Pisa University Hospital via Paradisa 2, 56100 Pisa, Italy; ⁵Department of Nuclear Medicine, University Hospital, LMU Munich, Munich, Germany; ⁶Department of Medicine II, Liver Center Munich, University Hospital, Munich, Germany; ⁷Internal Medicine, Gastroenterology and Hepatic Diseases Unit, IRCCS Fondazione Policlinico Universitario A. Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy; ⁸Department of Radiology and Nuclear Medicine, University of Magdeburg, Leipziger Str. 44, 39120 Magdeburg, Germany; ⁹Department of Internal Medicine and Gastroenterology, Klinikum Klagenfurt am Wörthersee, Klagenfurt, Austria; ¹⁰Clinical Institute of Radiology, University Medical Centre Ljubljana, Ljubljana, Slovenia; ¹¹APHP, Hôpital La Pitié Salpêtrière, Service d'Hépatogastroentérologie, Paris, France; ¹²Department of Gastroenterology, Hepatology and Diabetology, Internal Medicine II, HELIOS Hospital Emil von Behring, Berlin, Germany; ¹³University Hospital, LMU Munich, Munich, Germany; ¹⁴Department of Digestive Oncology, University Hospital Leuven, Leuven, Belgium; ¹⁵Liver Unit, Clínica Universidad de Navarra-IDISNA and CIBEREHD, Pamplona, Spain; ¹⁶Department of Gastroenterology, Hepatology and Infectious Diseases, Otto-von-Guericke-University Magdeburg, Magdeburg, Germany

Background & Aims: Sorafenib is the recommended treatment for patients with advanced hepatocellular carcinoma (HCC). We aimed to compare the efficacy and safety of a combination of sorafenib and selective internal radiation therapy (SIRT) – with yttrium-90 (⁹⁰Y) resin microspheres – to sorafenib alone in patients with advanced HCC.

Methods: SORAMIC is a randomised controlled trial comprising diagnostic, local ablation and palliative cohorts. Based on diagnostic study results, patients were assigned to local ablation or palliative cohorts. In the palliative cohort, patients not eligible for TACE were randomised 11:10 to SIRT plus sorafenib (SIRT + sorafenib) or sorafenib alone. The primary endpoint was overall survival (OS; Kaplan-Meier analysis) in the intention-to-treat (ITT) population.

Results: In the ITT cohort, 216 patients were randomised to SIRT + sorafenib and 208 to sorafenib alone. Median OS was 12.1 months in the SIRT + sorafenib arm, and 11.4 months in the sorafenib arm (hazard ratio [HR] 1.01; 95% CI 0.81–1.25; $p = 0.9529$). Median OS in the per protocol population was 14.0 months in the SIRT + sorafenib arm ($n = 114$), and 11.1 months in the sorafenib arm ($n = 174$; HR 0.86; $p = 0.2515$). Subgroup analyses of the per protocol population indicated a survival benefit of SIRT + sorafenib for patients without cirrhosis (HR 0.46; 0.25–0.86; $p = 0.02$); cirrhosis of non-

alcoholic aetiology (HR 0.63; $p = 0.012$); or patients ≤ 65 years old (HR 0.65; $p = 0.05$). Adverse events (AEs) of Common Terminology Criteria for AE Grades 3–4 were reported in 103/159 (64.8%) patients who received SIRT + sorafenib, 106/197 (53.8%) patients who received sorafenib alone ($p = 0.04$), and 8/24 (33.3%) patients who only received SIRT.

Conclusion: Addition of SIRT to sorafenib did not result in a significant improvement in OS compared with sorafenib alone. Subgroup analyses led to hypothesis-generating results that will support the design of future studies.

Lay summary: Sorafenib given orally is the recommended treatment for patients with advanced hepatocellular carcinoma (HCC). In selective internal radiation therapy (SIRT), also known as radioembolisation, microscopic, radioactive resin or glass spheres are introduced into the blood vessels that feed the tumours in the liver. This study found that the addition of SIRT with ⁹⁰yttrium-loaded resin microspheres to sorafenib treatment in people with advanced HCC did not significantly improve overall survival compared with sorafenib treatment alone. However, the results give an indication of how future studies using this combination therapy in people with advanced HCC could be designed.

Study Registration: EudraCT 2009-012576-27, NCT01126645.

© 2019 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

Keywords: Hepatocellular carcinoma; Selective internal radiation therapy; Yttrium-90; Sorafenib; Radioembolisation.

Received 4 April 2019; received in revised form 31 July 2019; accepted 2 August 2019; available online 14 August 2019

* Corresponding author. Address: Department of Radiology, Ludwig-Maximilians-Universität München, Marchioninistrasse 15, 81377 Munich, Germany. Tel.: +49 4400 72750.

E-mail address: jens.ricke@med.uni-muenchen.de (J. Ricke).

These authors made equal contributions to the manuscript.



Introduction

Hepatocellular carcinoma (HCC) is the most common type of malignant primary liver tumour, accounting for 80–90% of all liver cancers.¹ In the USA, for example, 30,640 new liver and

intrahepatic bile duct cancers are estimated to have occurred in 2013, with 21,670 associated deaths.^{2,3}

Only about 30% of patients are diagnosed early enough to benefit from potentially curative therapies, such as surgical resection, allogeneic liver transplantation or percutaneous ablation, which afford 5-year survival rates of 50–75%.⁴

For patients with inoperable (liver-confined) intermediate stage HCC, locoregional treatment by transarterial chemoembolisation (TACE) is the recommended treatment of choice in treatment guidelines.^{5–10} However, this recommendation is based on 2 randomised trials, with strict patient selection criteria, and the survival benefits were limited to patients with preserved liver function and limited tumour size and numbers.^{6,7} Systemic therapy with sorafenib (Nexavar®; Bayer Healthcare, Leverkusen, Germany) has been shown to provide a survival benefit and is 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.^{5,11,12}

Selective internal radiation therapy (SIRT; also known as radioembolisation) has been evaluated in a number of non-randomised trials with both yttrium-90 (⁹⁰Y) resin microspheres (SIR-Spheres®, Sirtex Medical Ltd, Sydney, Australia) and ⁹⁰Y glass microspheres (TheraSphere, BTG, London, UK) and has been shown to be effective and well tolerated in patients with unresectable HCC.^{13,14} SIRT appears to have similar efficacy to TACE for the cohort of ideal candidates for locoregional therapy, and encouraging results have been reported for patients who are poor candidates for TACE or have failed TACE.^{13–17} In 2 randomised trials, SARAH and SIRveNIB in patients with locally advanced HCC, SIRT with ⁹⁰Y-resin microspheres failed to meet the primary endpoint of improving survival over sorafenib. Tolerability seemed to be favourable for radioembolisation.^{18,19}

SORafenib in combination with local MICro-therapy guided by gadolinium-EOB-DTPA-enhanced MRI (SORAMIC) (EudraCT 2009-012576-27, NCT0112 6645) is a prospective study that comprised 3 sub-studies: (i) comparison of gadolinium-ethoxy benzyl-diethylenetriamine pentaacetic acid (gadoxetate disodium [Gd-EOB-DTPA] Primovist®)-enhanced magnetic resonance imaging (MRI) vs. contrast-enhanced multislice computed tomography (CT) for the stratification of patients to a local ablation (curative treatment) or palliative treatment group; (ii) comparison of radiofrequency ablation (RFA) plus sorafenib vs. control (RFA plus matching placebo) on time to recurrence; and (iii) comparison of SIRT with ⁹⁰Y resin microspheres combined with sorafenib compared with control (sorafenib alone) on overall survival (OS).

This paper reports on the outcomes of part iii (the palliative treatment group), which was designed to determine the efficacy, safety and tolerability of combining SIRT with sorafenib in patients with advanced HCC.

Patients and methods

SORAMIC is a prospective, phase II, open label, multicentre, randomised controlled trial. The study was conducted at 38 sites in 12 countries in Europe, and Turkey.

Ethical considerations

The study was approved by the institutional review boards of all participating centres prior to initiation of the trial. Before entering the study, all patients were fully informed by the treating physician of the scope and the goals of the trial, had given writ-

ten informed consent, and were willing to comply with the study protocol.

Study objectives

SORAMIC was comprised of 3 parts. In the palliative treatment sub-study, which is reported here, the primary objective was to determine if the combination of SIRT with ⁹⁰Y resin microspheres plus sorafenib improved OS compared with sorafenib alone in patients with advanced HCC. Secondary endpoints included the safety of the combination of SIRT + sorafenib therapy in comparison to sorafenib therapy alone, as well as OS in the subgroups of patients with and without portal thrombosis.

Study design and procedure

Screening stage

Patients with a diagnosis of HCC received gadoxetate disodium-enhanced MRI and contrast-enhanced CT.

Disease stage criteria was determined by the local investigator using all available clinical information including gadoxetate disodium-enhanced MRI and contrast-enhanced CT. Based on the disease stage the local investigator determined the treatment strategy with curative intention (local ablation) or with palliative treatment resided with the responsible treating physicians at the study sites.

Patient selection

Patients with HCC Barcelona Clinic Liver Cancer (BCLC) stages A, B, and C and Child-Pugh scores A to B7 were eligible for inclusion. Key selection criteria for the palliative treatment group were BCLC B (not eligible for TACE per investigator decision) and C; prior resection or local/locoregional treatments were permitted. Patients who had received prior TACE or TAE were included only after an interval of 3 months and if revascularisation was present. Extrahepatic disease was permitted if patients displayed liver-dominant disease and did not present with pulmonary metastases.

Key exclusion criteria in the palliative arm were a hepatopulmonary shunt leading to an estimated lung dose >30 Gy; previous external beam radiation therapy to the liver, or previous therapy with tyrosine kinase inhibitors. Patients were also excluded if presenting with serum bilirubin more than 1.5x the upper limit of the normal range.

Randomisation and masking

Following a predefined randomisation plan, patients eligible for the palliative treatment group were randomised 11:10 to the SIRT + sorafenib or sorafenib arm. The 11:10 ratio was chosen to account for patients lost in the combination arm for technical ineligibility of SIRT, assuming an equal patient number as result. Randomisation was performed employing an IVRS. Randomisation and stratification were carried out by centre and separately for patients with and without portal vein thrombosis.

SIRT

SIRT was performed after exclusion of relevant hepatopulmonary shunts using ^{99m}Tc-labeled macroaggregated albumin (MAA) and after exclusion of relevant risk of microsphere misplacement in extrahepatic organs as recommended by the manufacturer. SIRT with ⁹⁰Y-resin microspheres was administered separately to each liver lobe; using a selective segmental approach, when appropriate. To patients with bilobar disease, SIRT was initially performed on the dominant diseased liver

lobe, followed 4–6 weeks later by SIRT to the untreated contralateral lobe. When the patient's disease was limited to a single lobe, only selective SIRT in a single session was performed. Details of the dosimetry calculation can be found in the supplementary materials (S2).

Patients who were randomised to receive SIRT, but for whom SIRT could not be performed for technical reasons or due to pulmonary lung shunting, remained in the study, but were switched to the sorafenib only arm.

Sorafenib

All patients in the palliative group were to receive sorafenib with a target dose of 400 mg twice daily (BID). Patients in the sorafenib only arm received their treatment after randomisation. In patients in the SIRT + sorafenib arm, sorafenib was initiated on day 3 after the last SIRT procedure. In both treatment arms, patients received sorafenib 200 mg twice daily for 1 week before increasing the dose to 400 mg BID.

Sorafenib treatment was continued until tumour progression or the emergence of drug-related AEs which required discontinuation, following 2 dose reductions (to 400 mg once daily, then to 400 mg on alternate days).

Assessments

Patients were assessed at 2-month intervals for a minimum of 24 months or until death. At each visit, all treatment-emergent AEs were recorded and standard laboratory investigations (complete blood count, chemistry and coagulation panel and urinalysis) completed.

Patients who discontinued sorafenib because of AEs were asked to continue in the study for ongoing assessment of long-term safety and OS.

Statistical analysis

The statistical analysis of the palliative treatment group employed 3 data sets. The safety analysis set included all patients that received treatment, analysing them as treated, independent of any randomisation errors. This data set was used for the safety analysis. The intention-to-treat (ITT) population consisted of all patients undergoing randomisation. The ITT population was used for demographics as well as for the primary efficacy analysis of the palliative treatment arm. The per protocol (PP) set comprised a subset of the ITT that excluded patients with major protocol deviations, such as no or incomplete study treatment. The PP set was used as a secondary analysis set to assess efficacy in the palliative treatment group.

For the palliative study, group-sequential methods were used, planning for 2 interim analyses and a final data analysis after one-third, two-thirds and all of the planned number of deaths (events) had been reported. The necessary sample size was determined employing the log-rank test at a 1-sided type I error of 2.5%, a power of 80%, and an O'Brien-Fleming boundary, as specified using the Lan-DeMets type I error spending function (East-5, Cytel Software Corporation, Cambridge, MA). Patient accrual was targeted to be 75 individuals for the first year and 150 thereafter. The yearly dropout rate was assumed to be 10% for the SIRT + sorafenib group and 20% for the sorafenib only group. The median survival was assumed to be 15.4 months for SIRT + sorafenib and 10.7 months for sorafenib. A sample size of 375 patients was planned, with interim efficacy analyses to be performed after 80 and 160 reported deaths, and the nominal critical points for these interim analyses (and p val-

ues) being 3.710 ($p < 0.0001$) and 2.511 ($p = 0.006$). The final analysis was to be performed after 240 reported deaths with a nominal critical point of 1.993 ($p = 0.0231$).

OS as the primary endpoint was evaluated by the Kaplan-Meier method (product-limit method) to compute non-parametric estimates of the survivor functions. Right censoring was taken into account. The survival curves were compared between both treatment groups with the log-rank test at specified error level α (one-sided tests). The stratifying factor "portal vein thrombosis" (yes vs. no) was taken into account in the Cox proportional model.

Interim analyses were planned and performed after 80 and 160 reported deaths. The final analysis was to be performed after 240 reported deaths with a nominal critical point of 1.993 ($p = 0.0231$).

Following null hypothesis

$$H_0^{\text{palliative}}: OS_{\text{SIRT+sorafenib}} = OS_{\text{sorafenib}}$$

was tested with the predefined one-sided alpha against

$$H_1^{\text{palliative}}: OS_{\text{SIRT+sorafenib}} > OS_{\text{sorafenib}}$$

Superiority of SIRT + sorafenib could be concluded when the one-sided log-rank test was significant. Only the primary parameter was compared at $\alpha = 2.31\%$. All subgroup analyses and other study testing were considered exploratory with $\alpha = 5\%$.

All safety analyses were performed by study group and treatment arm. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) were calculated for each quantitative variable; frequency counts by category were made for each qualitative variable.

The frequencies of AEs, as well as number of patients with AEs, were reported by study group and treatment arm. Results were tabulated by body systems, severity categorised according to Common Terminology Criteria for Adverse Events (CTCAE version 4.0), seriousness, causal relationship to study drug or device, causal relationship to study conduct, and outcome of the AE. Any withdrawals from the study due to AEs were reported.

Subgroup analyses

All subgroup analyses were regarded as exploratory. In the palliative treatment group, the following subgroup analyses were pre-planned in the statistical analysis plan: age (≤ 65 years, > 65 years); sex (male, female); portal vein thrombosis (yes, no); Child-Pugh score 5, 6, 7; BCLC stage B vs. C; cirrhosis (present, not present); alcoholic aetiology (yes, no); hepatitis B (yes, no); hepatitis C (yes, no); extrahepatic metastasis (yes, no); liver dominant (yes, no); ECOG (0 vs. 1 vs. 2); albumin-bilirubin (ALBI) grade (1 vs. 2 vs. 3); pre-treatment (naïve vs. TACE vs. other); alpha-fetoprotein (AFP) (high vs. low); tumour load (high vs. low); tumour load inside/outside-up-to-seven (the sum of the number of tumours and the diameter of the largest tumour); hepatoma arterial-embolisation prognostic (HAP) score (0,1,2,3).

Results

Patients were recruited into SORAMIC between 5 January 2011 and 19 April 2016, and 424 were allocated to the palliative treatment cohort. In the ITT palliative treatment cohort, 216 patients were randomised to SIRT + sorafenib and 208 to sorafenib alone. The PP population comprised 114 patients randomised to SIRT + sorafenib and 174 who received sorafenib alone. The safety population comprised 159 patients who

received SIRT + sorafenib, 182 who received sorafenib alone, and initially 24 and 15 patients randomised to SIRT + sorafenib but who received only SIRT or only sorafenib (Fig. 1). In those patients receiving only SIRT, the reasons for failing to receive sorafenib were: withdrawal of consent, 3; clinical decompensation (anorexia, tumour progression, liver function), 13; non-liver-disease related medical causes (myocardial infarction, pulmonary embolism), 3; lost to follow-up before sorafenib initiation, 5).

Baseline patient and disease characteristics are summarised in Table 1. There were no significant differences between the treatment groups in either the ITT or PP populations. Patients' previous treatment for HCC is summarised in Table 2.

Treatment received is summarised in Table 3. In the combination arm, the median time to start the first SIRT treatment after randomisation was 22 days (IQR 12). The median time to start sorafenib after SIRT completion was 3 days (IQR 3). In the sorafenib only arm, the median time to start sorafenib was 4 days (IQR 6). After randomisation patients were followed for a median of 9.4 months (IQR 12.6) in the SIRT + sorafenib group and 6.57 months (IQR 11.1) in the sorafenib group. Sixteen out of 159 patients and 27 out of 197 patients who received SIRT + sorafenib or sorafenib monotherapy (including those 15 randomised to SIRT + sorafenib, but who received sorafenib only) underwent systemic second-line treatments after study completion, often as part of subsequent clinical trials ($p = 0.29$; Table S3).

Efficacy

Median OS in the ITT population was 12.1 months (95% CI 10.7–14.9) in the SIRT + sorafenib arm, and 11.4 months (95% CI 9.9–14.0) in the sorafenib arm (hazard ratio [HR] 1.01; 95%

CI 0.81–1.25; $p = 0.953$; Fig. 2A). In the PP population, median OS was 14.0 months (95% CI 11.5–17.0) in the SIRT + sorafenib arm ($n = 174$), and 11.1 months (95% CI 9.8–13.8) in the sorafenib arm ($n = 174$; HR 0.86; 95% CI 0.67–1.11; $p = 0.252$; Fig. 2B).

Subgroup analyses of the PP population (Fig. 3) suggested a survival benefit for patients receiving SIRT + sorafenib vs. sorafenib alone in: patients ≤ 65 years (HR 0.65; 95% CI 0.43–1.00; $p = 0.046$); non-cirrhotic patients (HR 0.46; 95% CI 0.25–0.86; $p = 0.013$), and patients with HCC of non-alcoholic aetiology (HR 0.63; 95% CI 0.45–0.89; $p = 0.009$) (Fig. 4A–C).

Patients with no previous TACE had a median survival of 14.0 months in the SIRT + sorafenib arm vs. 11.0 months in the sorafenib arm (HR 0.82; 95% CI 0.61–1.10), whereas in patients with previous TACE, median survival was 13.3 and 13.4 months, respectively (HR 1.0; 0.6–1.64). In patients displaying a tumour load >7 tumours, median survival in the SIRT + sorafenib arm was 14.5 months vs. 10.5 months in the sorafenib arm (HR 0.80; 95% CI 0.60–1.07) (Fig. 4D, E).

Adverse events

AEs of CTCAE Grade 3–4 were reported in 103/159 (64.8%) patients in the SIRT + sorafenib arm and in 97/182 (53.3%) patients who received sorafenib only, with the difference reaching statistical significance ($p = 0.036$) (Table 4).

Among the most frequent AEs, hyperbilirubinaemia was approximately 3-fold more common in the SIRT + sorafenib arm than in the sorafenib arm (14.5% vs. 4.4%). Fatigue was significantly more common in the SIRT + sorafenib arm than in the sorafenib arm with 35.2% vs. 24.2% of patients, respectively (Table S1).

Treatment-related Grade 5 AEs occurred in 2 patients (1.3%) in the SIRT + sorafenib group, in 2 patients (1.0%) who received

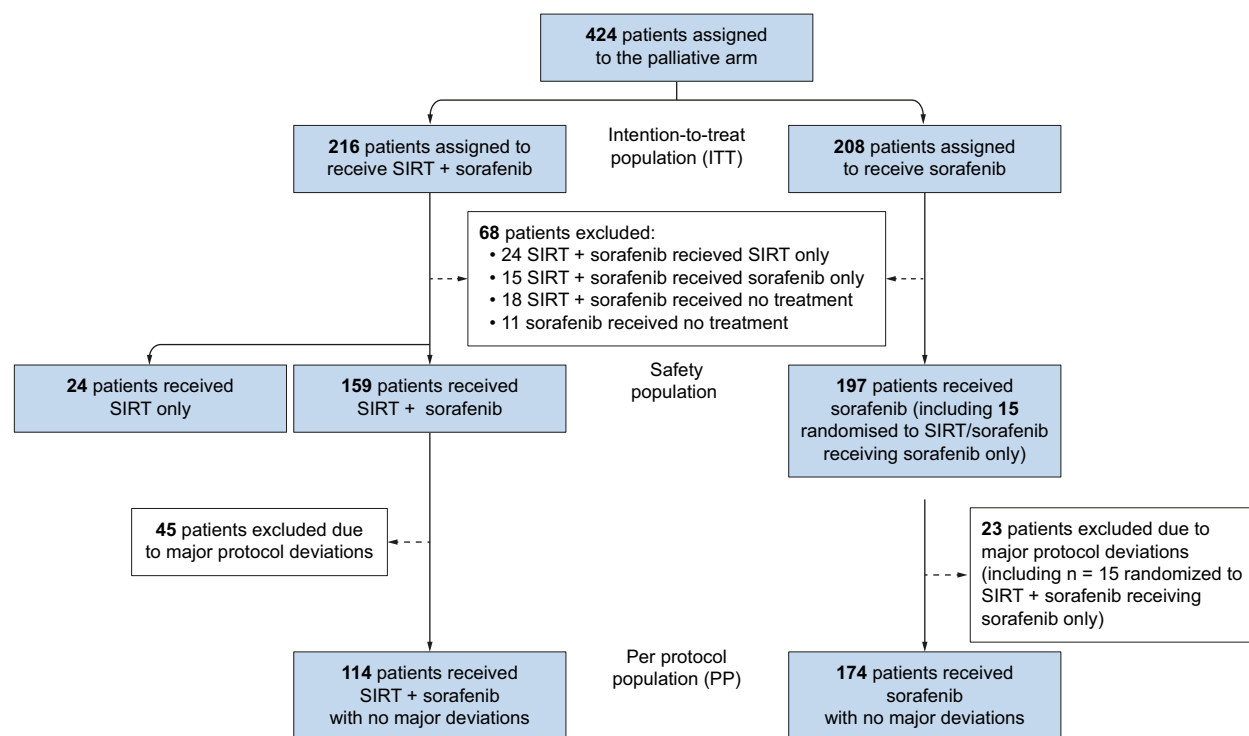


Fig. 1. Patient disposition in the palliative arm.

Table 1. Baseline characteristics.

	ITT population		PP population	
	SIRT + sorafenib (n = 216)	Sorafenib (n = 208)	SIRT + sorafenib (n = 114)	Sorafenib (n = 174)
Age, years: median (IQR)	66 (13)	66 (13)		
Age, years				
<65			43 (37.7)	75 (43.1)
≥65			71 (62.3)	99 (56.9)
Sex, n (%)				
Male	181 (85.4)	177 (85.5)	100 (87.7)	151 (86.8)
Female	31 (14.6)	30 (14.5)	14 (12.3)	23 (13.2)
Cirrhosis, n (%)	165 (80.1)	164 (80.0)	89 (80.2)	138 (79.8)
Alcoholic aetiology, n (%)	88 (41.5)	80 (38.6)	50 (43.9)	73 (42.0)
Hepatitis				
B	17 (8.0)	24 (11.6)	12 (10.5)	21 (12.1)
C	58 (27.4)	48 (23.2)	28 (24.6)	37 (21.3)
Child-Pugh class, n (%):				
A	190 (90.0)	190 (90.0)	107 (93.9)	160 (92.0)
B	21 (10.0)	17 (8.2)	7 (6.1)	14 (8.0)
BCLC stage, n (%):				
A	6 (2.8)	3 (1.5)	4 (3.5)	3 (1.7)
B	62 (29.4)	62 (30.1)	32 (28.1)	48 (27.7)
C	143 (67.8)	141 (68.4)	78 (68.4)	122 (70.5)
Liver dominant, n (%)	198 (96.1)	203 (98.5)	107 (97.3)	171 (98.8)
Extrahepatic metastasis, n (%)	52 (24.6)	46 (22.2)	29 (25.4)	35 (20.1)
Number target lesions:				
Median (IQR)	3.0 (3.0)	2.0 (3.0)	3.0 (4.0)	2.0 (3.0)
Range	1.0–50.0	1.0–30.0	1.0–45.0	1.0–30.0
Largest lesion:				
Median (IQR)	70.0 (67.0)	61.0 (59.0)	58.0 (58.0)	62.0 (55.0)
Range	8.0–237.0	10.0–500.0	8.0–180.0	10.0–500.0
Sum of lesion diameters:				
Mean (SD)	12.7 (6.3)	11.1 (5.4)	11.6 (5.9)	11.1 (5.5)
Median (IQR)	11.9 (8.6)	10.3 (6.5)	10.1 (7.8)	10.3 (7.2)
Bilobar disease, n (%)	96 (56.8)	99 (56.6)	47 (50.0)	86 (55.8)
Single nodule, n (%)	26 (12.5)	40 (19.6)	16 (14.2)	34 (19.9)
Multiple nodules, n (%)	182 (87.5)	168 (80.4)	98 (85.8)	140 (80.1)
Portal vein invasion, n (%)	91 (43.1)	90 (43.7)	44 (38.6)	76 (43.7)
Laboratory values	(n = 159) ^a	(n = 182) ^a		
Mean total bilirubin, mg/dl (SD)*	0.9 (0.4)	0.9 (0.5)		
Mean albumin, g/dl (SD)*	3.8 (8.4)	3.8 (7.6)		
Mean ALBI score (SD)*	–2.5 (0.8)	–2.4 (0.7)		

ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; ITT, intention-to-treat; PP, per protocol; SIRT, selective internal radiation therapy.

^a Safety population

Table 2. Prior treatment received for hepatocellular carcinoma (ITT population).

Treatment	SIRT + sorafenib (n = 216)	Sorafenib (n = 208)	p value
Transarterial chemoembolisation, %	24.5	23.1	0.725
Transarterial embolisation, %	0.9	1.0	0.970
Resection, %	8.3	13.5	0.090
Radio frequency ablation, %	9.3	8.2	0.692
Brachytherapy, %	0.5	2.4	0.091
Other prior treatments ^a , %	7.9	8.7	0.770

p values were calculated by the Chi-square test.

ITT, intention-to-treat; SIRT, selective internal radiation therapy.

^a Includes portal vein embolisation, laparoscopic ablation, percutaneous ethanol injection, open thermal ablation.

Table 3. Treatment received (safety population).

	SIRT + sorafenib (n = 159)	Sorafenib (n = 182)	p value
Days on sorafenib: median (IQR)	206 (273.0)	135 (280.0)	0.073
Daily dose (mg): median (IQR)	474.4 (335.0)	523.1 (343.9)	0.202
⁹⁰ Y activity GBq: median (IQR)	1.7 (0.7)	n.a.	0.229
Bilobar treatment: n (%)	69 (43.4)		
Lobar treatment: n (%)	71 (44.7)		
Unspecified: n (%)	19 (11.9)		

Variables were summarised by median and interquartile range, and groups compared by Mann-Whitney U test.

⁹⁰Y, ⁹⁰yttrium; n.a., not applicable.

sorafenib alone, and in 1 patient randomised to SIRT + sorafenib who received only SIRT (Table 4 and Table S4). Two deaths were considered to be AEs of interest: 1 case of decreased appetite in the sorafenib group and 1 case of radiation pneumonitis in the SIRT group (because of overexposure beyond the proposed 30 Gy limit due to a technical failure), and 1 case of liver failure in a patient receiving SIRT only. The other 2 deaths were

recorded as due to hepatic encephalopathy and as a surgical complication of pulmonary thromboembolism.

Serious AEs (SAEs) were reported in 63 (39.6%) patients in the SIRT + sorafenib arm and 70 (70.5%) patients who received sorafenib only. Hepatic failure as an SAE was reported in 6 patients (3.8%) in the SIRT + sorafenib arm and 8 patients

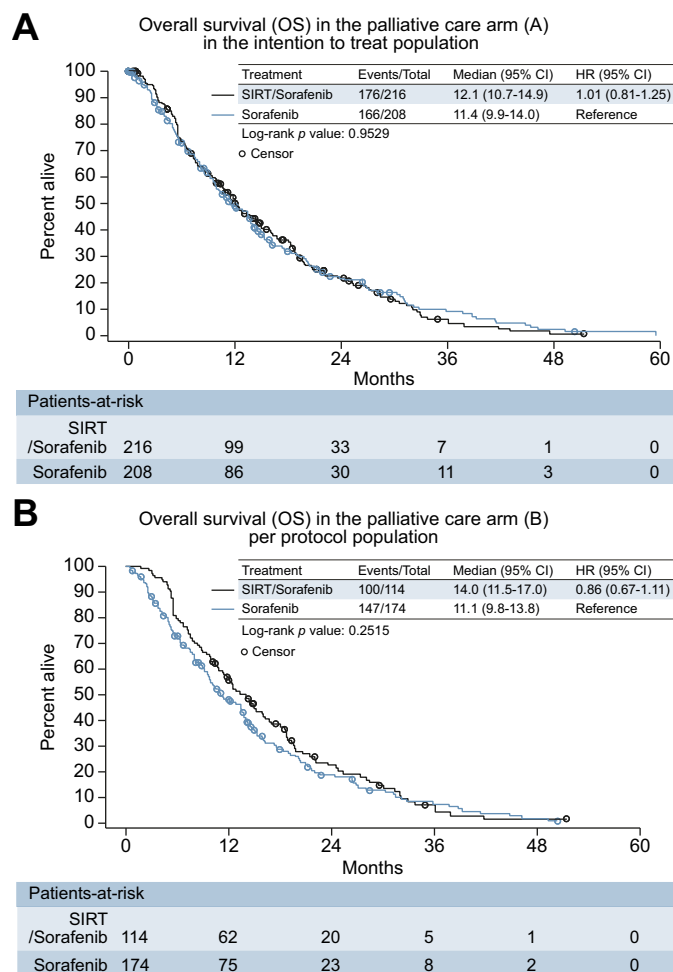


Fig. 2. Overall survival in the palliative care arm. A) Overall survival in the intention-to-treat population; (B) overall survival in the per protocol population. *p* values calculated by log-rank test.

(4.1%) in the sorafenib arm. Hepatobiliary SAEs considered to be serious and treatment related are summarised in Table 5.

Among AEs of particular interest, Grade 3–4 hand foot syndrome was reported in 15/159 (9.4%) patients in the SIRT + sorafenib arm, and in 17/182 (9.3%) patients who received sorafenib alone (Table 5). A Grade 3–4 duodenal or gastric ulcer was reported in 2 patients (1.3%) in the SIRT + sorafenib arm. Grade 3–4 gastrointestinal bleeding/haemorrhage occurred in 6 patients (3.8%) in the SIRT + sorafenib arm, in 5 patients (2.5%) in the sorafenib arm, and in 1 patient (4.2%) who received only SIRT. Ascites was the most frequently reported Grade 3–4 hepatic AE, occurring in 6 patients (3.8%) in the SIRT + sorafenib group and in 13 patients (6.6%) who received sorafenib alone. Grade 3–4 liver dysfunction/failure occurred in 1 patient each in the SIRT + sorafenib arm, in patients who received sorafenib only and in patients who received only SIRT. A case of Grade 3–4 radiation hepatitis was reported in 1 patient who received only SIRT (Table 5).

Discussion

SORAMIC is the first large randomised controlled trial comparing the efficacy and safety of combining SIRT and

systemic therapy for the palliative treatment of unresectable HCC not suitable for TACE.

In the overall study population, the addition of SIRT to sorafenib did not result in a significant improvement in OS compared with sorafenib alone. However, subgroup analyses of the PP population led to hypothesis-generating results for patient groups with potential clinical benefit from adding SIRT: non-cirrhotic patients, younger patients (≤ 65 years) and patients presenting with HCC of non-alcoholic aetiology.

As expected, due to their non-overlapping toxicity profile, a higher proportion of patients in the SIRT + sorafenib arm experienced Grade 3–4 AEs than in the sorafenib arm. However, the number of patients who experienced treatment-related Grade 5 events was low, and similar in the treatment arms. Observed toxicities were in accordance with published experiences with sorafenib and ^{90}Y -resin microspheres.

The potential of demonstrating a significant benefit in OS, with the addition of SIRT, may have been diminished by the high proportion of patients (47.2%) who did not receive SIRT per ITT or were excluded from the analysis due to protocol deviations. In the total PP cohort of patients receiving SIRT + sorafenib or sorafenib alone, without major protocol deviations, median survival was 14.0 months vs. 11.1 months, respectively. However statistical significance was not reached in part as a result of the limited number of patients (114 vs. 174, HR 0.86).

Suboptimal SIRT in some patients may also lie behind the lack of benefit in the combination arm. Dosimetry in SIRT is a subject of ongoing debate. Studies have indicated that achieving a threshold dose, by ^{90}Y microsphere uptake into the tumour, leads to better remission rates and may even improve survival.²⁰ However, the higher the dose, the more likely it is that significant parenchymal deposition of microspheres will occur, which is potentially harmful to liver function on a subclinical level and could lead to liver decompensation weeks or months after treatment. A high tumour to liver uptake ratio is likely to be crucial for treatment outcomes.

We hypothesise that a dominant factor in failing to demonstrate a therapeutic benefit from the addition of SIRT to sorafenib in this study was the recruitment of much too broad a patient population, particularly through including patients with compromised liver function. The results of 2 head-to-head comparisons of SIRT vs. sorafenib have demonstrated improved tumour control with SIRT compared with sorafenib, but no survival benefits.^{18,19} In SARAH, the cumulative incidence of progression in the liver was significantly lower with SIRT compared with sorafenib (HR 0.72; 95% CI 0.56–0.93; $p = 0.0143$), but the cumulative incidence of death was significantly higher with SIRT compared with sorafenib ($p = 0.0265$). In SIRT, a certain dose of radiation is delivered to the non-tumoural liver compartment. Radiation may produce tissue damage, including sinusoidal congestion similar to venous occlusive disease, which is potentially accessible for medical prevention.²¹ When such damage is intense, liver decompensation may occur. SIRT-associated radiation-induced liver disease was defined as a bilirubin increase associated with symptomatic ascites, occurring up to 3 months post-SIRT;²² it may even occur after lobar SIRT in cirrhotic patients.²³ However, among patients with HCC at various stages of cirrhosis and liver dysfunction, these signs and symptoms are difficult to discriminate from the natural course of cirrhosis and it would be very difficult to identify more subtle negative effects on liver function with uncertain prognostic impact.

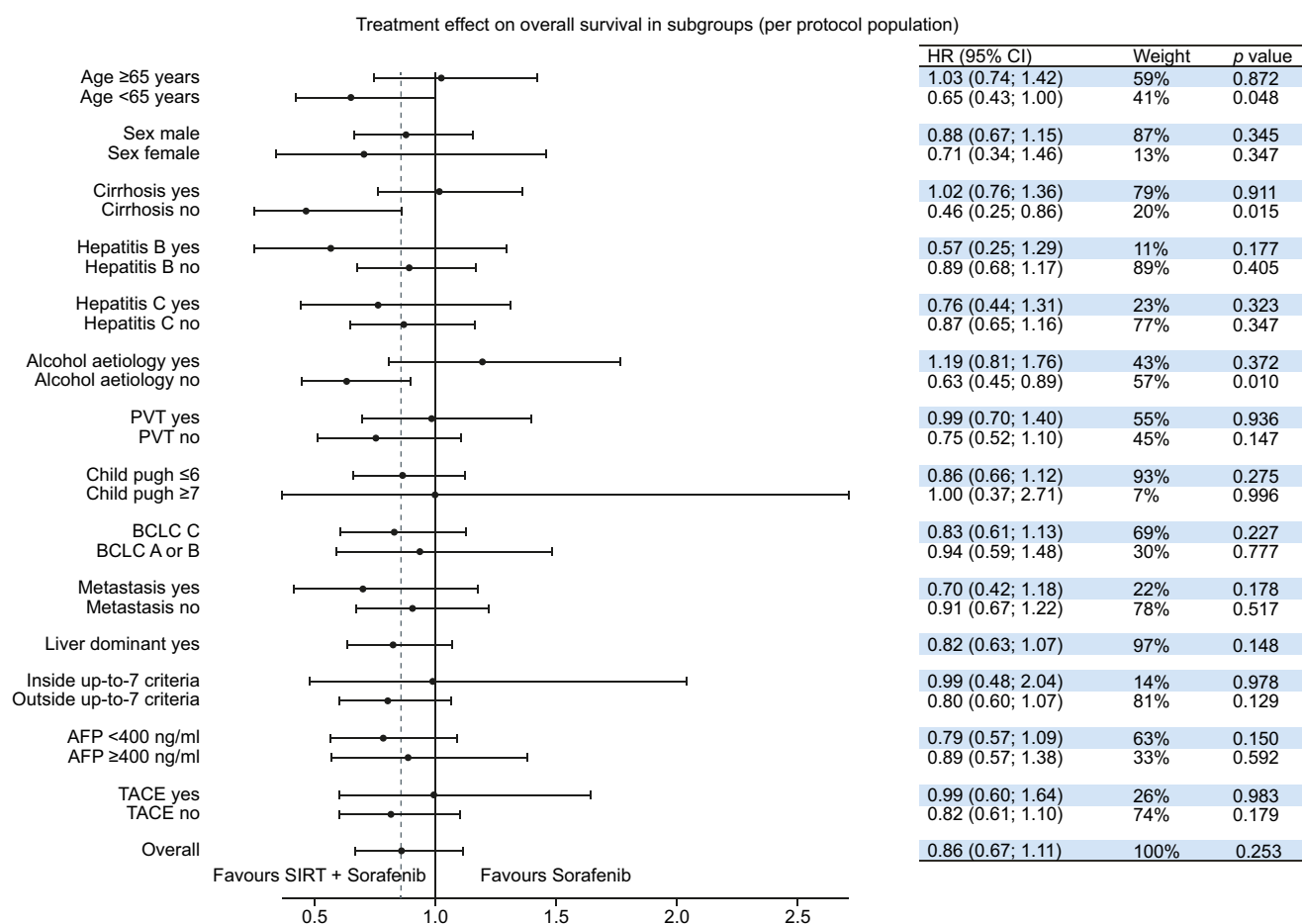


Fig. 3. Treatment effect on overall survival in subgroups (per protocol population). AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; PVT, portal vein thrombosis; TACE, transarterial chemoembolisation. Hazard ratios calculated by Cox regression analysis.

The pre-planned PP analyses of the SORAMIC trial identified several subgroups that could potentially benefit, in terms of survival, from the combined use of SIRT and sorafenib, including non-cirrhotic patients (HR 0.43), or those with non-alcoholic aetiology (HR 0.63), who are known to be functionally more stable than individuals with cirrhosis or alcoholic aetiology.²⁴ Similarly, in patients who had not previously received TACE, survival in the SIRT + sorafenib arm was longer than in the sorafenib arm, 14.0 vs. 11.0 months (HR 0.82); these patients are more likely to present with preserved liver function than patients who have received TACE. Patients in the SIRT + sorafenib arm with diffuse or very large tumours outside up-to-seven (in whom the relative dose of radiation delivered to the liver is likely lower), with Child-Pugh score ≤6 and no previous TACE, showed a trend towards improved survival compared to equivalent patients in the sorafenib arm (14.5 vs. 10.5 months, HR 0.76, $p = 0.1$; Fig. S3). However, SIRT + sorafenib did not confer a survival benefit in patients with a Child-Pugh score ≤6, who were not outside up-to-seven and who had previously received TACE (15.2 vs. 12.9, HR 1.01, $p = 0.99$) (Fig. S3).

We hypothesise that the potential benefit of the combination occurred specifically in patients with a better functional liver reserve, in whom the non-tumoural liver was less exposed to radiation. In this population, the subclinical effects of radiation would have minimal or no impact on long-term patient outcome. Although Child-Pugh score at inclusion (A5 vs. A6 vs.

B7) did not influence survival, we observed a correlation between a higher Child-Pugh score and an increase in protocol deviations in the SIRT + sorafenib arm, mostly missing a second SIRT procedure and/or missing the induction of sorafenib treatment. In the SIRT + sorafenib arm, major protocol deviations occurred in 41%, 50% and 66%, of patients with Child-Pugh scores of 5, 6 and 7, respectively, while in the sorafenib arm they were evenly distributed (15%, 14%, and 13%, respectively; $p < 0.05$).

Our study did not demonstrate a benefit from adding SIRT to systemic treatment in advanced tumours, in the ITT or PP populations. These results are in line with previous head-to-head comparisons of ⁹⁰Y SIRT against sorafenib, the SARAH and the SIRveNIB trials, which both demonstrated similar survival in patients with very advanced disease, but were not powered to demonstrate non-inferiority.^{18,19} We hypothesise, based on our exploratory subgroup analyses, that these studies recruited from too broad a patient population, including patients with compromised liver function, to demonstrate survival benefits from SIRT.

Our study was limited by the high proportion of patients (47.2%) who did not receive the allocated treatment or received the allocated treatment, but were excluded from the PP analysis because of major protocol deviations. Large numbers of protocol deviations were also observed in the SIRT arms of the SIRT monotherapy trials (26.5% of patients in SARAH and 28.5% in SIRveNIB).^{8,19} In SORAMIC, we applied the exclusion criteria

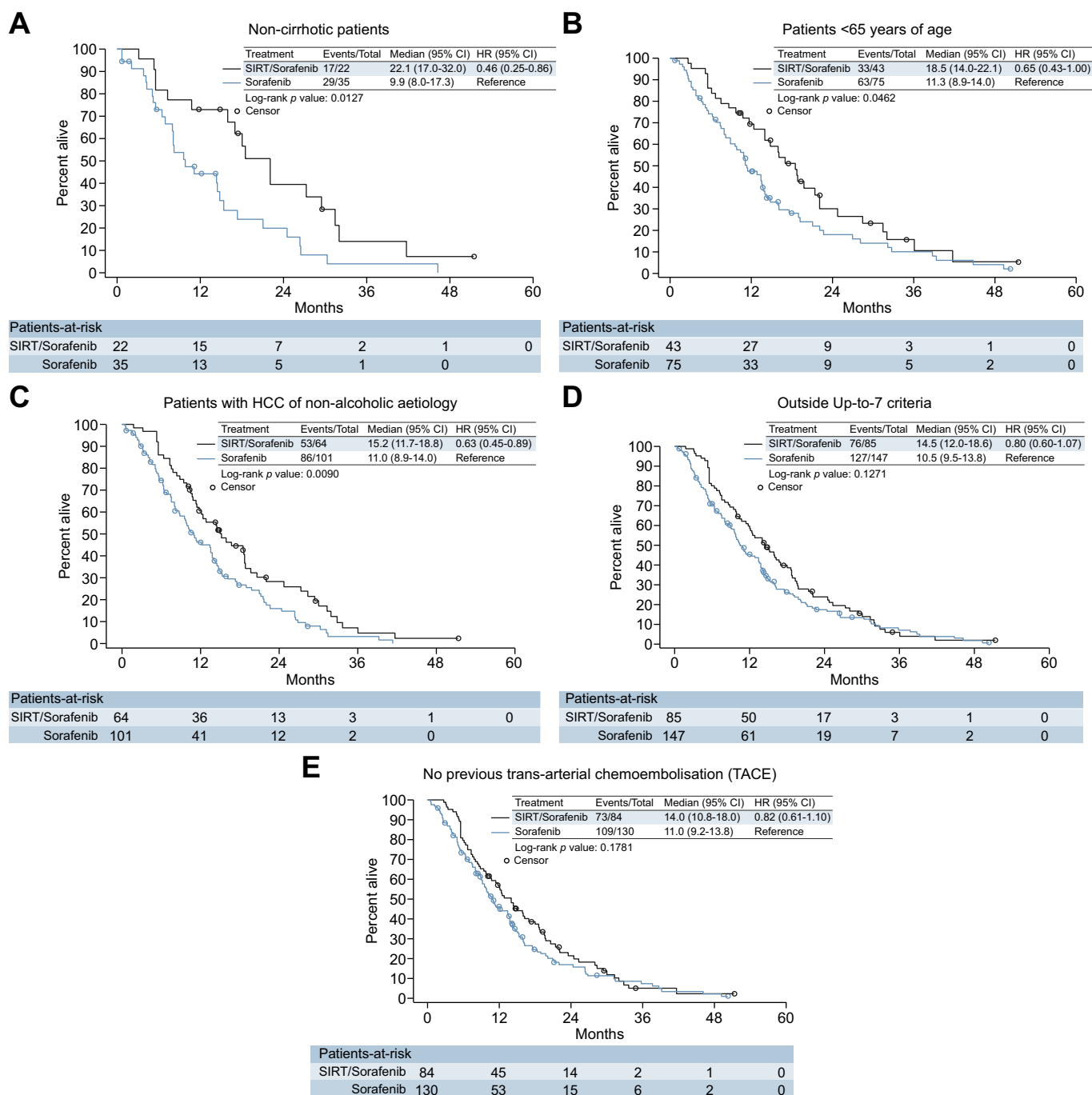


Fig. 4. Overall survival (per protocol population) in relevant patients. Subgroups: (A) non-cirrhotic patients; (B) patients <65 years of age; (C) patients with HCC of non-alcoholic aetiology; (D) patients outside Up-to-7 criteria; (E) patients without previous TACE. *p* values calculated by Log-rank test. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolisation.

rigorously, *i.e.* excluding any patient receiving inappropriate doses or with a delayed start to systemic therapy after SIRT. We believe that the high number of protocol deviations reflects the challenges of an interdisciplinary clinical routine across Europe today. Several factors hinder interdisciplinary communication among physicians, at times leading to delays of scheduling, loss of information, and suboptimal patient guidance, all of which are determinant of harmonious combination of an interventional procedure and drug treatment. Accordingly, we propose that the outcome in this PP population is highly

representative of what could be expected in optimal clinical practice.

Our study provides a sound basis for future clinical development of SIRT in intermediate to advanced HCC. Future randomised controlled trials should target less advanced disease with uncompromised liver functional reserve. Favourable outcomes with SIRT have been reported in a retrospective study in a cohort of patients at the BCLC B2 stage, a substage of BCLC B, displaying tumours outside-up-to-seven and preserved liver function Child-Pugh score A.^{25,26} This is of particular interest

Table 4. Adverse event summary.

	SIRT + sorafenib ^a		Sorafenib ^a		<i>p</i> value ^b
	Total AEs (n = 1,315)	Total patients (n = 159)	Total AEs (n = 1,162)	Total patients (n = 182)	
Total adverse events	1,315 (100.0)	151 (95.0)	1,221 (100.0)	172 (94.5)	1.000
Serious adverse events	125 (9.5)	63 (39.6)	134 (11.5)	70 (38.5)	0.911
Related AEs (Def./Prob.)	417 (31.7)	113 (71.1)	440 (37.9)	133 (73.1)	0.717
CTCAE grade ^c					
1	623 (47.4)	9 (5.7)	524 (45.1)	10 (5.5)	0.295
2	498 (37.9)	39 (24.5)	459 (39.5)	62 (34.1)	
3	172 (13.1)	84 (52.8)	151 (13.0)	76 (41.8)	
4	15 (1.1)	12 (7.5)	19 (1.6)	15 (8.2)	
5	7 (0.5)	7 (4.4)	9 (0.8)	9 (4.9)	
CTCAE grade 3–4					
Related	46 (24.6)	38 (23.9)	56 (32.9)	48 (26.4)	0.619
Unrelated	141 (75.4)	77 (48.4)	114 (67.1)	69 (37.9)	0.062
Total	187 (14.2)	103 (64.8)	170 (14.6)	97 (53.3)	0.036*
CTCAE grade 5					
Related	2 (28.6)	2 (1.3)	2 (22.2)	2 (1.1)	1.000

AE, adverse event; CTCAE, Common Terminology Criteria for AE Grades; Def., definitely related; Prob., probably related; SIRT, selective internal radiation therapy.

^a Population as randomised. Patients randomised to SIRT + sorafenib receiving SIRT or sorafenib only (see supplementary Table S4).

^b SIRT + sorafenib vs. sorafenib.

^c Not included are AEs of CTCAE Grade 0 (not codable): n = 335 AEs. *p* values for between group comparisons were calculated using Fisher's exact test and the Chi-square test. **p* < 0.05.

Table 5. Adverse events of interest.

AEs of interest	SIRT + sorafenib (n = 159)		Sorafenib ^a (n = 182)			
	Grade 3–4	Grade 5, rel.	Grade 3–4		Grade 5, rel.	
	n (%)	n (%)	n (%)	<i>p</i> value	n (%)	<i>p</i> value
Total AEs of interest (with CTCAE Grade 3/4 or related Grade 5)	64 (40.3)	1 (0.6)	61 (33.5)	0.216	1 (0.5)	1.000
Constitutional disorders:						
Fatigue	2 (1.3)	0	3 (1.6)	1.000	0	
Fever	1 (0.6)	0	0	0.466	0	
Oedema	1 (0.6)	0	1 (0.5)	0.600	0	
Dermatological disorders:						
Hand foot syndrome	15 (9.4)	0	17 (9.3)	1.000	0	
Pruritus	1 (0.6)	0	0	0.466	0	
Rash	2 (1.3)	0	1 (0.5)	0.600	0	
Gastrointestinal disorders:						
Abdominal discomfort/pain	4 (2.5)	0	5 (2.7)	1.000	0	
Decreased appetite	0	0	2 (1.1)	0.501	1 (0.5)	1.000
Diarrhoea	6 (3.8)	0	12 (6.6)	0.333	0	
Duodenal/gastric ulcer	2 (1.3)	0	0	0.217	0	
Gastrointestinal bleeding/haemorrhage	6 (3.8)	0	5 (2.7)	0.761	0	
Nausea/vomiting	1 (0.6)	0	0	0.466	0	
Liver disorders:						
Ascites	6 (3.8)	0	12 (6.6)	0.333	0	
Jaundice	1 (0.6)	0	0	0.446	0	
Liver dysfunction/hepatic failure	1 (0.6)	0	1 (0.5)	1.000	0	
Radiation hepatitis	0	0	0		0	
Hypertension	7 (4.4)	0	9 (4.9)	1.000	0	
Radiation pneumonitis	0	1 (0.6)	0		0	0.466
Cardiac failure	2 (1.3)	0	1 (0.5)	0.600	0	
Haemorrhage (non-gastrointestinal)	1 (0.6)	0	0	0.466	0	
Laboratory abnormalities:						
Anaemia	6 (3.8)	0	7 (3.8)	1.000	0	
Hyperbilirubinaemia	14 (8.8)	0	4 (2.2)	0.007*	0	
Other increased liver values	5 (3.1)	0	3 (1.6)	0.480	0	

p values for between group comparison were calculated by Fisher's exact test.

AE, adverse event; CTCAE, Common Terminology Criteria for AE Grades; rel, related to treatment (definitely or probably); SIRT, selective internal radiation therapy.

since TACE has failed to demonstrate efficacy in large and multiple tumours at BCLC stage B.^{7,26,27} The role of dosimetry should be considered, whereby only those patients that may receive a significant amount of radiation to the tumour com-

partment with minimal exposure of the non-tumoural compartment deserve prospective investigation of SIRT in future trials.

In SORAMIC, the addition of SIRT to sorafenib did not result in a significant improvement in OS compared with sorafenib

alone. Grade 3–4 AEs were significantly more common in the SIRT+ sorafenib arm. Subgroup analyses led to hypothesis-generating results for patient groups in which combination therapy has potential clinical benefit.

Financial support

Financial support provided by Sirtex Medical and Bayer Healthcare.

Conflict of interest

Dr. Ricke reports grants from Sirtex Medical, grants from Bayer AG, during the conduct of the study; personal fees from Sirtex Medical, personal fees from Bayer, personal fees from Bristol-Myers Squibb, personal fees from LaForce, personal fees from Roche, personal fees from Lilly Deutschland GmbH, personal fees from Siemens Healthineers, personal fees from Medison Pharma, personal fees from MCI Deutschland, personal fees from LIAM GmbH, outside the submitted work. Dr. Klumpen reports other fees from Ipsen, grants from Bayer, outside the submitted work. Dr. Amthauer reports grants from Sirtex Medical, grants from Bayer, during the conduct of the study; personal fees from Sirtex Medical, grants from GE Healthcare, grants and personal fees from Novartis, outside the submitted work. Dr. Bargellini reports grants from Sirtex, during the conduct of the study; personal fees from Bayer, personal fees from Sirtex, personal fees from Biocompatibles, personal fees from Terumo, outside the submitted work. Dr. Bartenstein reports grants from Sirtex Medical, outside the submitted work. Dr. de Toni reports personal fees from Bayer, during the conduct of the study; personal fees from Ipsen; personal fees from Eli Lilly & Co; personal fees from Eisai, outside the submitted work. Dr. Gasbarrini has nothing to disclose. Dr. Pech reports grants from Bayer, grants from Sirtex, during the conduct of the study. Dr. Peck-Radosavljevic reports grants from Bayer Healthcare, during the conduct of the study; grants and personal fees from Bayer Healthcare, personal fees from Eisai, personal fees from Lilly, personal fees from Ipsen, personal fees from MSD, personal fees from BMS, outside the submitted work. Dr. Popovič has nothing to disclose. Dr. Rosmorduc reports personal fees and non-financial support from Bristol-Meyers Squibb, personal fees from Eisai, personal fees and non-financial support from Bayer, non-financial support from Gilead, Outside the submitted work. Dr. Schott reports personal fees from Bayer, personal fees from Bayer, outside the submitted work. Dr. Seidensticker reports grants from Sirtex Medical, grants from Bayer, during the conduct of the study; grants, personal fees and non-financial support from Sirtex Medical, personal fees from BTG, personal fees and non-financial support from Bayer, outside the submitted work. Dr. Verslype reports grants and personal fees from Bayer, grants and personal fees from Sirtex, Grants from Ipsen, outside the submitted work. Dr. Sangro reports personal fees and non-financial support from Sirtex Medical, personal fees from BTG, personal fees from Bayer, personal fees and non-financial support from BMS, personal fees from Astra Zeneca, personal fees from Eli Lilly, personal fees from Merck, personal fees from Novartis, personal fees from Terumo, personal fees from Adaptimmune, outside the submitted work. Dr. Malfertheiner reports grants from Bayer, grants from Sirtex, during the conduct of the study.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Jens Ricke is responsible for the trial design, is a study protocol author, is the global principal investigator, contributed to data collection, data analysis, data interpretation and is a manuscript author. Heinz Joseph Klumpen contributed to data collection, data analysis, data interpretation. Holger Amthauer contributed to data collection, data analysis, data interpretation. Irene Bargellini contributed to data collection. Peter Bartenstein contributed to data collection, data analysis, data interpretation. Enrico de Toni contributed to data collection, data analysis interpretation, and to writing the manuscript. Antonio Gasbarrini contributed to data collection, data analysis. Maciej Pech contributed to data collection, data analysis, data interpretation. Markus Peck-Radosavljevic undertook steering committee activities, and contributed to patient selection and treatment, data collection and data analysis, data interpretation, and critical review of the manuscript. Peter Popovič contributed to data collection. Olivier Rosmorduc contributed to data collection, data analysis. Eckart Schott contributed to patient treatment and data acquisition. Max Seidensticker contributed to data collection, data analysis, data interpretation. Chris Verslype contributed to data collection, a data analysis and writing. Bruno Sangro undertook steering committee activities, is a principal investigator's deputy, and contributed to data collection, data analysis, data interpretation. Peter Malfertheiner is a study protocol co-author, global principal investigator's deputy, and contributed to data collection, data analysis, data interpretation.

Acknowledgement

SORAMIC is an investigator-initiated trial sponsored by the University of Magdeburg. Financial support is granted by Sirtex Medical and Bayer Healthcare. We acknowledge editorial support from Martin Gilmour and Tim Latham of ESP Bioscience Crowthorne, funded by Sirtex Medical.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2019.08.006>.

References

- [1] Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol* 2006;45:529–538. <https://doi.org/10.1016/j.jhep.2006.05.013>.
- [2] Crissien AM, Frenette C. Current management of hepatocellular carcinoma. *Gastroenterol Hepatol (N Y)* 2014;10:153–161.
- [3] Balogh J, Victor 3rd D, Asham EH, Burroughs SG, Boktour M, Saharia A, et al. Hepatocellular carcinoma: a review. *J Hepatocell Carcinoma* 2016;3:41–53. <https://doi.org/10.2147/JHC.S61146>.
- [4] Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol* 2009;10:35–43. [https://doi.org/10.1016/S1470-2045\(08\)70284-5](https://doi.org/10.1016/S1470-2045(08)70284-5).
- [5] European Association for the Study of the Liver/European Organisation for Research and Treatment of Cancer. EASL–EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012;56:908–943. <https://doi.org/10.1016/j.jhep.2011.12.001>.

- [6] Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002;359:1734–1739. [https://doi.org/10.1016/S0140-6736\(02\)08649-X](https://doi.org/10.1016/S0140-6736(02)08649-X).
- [7] Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002;35:1164–1171. <https://doi.org/10.1053/jhep.2002.33156>.
- [8] Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. *Hepatology* 2003;37:429–442. <https://doi.org/10.1053/jhep.2003.50047>.
- [9] Cammà C, Schepis F, Orlando A, Albanese M, Shahied L, Trevisani F, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. *Radiology* 2002;224:47–54. <https://doi.org/10.1148/radiol.2241011262>.
- [10] Tsochatzis EA, Fatourou E, O'Beirne J, Meyer T, Burroughs AK. Transarterial chemoembolization and bland embolization for hepatocellular carcinoma. *World J Gastroenterol* 2014;20:3069–3077. <https://doi.org/10.3748/wjg.v20.i12.3069>.
- [11] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378–390. <https://doi.org/10.1056/NEJMoa0708857>.
- [12] Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009;10:25–34. [https://doi.org/10.1016/S1470-2045\(08\)70285-7](https://doi.org/10.1016/S1470-2045(08)70285-7).
- [13] Sangro B, Carpanese L, Cianni R, Golfieri R, Gasparini D, Ezziddin S, et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. *Hepatology* 2011;54:868–878. <https://doi.org/10.1002/hep.24451>.
- [14] Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, et al. Radioembolization for hepatocellular carcinoma using yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology* 2010;138:52–64. <https://doi.org/10.1053/j.gastro.2009.09.006>.
- [15] Salem R, Lewandowski RJ, Kulik L, Wang E, Riaz A, Ryu RK, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology* 2011;140:497 e2–507 e2. <https://doi.org/10.1053/j.gastro.2010.10.049>.
- [16] Sangro B, Inarrairaegui M, Bilbao JL. Radioembolization for hepatocellular carcinoma. *J Hepatol* 2012;56:464–473. <https://doi.org/10.1016/j.jhep.2011.07.012>.
- [17] Moreno-Luna LE, Yang JD, Sanchez W, Paz-Fumagalli R, Harnois DM, Mettler TA, et al. Efficacy and safety of transarterial radioembolization versus chemoembolization in patients with hepatocellular carcinoma. *Cardiovasc Intervent Radiol* 2013;36:714–723. <https://doi.org/10.1007/s00270-012-0481-2>.
- [18] Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *Lancet Oncol* 2017;18:1624–1636. [https://doi.org/10.1016/S1470-2045\(17\)30683-6](https://doi.org/10.1016/S1470-2045(17)30683-6).
- [19] Chow PKH, Gandhi M, Tan SB, Khin MW, Khasbazar A, Ong J, et al. SIRveNIB: Selective internal radiation therapy versus sorafenib in Asia-Pacific patients with hepatocellular carcinoma. *J Clin Oncol* 2018;36:1913–1921. <https://doi.org/10.1200/JCO.2017.76.0892>.
- [20] Hermann A-L, Dieudonné A, Ronot M, Dinut A, Castera L, Chatellier G, et al. Role of 99mTc-Macroaggregated Albumin SPECT/CT based dosimetry in predicting survival and tumour response of patients with locally advanced and inoperable hepatocellular carcinoma (HCC) treated by selective intra-arterial radiation therapy (SIRT) with yttrium-90 resin microspheres, a cohort from SARAH study. *J Hepatol* 2018;68(Suppl): S13.
- [21] Seidensticker M, Seidensticker R, Damm R, Mohnike K, Pech M, Sangro B, et al. Prospective randomized trial of enoxaparin, pentoxifylline and ursodeoxycholic acid for prevention of radiation-induced liver toxicity. *PLoS ONE* 2014;9. <https://doi.org/10.1371/journal.pone.0112731>.
- [22] Sangro B, Gil-Alzugaray B, Rodriguez J, Sola I, Martinez-Cuesta A, Viudez A, et al. Liver disease induced by radioembolization of liver tumors: description and possible risk factors. *Cancer* 2008;112:1538–1546. <https://doi.org/10.1002/cncr.23339>.
- [23] Gil-Alzugaray B, Chopitea A, Inarrairaegui M, Bilbao JL, Rodriguez-Fraile M, Rodriguez J, et al. Prognostic factors and prevention of radioembolization-induced liver disease. *Hepatology* 2013;57:1078–1087. <https://doi.org/10.1002/hep.26191>.
- [24] Hernaez R, Sola E, Moreau R, Gines P. Acute-on-chronic liver failure: an update. *Gut* 2017;66:541–553. <https://doi.org/10.1136/gutjnl-2016-312670>.
- [25] Bolondi L, Burroughs A, Dufour JF, Galle PR, Mazzaferro V, Piscaglia F, et al. Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions. *Semin Liver Dis* 2012;32:348–359. <https://doi.org/10.1055/s-0032-1329906>.
- [26] Cappelli A, Sangro P, Mosconi C, Deppe I, Terzi E, Bilbao JL, et al. Transarterial radioembolization in patients with hepatocellular carcinoma of intermediate B2 substage. *Eur J Nucl Med Mol Imaging* 2018. <https://doi.org/10.1007/s00259-018-4152-7>.
- [27] Golfieri R, Renzulli M, Mosconi C, Forlani G, Giampalma E, Piscaglia F, et al. Hepatocellular carcinoma responding to superselective transarterial chemoembolization: an issue of nodule dimension?. *J Vasc Interv Radiol* 2013;24:509–517. <https://doi.org/10.1016/j.jvir.2012.12.013>.