VESPRO

Statistical Report

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An individual patient data prospective meta-analysis (IPD_PMA) of selective internal radiation therapy (SIRT) versus sorafenib for advanced, locally advanced or recurrent hepatocellular carcinoma (HCC) of the SARAH and SIRveNIB trials

ABBREVIATIONS

HCC	Hepatocellular Carcinoma
SIRT	Selective internal radiation therapy (also called radioembolisation)
OS	Overall Survival
PFS	Progression free survival
ORR	Overall Response Rate
HR	Hazard Ratio
PH	Proportional Hazards
CI	Confidence Interval

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1 STUDY OBJECTIVES

This study is an individual patient-level prospective meta-analysis, from two randomised open label phase III efficacy trials examining survival benefits as their primary outcome, SARAH and SIRveNIB, both which have completed recruitment. To date, no results regarding the survival by randomised treatment groups have been reported. The aim of this meta-analysis is to improve the strength of the evidence on the benefit or potential non-inferiority of selective internal radiation therapy (SIRT), also known as radioembolisation, compared to sorafenib with respect to overall survival.

1.1 Primary Objective

To compare the efficacy, defined as the mortality reduction and measured as the overall survival time of the infusion of SIRT compared to a daily dose of Sorafenib.

1.2 Secondary Objectives

To compare:

- Time to progression in the liver as the first event between SIRT and sorafenib
- Progression free survival between SIRT and sorafenib
- Tumour response rates between SIRT and sorafenib
- Disease control rates between SIRT and sorafenib
- Toxicities between SIRT and sorafenib

1.3 Primary Endpoint

All-cause mortality as measured by the overall survival time

1.4 Secondary Endpoints

- Progression in the liver as the first event
- Progression free survival (PFS)
- Tumour response rate
- Disease control rate
- Rate of serious adverse events (SAEs)

2 STATISTICAL CONSIDERATIONS

2.1 Sample Size individual trials

In the SARAH trial, the hypothesized median survival time for sorafenib and SIRT arms were taken to be 10.7 months and 15.0 months respectively. This corresponds to a hazard ratio (HR) of 0.71. The enrolment of 400 patients in total (200 per group) would provide 80% power with 95% confidence to detect this risk reduction based on an accrual period of 24 months

and a minimum follow-up of 12 month. To account for an approximately 16.5%, rate of patient non-compliance and dropouts, the final sample size was set to 466 patients (459 actually randomized). The expected number of events, accounting for this cross-over rate, was 153 in the SIRT group and 179 in the sorafenib group.

In the SIRveNIB trial, the hypothesized median survival times were 9.35 months and 14.0 months in the sorafenib group and the SIRT group corresponding to a HR of 0.67. The enrolment of 360 patients in total (180 per group) would provide 90% power with 95% confidence to detect this risk reduction with an accrual of 36 months and minimum follow-up of 24 months. This sample size also allows for up to a 20% drop-out rate. Factoring in this high drop-out rate was a pragmatic decision due to the patient recruitment being in developing countries. The expected number of events was 127 in the SIRT group and 139 for the sorafenib group.

2.2 Prospective Meta-Analysis

Regardless of the results of each individual trial (statistical significance, or extent of therapeutic benefit), a prospectively designed pooled analysis may help clarify several findings useful for medical-decision making. Thus, the total number of events for the two trials combined will provide increased power or precision for assessing the overall treatment effect, and for performing additional analyses among pre-specified subgroups. However, pooled analyses resulting in estimates of benefit which may be small and/or statistically not significant will raise challenges as to how the results should be clinically interpreted. In this context, a complementary approach is to define a non-inferiority (NI) margin of which is considered clinically to be *not appreciable worse*.

Both trials are anticipating a benefit and as such, no specific hypotheses will be tested and issues of statistical power do not arise. The question of interest is whether the 95% CI (one-sided) crosses the NI margin in the event the pooled result does not reach statistical significance. By exploiting the prospective nature of determining the NI margin, we provide scientific underpinning for the subsequent clinical interpretation of the results. This approach is based on the assumption that, beside the SIRT specific therapeutic action, other aspects of the SIRT intervention could also make it an attractive alternate therapy. Thus, SIRT consists in a single administration of the product while sorafenib is required to be taken daily until disease progression. Compared to Sorafenib, one can therefore expect both a better toxicity profile and lower costs. In the absence of superiority over sorafenib, SIRT may therefore still be considered a desirable option if the NI boundary is satisfied.

2.3 Defining the non-inferiority margin

2.3.1 Fraction of active control retained

To establish a NI margin, it is important to determine the minimum fraction of retained benefit from the active control (sorafenib). The ICH E10 recommends that NI margins should not exceed the smallest effect size which would be expected if the intervention were

compared to a placebo. The European SHARP Trial[1] compared sorafenib to placebo among 602 patients and showed that Sorafenib provided a 31% reduction of the risk of mortality (HR: 0.69; 95% CI 0.55-0.87) over placebo. Similarly, among 226 patients, the sorafenib Asia–Pacific trial[2,3] showed a 32% reduction of the risk of mortality (HR: 0.68; 95% CI: 0.50–0.93). The pooled overall HR of sorafenib over placebo is 0.69 (95% CI: 0.57-0.83), or, if placebo is compared to sorafenib, 1.46 (95% CI: 1.21-1.75), a mortality risk increase of at least 21% (the lower limit of the confidence interval) over sorafenib. The FDA[4] recommends that the minimum fraction of active control retained should not be lower than 50%. For different fractions of active control retained NI margins are given in the following table (based on a one-sided 95% CI).

Table 1 – Active control effect retained

Active control retained (from an HR of 1.21)	NI Boundary
50%	1.10
70%	1.06
75%	1.05
80%	1.04

2.3.2 Sample size and non-inferiority margin

A boundary of 10% is considered to be clinically acceptable for potential relative detriment of SIRT compared to sorafenib. For example if the pooled median survival for both trials for the sorafenib arm is 9.5 months, such a margin would translate to an absolute detriment between the two groups of less than 5% at 9.5 months. With a 10% NI margin and a fixed sample size of the pooled cohort of 819 with > 495 expected events, a survival benefit of SIRT compared to sorafenib of at least 7% (HR: 0.93) would be needed to be observed to satisfy this margin at a median survival for sorafenib of 9.5 months.

3 ANALYSIS SETS

All patients from the SARAH and SIR*ve*NIB trials will be included in this individual patient data prospective meta-analysis (IPD_PMA). Patients had to satisfy the inclusion criteria as stated in the protocol (and published elsewhere[3,5]) for the respective trials. In the SIR*ve*NIB trial, patients only have locally advanced hepatocellular carcinoma (HCC) whereas, in the SARAH trial, patients with either advanced or recurrent HCC are included.

4 PRIMARY AND SECONDARY VARIABLES

- The primary endpoint, overall survival, is defined as the time from randomisation until death (any cause), with living patients and lost to follow-up patients censored on the date of last follow-up at which they are known to be alive.

- PFS is defined as the time from randomisation until disease progression at any site (RECIST criteria 1.1) or death. Non-progressing patients and patients who are lost to follow-up before progression will be censored on the date of last evaluable tumour assessment. Patients who commence other anti-cancer treatment while on study and then progress will be analysed as an event on the allocated randomised treatment as per the intention to treat definition. Similarly, patients commencing other anti-cancer treatment and not-progressing will be censored at the last known follow-up time.
- Progression in the liver as first event was defined as the time from randomisation until the first progression in the liver. Death or progression outside the liver as the first event is considered as a competing risk. Patients alive and progression free will be censored on the date of last evaluable tumour assessment. Similarly, patients who are lost to follow-up before progression in the liver will be censored on the date of last tumour status assessment.
- Disease control rate is defined as the number of subjects whose best overall response is Partial Response (PR), Complete Response (CR) or Stable Disease (SD), divided by the total number of subjects in the analysis population.
- Tumour Response Rate: Tumour response rate is defined as the number of subjects whose best overall response is PR or CR, divided by the total number of subjects in the analysis population.

5 ANALYSIS METHODS

Primary endpoint

Analyses of the primary endpoint will be performed using the intention-to-treat (ITT) principle (patients analysed according to the treatment to which they were randomised). The primary outcome will be compared using the inverse-variance weighted hazard ratio of the individual trials.

A sensitivity analysis using a stratified log-rank test and an unadjusted stratified proportional hazards model (stratified by trial) will also be performed. The comparison will be one based on superiority. In the event that the 95% CI for the hazard ratio crosses the null, if the one-sided upper 95% CI for this hazard ratio does not breach the NI boundary of 1.10 then this will be interpreted as supporting evidence that the SIRT therapy is not appreciably worse than Sorafenib.

Secondary endpoints

The same methods as described for the primary outcome will be performed for PFS.

Analyses accounting for competing risks will be conducted for the “progression in the liver” endpoint. Groups will be summarised using cumulative incidence curves and compared using Gray’s test[6]. Fine and Gray model[7] will be used to estimate the sub-distribution hazard ratio.

The toxicities between the two groups will be described as the frequency of the worst toxicity grade experienced for each patient per toxicity. These counts will be compared, stratifying (e.g. Mantel-Haenszel) for study, with the main interest being the proportion of toxicities greater than grade 3. The worst grade of all toxicities experienced per person will be compared using a Mantel-Haenszel test. When there are sufficient numbers for each of the individual toxicities and for any toxicity, time to the first grade ≥ 3 will be compared using a stratified log-rank test and an unadjusted stratified proportional hazards model (stratified by trial). If a patient does not have a grade ≥ 3 for the given toxicity, prior to progression or last date known not to have progressed, then the patient will be censored and given the time to progression as their time to event.

Disease control rate and tumour response rate will be analysed by comparing the counts for the two arms, stratifying by study, by using the Mantel-Haenszel test. Results will be represented as a difference in the proportions with a 95% confidence interval.

This disease has a poor prognosis and a landmark analysis[8] will be performed at 2-months post-randomization for overall survival, progression free survival and progression in the liver. This conditional analysis will exclude patients who die within 2-months (patients dying within 2 months are so severe that neither treatment can provide them any therapeutic benefit).

Subgroup analysis

Subgroup analyses will be performed for overall survival, progression free survival and progression in the liver according to the following patients' baseline characteristics:

- Age (<65 years, ≥65 years)
- Gender
- ECOG performance status (0 , 1)
- Tumour burden (≤ 50% of liver, > 50% of liver)
- Presence or absence of portal vein thrombosis
- BCLC stage (A, B, C)
- BCLC sub-stage (B1, B2, B3, B4) (Using Bolondi Criteria)
- Prior HCC treatment (yes, no)
- Hepatitis status (B, C, Both)
- Unilobar vs Bilobar
- Single focal vs multifocal
- Serum alpha-feto protein level (≤100 ng/ml versus >100 ng/ml)

Results of all performed analyses will be reported. If appropriate, analysis including treatment by subgroup interaction analysis will also be performed.

6 RESULTS

6.1 Background

Table 2: Patient Characteristics at Baseline- Categorical variables (ITT Population)

Characteristic	*Level*	*SARAH (N=459)*	*SIRveNIB (N=360)*	*Both groups (N=819)*	*Sorafenib (N=400)*	*SIRT (N=419)*
Age	<65 Years	210 (45.8%)	243 (67.5%)	453 (55.3%)	239 (59.8%)	214 (51.1%)
	≥65 Years	249 (54.2%)	117 (32.5%)	366 (44.7%)	161 (40.3%)	205 (48.9%)
Gender	Female	45 (9.8%)	62 (17.2%)	107 (13.1%)	47 (11.8%)	60 (14.3%)
	Male	414 (90.2%)	298 (82.8%)	712 (86.9%)	353 (88.3%)	359 (85.7%)
ECOG*	0	284 (61.9%)	276 (76.7%)	560 (68.4%)	280 (70.0%)	280 (66.8%)
	1	174 (37.9%)	84 (23.3%)	258 (31.5%)	120 (30.0%)	138 (32.9%)
Tumour burden within liver	≤ 50%	408 (88.9%)	274 (76.1%)	682 (83.3%)	328 (82.0%)	354 (84.5%)
	> 50%	51 (11.1%)	86 (23.9%)	137 (16.7%)	72 (18.0%)	65 (15.5%)
Unilobar/bilobar	Unilobar	374 (81.5%)	144 (40.0%)	518 (63.2%)	259 (64.8%)	259 (61.8%)
	Bilobar	85 (18.5%)	167 (46.4%)	252 (30.8%)	121 (30.3%)	131 (31.3%)
	Unknown		49 (13.6%)	49 (6.0%)	20 (5.0%)	29 (6.9%)

Characteristic	*Level*	*SARAH (N=459)*	*SIRveNIB (N=360)*	*Both groups (N=819)*	*Sorafenib (N=400)*	*SIRT (N=419)*
Unifocal/multifocal	Unknown		49 (13.6%)	49 (6.0%)	20 (5.0%)	29 (6.9%)
	Unifocal	206 (44.9%)	99 (27.5%)	305 (37.2%)	143 (35.8%)	162 (38.7%)
	Multifocal	253 (55.1%)	212 (58.9%)	465 (56.8%)	237 (59.3%)	228 (54.4%)
Main portal vein thrombosis	Yes	87 (19.0%)	110 (30.6%)	197 (24.1%)	92 (23.0%)	105 (25.1%)
	No	372 (81.0%)	250 (69.4%)	622 (75.9%)	308 (77.0%)	314 (74.9%)
BCLC stage	Missing		1 (0.3%)	1 (0.1%)		1 (0.2%)
	A	21 (4.6%)	1 (0.3%)	22 (2.7%)	13 (3.3%)	9 (2.1%)
	B	127 (27.7%)	190 (52.8%)	317 (38.7%)	158 (39.5%)	159 (37.9%)
	C	311 (67.8%)	168 (46.7%)	479 (58.5%)	229 (57.3%)	250 (59.7%)
BCLC Sub-stage	Unknown B	2 (1.6%)	34 (17.9%)	538 (65.7%)	14 (8.9%)	22 (13.8%)
	B1	64 (50.4%)	8 (4.2%)	72 (8.8%)	32 (20.3%)	40 (25.2%)
	B2	56 (44.1%)	136 (71.6%)	192 (23.4%)	103 (65.2%)	89 (56%)
	B3	5 (3.9%)	10 (5.3%)	15 (1.8%)	8 (5.1%)	7 (4.4%)
	B4	(0%)	2 (1.1%)	2 (0.2%)	1 (0.6%)	1 (0.6%)
Beyond Milan and within Ut-7	.	334 (72.8%)	49 (13.6%)	383 (46.8%)	181 (45.3%)	202 (48.2%)
	IN	64 (13.9%)	19 (5.3%)	83 (10.1%)	37 (9.3%)	46 (11.0%)
	OUT	61 (13.3%)	292 (81.1%)	353 (43.1%)	182 (45.5%)	171 (40.8%)

Characteristic	*Level*	*SARAH (N=459)*	*SIRveNIB (N=360)*	*Both groups (N=819)*	*Sorafenib (N=400)*	*SIRT (N=419)*
Hepatitis Status	Unknown	43 (9.4%)	38 (10.6%)	81 (9.9%)	35 (8.8%)	46 (11.0%)
	B	27 (5.9%)	197 (54.7%)	224 (27.4%)	119 (29.8%)	105 (25.1%)
	C	103 (22.4%)	45 (12.5%)	148 (18.1%)	68 (17.0%)	80 (19.1%)
	Both	1 (0.2%)	9 (2.5%)	10 (1.2%)	5 (1.3%)	5 (1.2%)
	None	285 (62.1%)	71 (19.7%)	356 (43.5%)	173 (43.3%)	183 (43.7%)
Prior HCC treatments	Yes	98 (21.4%)	95 (26.4%)	193 (23.6%)	100 (25.0%)	93 (22.2%)
	No	361 (78.6%)	265 (73.6%)	626 (76.4%)	300 (75.0%)	326 (77.8%)
Ethnicity	Unknown/Other	71 (15.5%)		71 (8.7%)	40 (10.0%)	31 (7.4%)
	North-African	12 (2.6%)		12 (1.4%)	5 (1.3%)	7 (1.7%)
	Sub-Saharan	8 (1.7%)		8 (1.0%)	3 (0.8%)	5 (1.2%)
	Asian	5 (1.1%)	272 (75.6%)	277 (33.8%)	138 (34.5%)	139 (33.2%)
	Caucasian	363 (79.1%)	3 (0.8%)	366 (44.7%)	175 (43.8%)	191 (45.6%)
	Islander	0 (0.0%)	85 (23.6%)	85 (10.4%)	39 (9.8%)	46 (11.0%)
Child Pugh score	Unknown	2 (0.4%)	2 (0.6%)	4 (0.5%)	1 (0.3%)	3 (0.7%)
	A	383 (83.4%)	319 (88.6%)	702 (85.7%)	343 (85.8%)	359 (85.7%)
	B	73 (15.9%)	39 (10.8%)	112 (13.7%)	56 (14.0%)	56 (13.4%)
	C	1 (0.2%)		1 (0.1%)		1 (0.2%)

*One patient in the SIRT group (SHAAH study) had an ECOG score of 2

Table 3: Patient Characteristics at Baseline- Continuous variables (ITT Population)

Characteristic	*Level*	*SARAH (N=459)*	*SIRveNIB (N=360)*	*Both groups (N=819)*	*Sorafenib (N=400)*	*SIRT (N=419)*
Age (years)	N	459	360	819	400	419
	Mean(SD)	65.24 (9.38)	58.64 (11.83)	62.34 (11.02)	61.56 (10.48)	63.08 (11.48)
	Range	(34,89)	(17,88)	(17,89)	(32,85)	(17,89)
	Median(IQR)	66 (59,73)	60 (52.5,66)	63 (56,70)	62 (55,69)	64 (57,71)
Weight (kg)	N	457	350	807	396	411
	Mean(SD)	80.16 (15.06)	63.94 (13.54)	73.13 (16.5)	74.03 (16.2)	72.25 (16.76)
	Range	(38,121)	(35,145)	(35,145)	(35,124)	(38,145)
	Median(IQR)	80 (70,90)	62.3 (54.6,69.9)	71.2 (61,84)	73.7 (62,85.6)	70 (60,83)
Height (cm)	N	456	351	807	394	413
	Mean(SD)	171.58 (7.33)	164.29 (7.91)	168.41 (8.4)	168.63 (8.27)	168.2 (8.53)
	Range	(149,193)	(141,184)	(141,193)	(144,192)	(141,193)
	Median(IQR)	172 (166,176)	165 (159,170)	169 (164,174)	169 (164,174)	169 (163,174)
Body Mass Index (kg/m2)	N	454	350	804	393	411
	Mean(SD)	27.23 (4.93)	23.64 (4.4)	25.67 (5.03)	25.91 (4.86)	25.44 (5.18)
	Range	(15.1,43.9)	(14.33,43.77)	(14.33,43.9)	(14.51,42.8)	(14.33,43.9)
	Median(IQR)	27.1 (23.7,30.1)	22.82 (20.58,26.4)	25.2 (22,29)	25.6 (22.27,29.24)	24.8 (21.78,28.7)

Characteristic	*Level*	*SARAH (N=459)*	*SIRveNIB (N=360)*	*Both groups (N=819)*	*Sorafenib (N=400)*	*SIRT (N=419)*
Body Surface Area (m2)	N	454	350	804	393	411
	Mean(SD)	1.92 (0.18)	1.69 (0.18)	1.82 (0.22)	1.83 (0.21)	1.81 (0.22)
	Range	(1.29,2.47)	(1.24,2.59)	(1.24,2.59)	(1.24,2.47)	(1.28,2.59)
	Median(IQR)	1.92 (1.81,2.04)	1.69 (1.57,1.8)	1.82 (1.68,1.98)	1.83 (1.69,1.98)	1.8 (1.67,1.96)
Size of the largest lesions (index) (cm)	N	454	360	814	399	415
	Mean(SD)	7.08 (4.19)	9.08 (4.89)	7.97 (4.62)	7.9 (4.59)	8.03 (4.65)
	Range	(1,24)	(1.3,27.1)	(1,27.1)	(1,27.1)	(1.1,24)
	Median(IQR)	6.2 (3.8,9.4)	8.2 (4.9,12.8)	7.02 (4.3,11)	7.02 (4.3,10.7)	7.02 (4.3,11.2)
Level of alpha-fetoprotein (ng/mL)	N	416	355	771	373	398
	Mean(SD)	13424.58 (132064.43)	12252.37 (40967.33)	12884.85 (100856.14)	18016.59 (142451.36)	8075.45 (25817.23)
	Range	(2,2302400)	(0.33,465944.4)	(0.33,2302400)	(0.62,2302400)	(0.33,265900)
	Median(IQR)	83.5 (9,1195.5)	441 (28.8,2066.12)	203 (13,2066.12)	174.1 (11,2066.12)	237.83 (14,2082)
Level of albumin (g/L)	N	444	360	804	396	408

Characteristic	*Level*	*SARAH (N=459)*	*SIRveNIB (N=360)*	*Both groups (N=819)*	*Sorafenib (N=400)*	*SIRT (N=419)*
	Mean(SD)	36.02 (4.94)	36.6 (5.2)	36.28 (5.07)	36.72 (5.15)	35.85 (4.95)
	Range	(23,49)	(25,53.5)	(23,53.5)	(24,51.1)	(23,53.5)
	Median(IQR)	36 (32,39)	37 (33,40)	36 (33,40)	37 (33,41)	36 (32,39)
Level of alkaline phosphate (IU)	N	447	360	807	393	414
	Mean(SD)	195.83 (134.47)	153.25 (74.43)	176.83 (113.67)	175.81 (103.83)	177.81 (122.41)
	Range	(45,1469)	(35,578)	(35,1469)	(35,755)	(42,1469)
	Median(IQR)	163 (113,231)	139 (102.45,185.22)	150 (110,213)	152 (111,207)	148 (108,217)
Level of platelets (x10^9/L)	N	457	359	816	399	417
	Mean(SD)	164.7 (93.13)	225.44 (118.2)	191.43 (109.09)	190.46 (109.36)	192.35 (108.95)
	Range	(16,780)	(71,744)	(16,780)	(16,744)	(45,780)
	Median(IQR)	142 (99,207)	198 (136,280)	165 (115,243.5)	164 (115,236)	167 (115,246)
Level of bilirubin total (µmol/L)	N	458	359	817	400	417
	Mean(SD)	18.45 (10.47)	15.99 (8.89)	17.37 (9.87)	17.44 (10.19)	17.3 (9.58)
	Range	(3,80)	(2.25,104.3)	(2.25,104.3)	(2.25,104.3)	(3,80)
	Median(IQR)	16 (11,23)	14.54 (10.26,19.9)	15 (10.6,22)	15 (11,22)	15.1 (10.26,21)

6.2 Primary outcome

6.2.1 All-cause mortality

Figure 1: Kaplan Meier curve for overall survival by treatment (ITT Population)

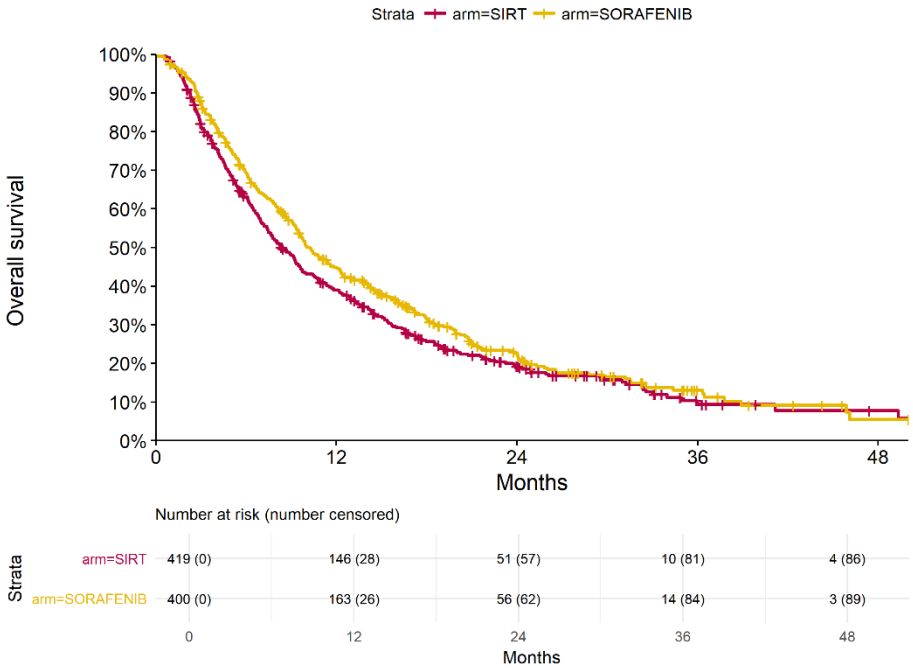


Figure 2: Kaplan Meier curve for overall survival by treatment and trial (ITT Population)

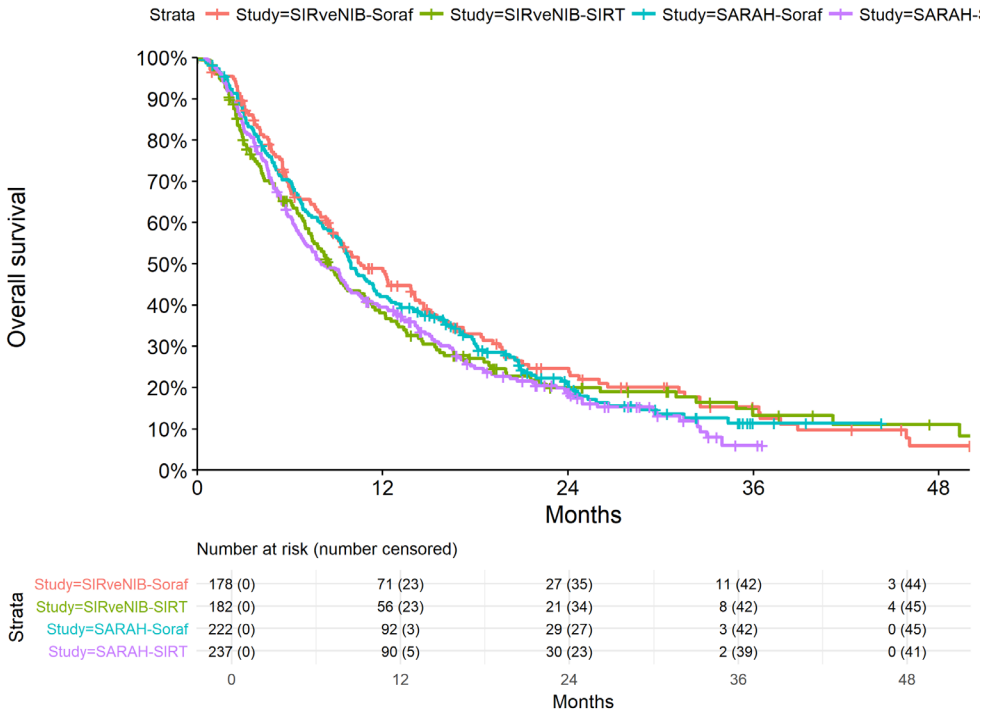


Table 4: Median overall survival (ITT Population)

		Sorafenib (N=400)	*SIRT (N=419)*	*Combined (N=819)*
Median Survival Time (95% CI) (Months)	Combined	9.9(9.2,11.4)	8.6(7.5,9.6)	9.3(8.6,10)
	SARAH	9.9(8.8,11.4)	8(6.7,9.9)	9.4(8.1,10.3)
	SIRVENIB	10(8.6,13.8)	8.8(7.5,10.8)	9.3(8.5,10.8)

Table 5: Median Follow-up (ITT Population)

		Sorafenib (N=400)	*SIRT (N=419)*	*Combined (N=819)*
Median Follow-Up (95% CI)(Months)	Combined	28.1(24.5,33.2)	27.9(24.6,30.5)	28.1(25.4,30.4)
	SARAH	28.1(23.8,35)	27.9(24.2,29.8)	28.1(24.6,30.4)
	SIRVENIB	30.2(21.9,42.3)	27.9(19.2,35.9)	30.2(22.8,33.2)

Table 6: Overall survival treatment effect estimates (ITT Population)

		Hazard Ratio	*95% Lower Confidence Limit for Hazard Ratio*	*95% Upper Confidence Limit for Hazard Ratio*	*P-value (superiority)*
Treatment effect(SIRT vs Sorafenib)	SIRveNIB	1.119	0.880	1.423	0.3603
	SARAH	1.150	0.938	1.409	0.1793
	Combined	1.137	0.973	1.328	0.1061
	Stratified Log-rank	.	.	.	0.1056
	PH Regression	1.137	0.973	1.328	0.1060

6.3 Secondary outcomes

Table 7: Patient status (ITT Population)

Outcome	*Event type*	*SARAH (N=459)*	*SIRveNIB (N=360)*	*Both groups (N=819)*	*Sorafenib (N=400)*	*SIRT (N=419)*
Survival Status	Dead	373 (81.3%)	266 (73.9%)	639 (78.0%)	308 (77.0%)	331 (79.0%)
	Alive/Lost to follow-up	86 (18.7%)	94 (26.1%)	180 (22.0%)	92 (23.0%)	88 (21.0%)
Progression status	Alive With No Progression	36 (7.8%)		36 (4.4%)	17 (4.3%)	19 (4.5%)
	Censored	36 (7.8%)	62 (17.2%)	98 (12.0%)	43 (10.8%)	55 (13.1%)
	Death	146 (31.8%)	147 (40.8%)	293 (35.8%)	124 (31.0%)	169 (40.3%)
	Not Progressed/Not Known To Have Progressed		62 (17.2%)	62 (7.6%)	26 (6.5%)	36 (8.6%)
	Progressed Inside The Liver	239 (52.1%)	145 (40.3%)	384 (46.9%)	218 (54.5%)	166 (39.6%)
	Progressed Outside The Liver	38 (8.3%)	6 (1.7%)	44 (5.4%)	15 (3.8%)	29 (6.9%)
	Progressed*	423 (92.2%)	298 (82.8%)	721 (88.0%)	357 (89.3%)	364 (86.9%)

*Composite event: progression in any location or death.

6.3.1 Progression in the liver

Table 8: Progression in the liver (ITT Population)

		Hazard Ratio	*95% Lower Confidence Limit for Hazard Ratio*	*95% Upper Confidence Limit for Hazard Ratio*	*P-value (superiority)*
Treatment effect(SIRT vs Sorafenib)	SIRveNIB	0.471	0.338	0.657	<.0001
	SARAH	0.723	0.562	0.932	0.0121
	Combined	0.618	0.505	0.756	<.0001
	PH Regression	0.617	0.505	0.754	<.0001

6.3.2 Progression free survival

Figure 3: Kaplan Meier curve for progression free survival by treatment (ITT Population)

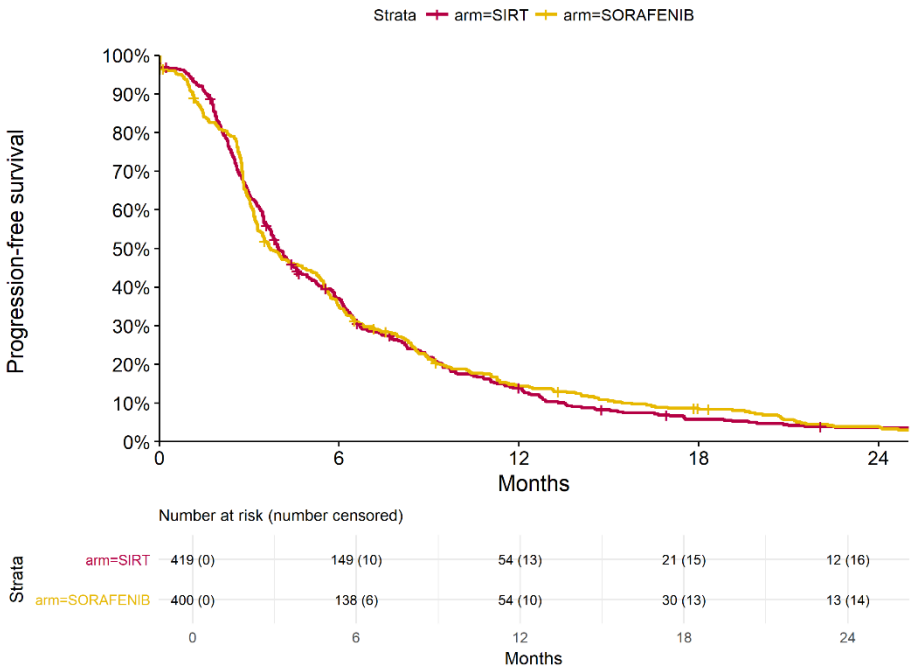


Figure 4: Kaplan Meier curve for progression free survival by treatment by trial (ITT Population)

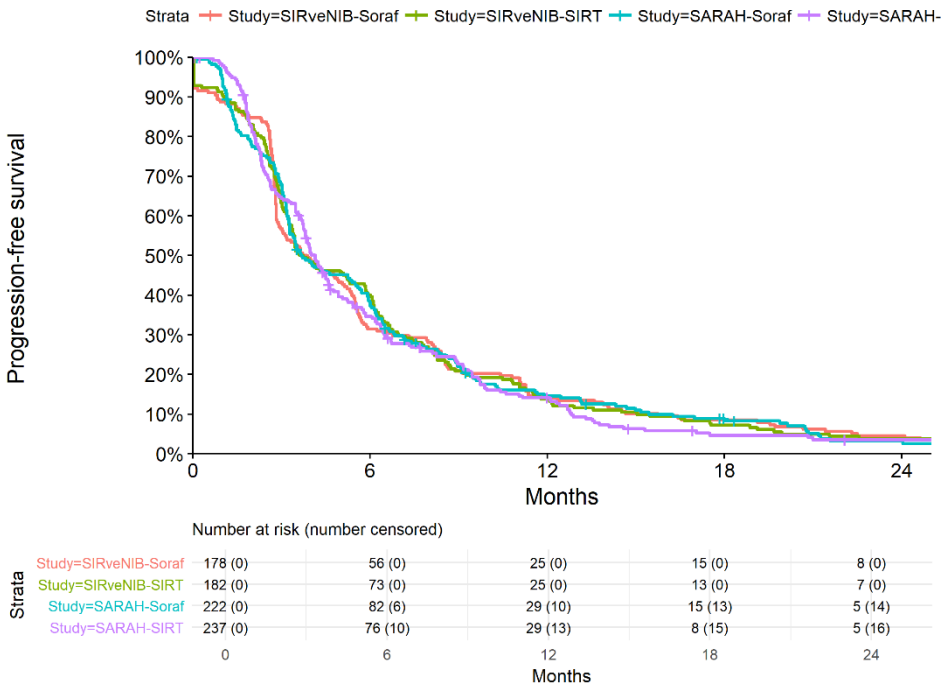


Figure 5: Cumulative incidence of progression by treatment and type (ITT Population)

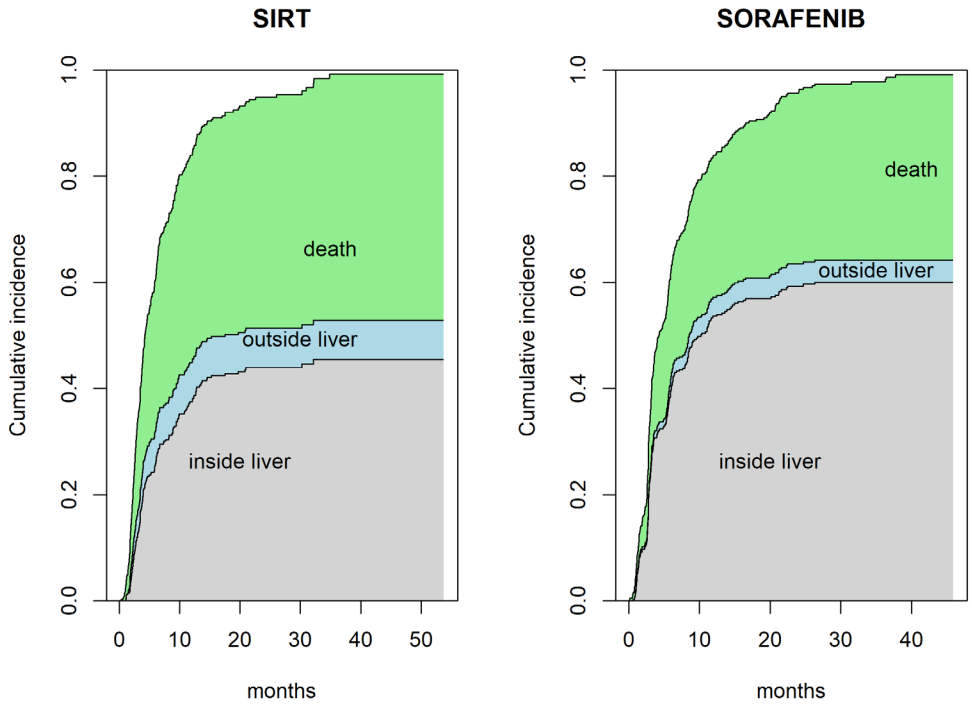


Table 9: Median Progression Free survival (ITT Population)

		Sorafenib (N=400)	*SIRT (N=419)*	*Combined (N=819)*
Median PFS Time (95% CI)(Months)	Combined	4.3(3.6,5.4)	4.4(3.9,5.1)	4.3(3.9,5)
	SARAH	3.7(3.3,5.4)	4.1(3.8,4.6)	4(3.7,4.5)
	SIRVENIB	5.1(3.9,5.6)	5.8(3.7,6.3)	5.3(4.2,5.8)

Table 10: Progression Free Survival treatment effect estimates (ITT Population)

		Hazard Ratio	*95% Lower Confidence Limit for Hazard Ratio*	*95% Upper Confidence Limit for Hazard Ratio*	*P-value (superiority)*
Treatment effect(SIRT vs Sorafenib)	SIRveNIB	0.888	0.707	1.115	0.3060
	SARAH	1.030	0.851	1.247	0.7607
	Combined	0.969	0.837	1.122	0.6709
	Stratified Log-rank	.	.	.	0.6739
	PH Regression	0.969	0.837	1.122	0.6713

6.3.3 Landmark analyses

The following landmark analyses are conducted within the patients who were at risk in each analysis at 2 months post-randomisation.

Table 11: Landmark analysis - Patient status (beyond 2 months) (ITT Population)

Outcome	*Event type*	*SARAH (N=424)*	*SIRveNIB (N=329)*	*Sorafenib (N=371)*	*SIRT (N=382)*
Survival Status	Dead	340 (80.2%)	244 (74.2%)	286 (77.1%)	298 (78.0%)

Table 12: Landmark analysis - Patient progression status (beyond 2 months) (ITT Population)

Outcome	*Event type*	*SARAH (N=361)*	*SIRveNIB (N=302)*	*Sorafenib (N=320)*	*SIRT (N=343)*
Progression Status	Progressed Inside The Liver	193	137	181	149
	Progressed	334	268	297	305

Table 13: Landmark analysis - Overall Survival (ITT Population)

		Hazard Ratio	*95% Lower Confidence Limit for Hazard Ratio*	*95% Upper Confidence Limit for Hazard Ratio*	*P-value (superiority)*
Treatment effect(SIRT vs Sorafenib)	SIRveNIB	1.132	0.880	1.455	0.3347
	SARAH	1.138	0.920	1.409	0.2328
	Combined	1.136	0.965	1.336	0.1251
	PH Regression	1.136	0.965	1.336	0.1250

Figure 6: Kaplan Meier curve for overall survival beyond 2 months by treatment (ITT Population)

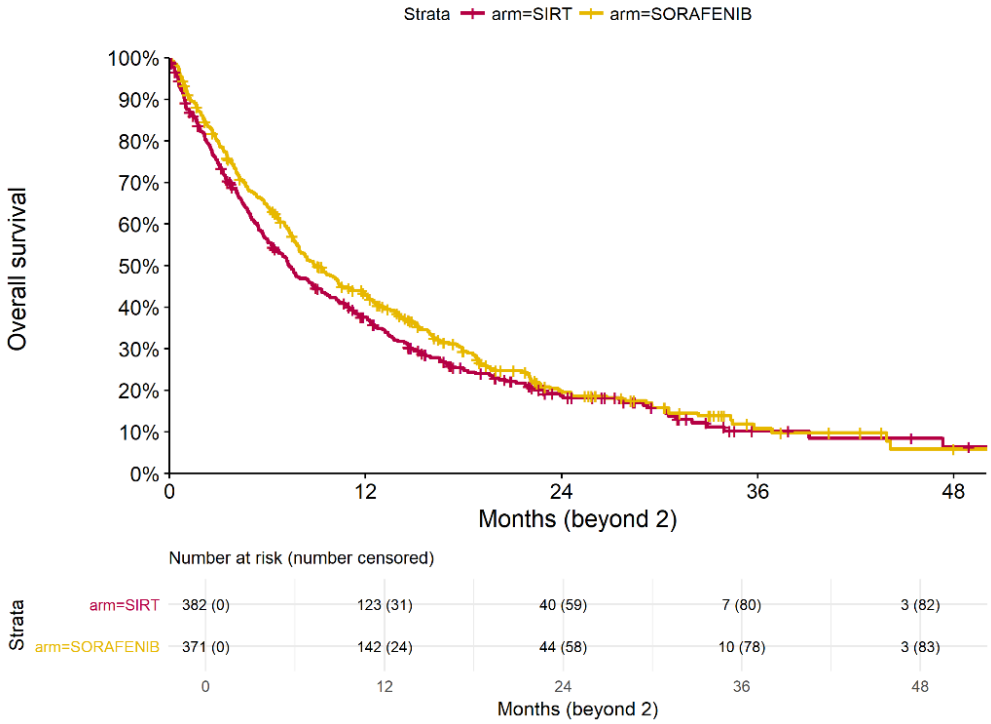


Figure 7: Kaplan Meier curve for overall survival beyond 2 months by treatment and trial (ITT Population)

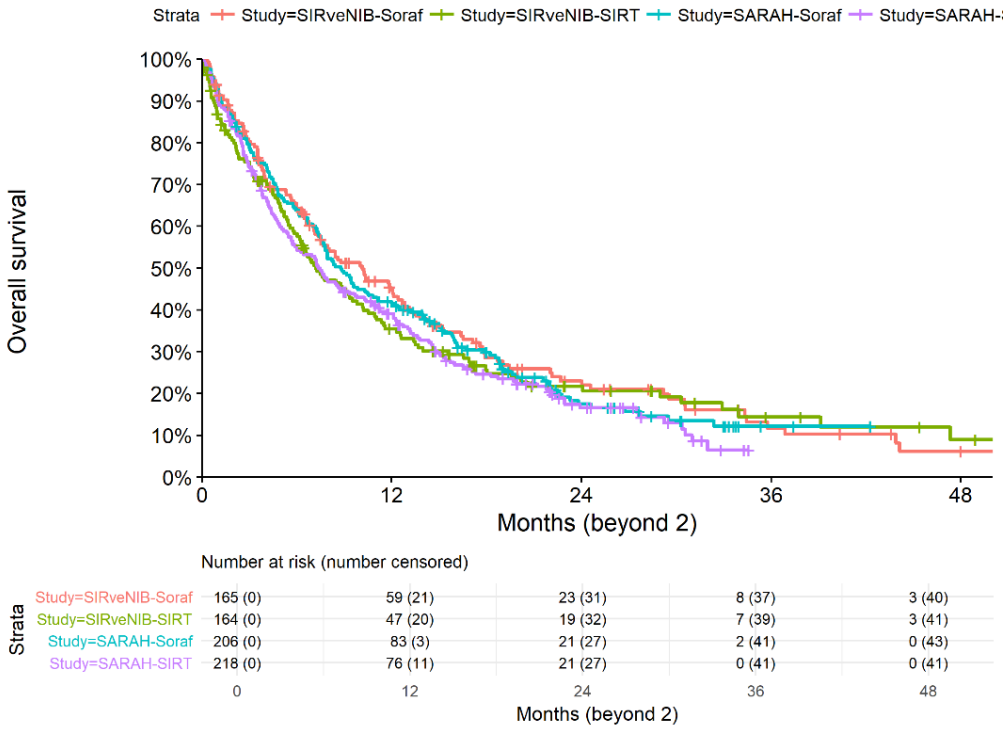


Table 14: Landmark analysis - Progression Free Survival (ITT Population)

		Hazard Ratio	*95% Lower Confidence Limit for Hazard Ratio*	*95% Upper Confidence Limit for Hazard Ratio*	*P-value (superiority)*
Treatment effect(SIRT vs Sorafenib)	SIRveNIB	0.891	0.700	1.133	0.3466
	SARAH	1.127	0.908	1.398	0.2770
	Combined	1.015	0.864	1.192	0.8555
	Stratified Log-rank	.	.	.	0.8492
	PH Regression	1.015	0.865	1.192	0.8544

Table 15: Landmark analysis - Progression in the liver (ITT Population)

		Hazard Ratio	*95% Lower Confidence Limit for Hazard Ratio*	*95% Upper Confidence Limit for Hazard Ratio*	*P-value (superiority)*
Treatment effect(SIRT vs Sorafenib)	SIRveNIB	0.465	0.330	0.654	<.0001
	SARAH	0.896	0.676	1.187	0.4424
	Combined	0.687	0.553	0.854	0.0007
	PH Regression	0.686	0.553	0.851	0.0006

Figure 8: Kaplan Meier curve for progression free survival beyond 2 months by treatment (ITT Population)

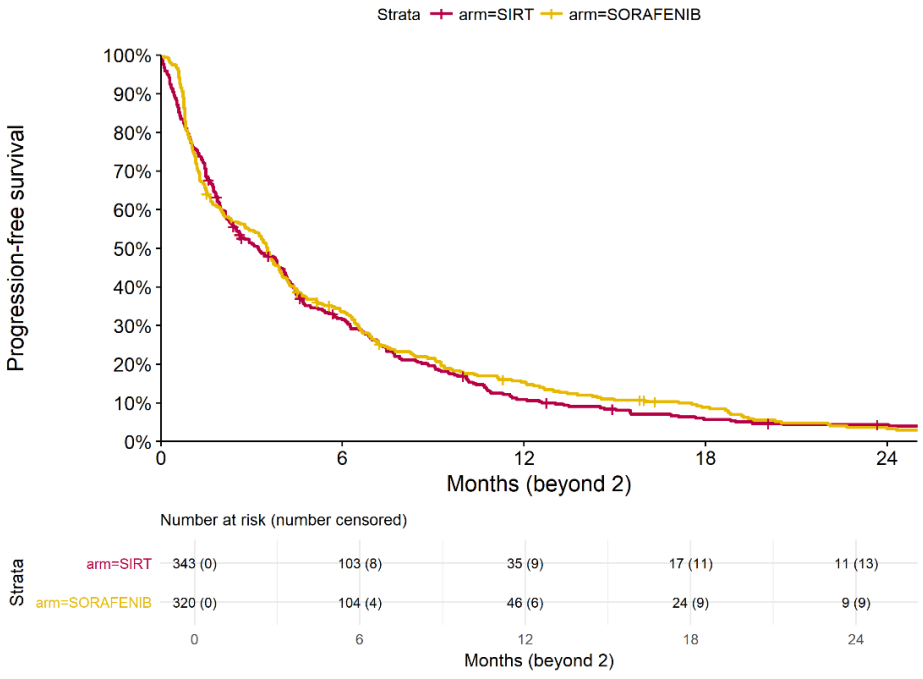


Figure 9: Kaplan Meier curve for progression free survival beyond 2 months by treatment by trial (ITT Population)

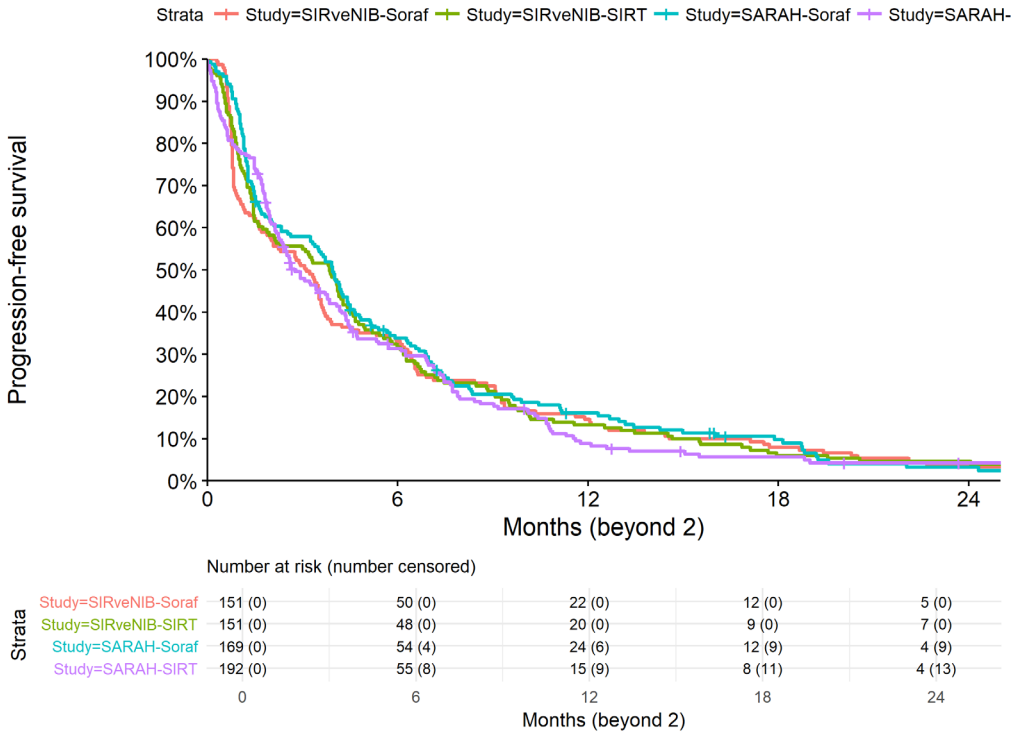
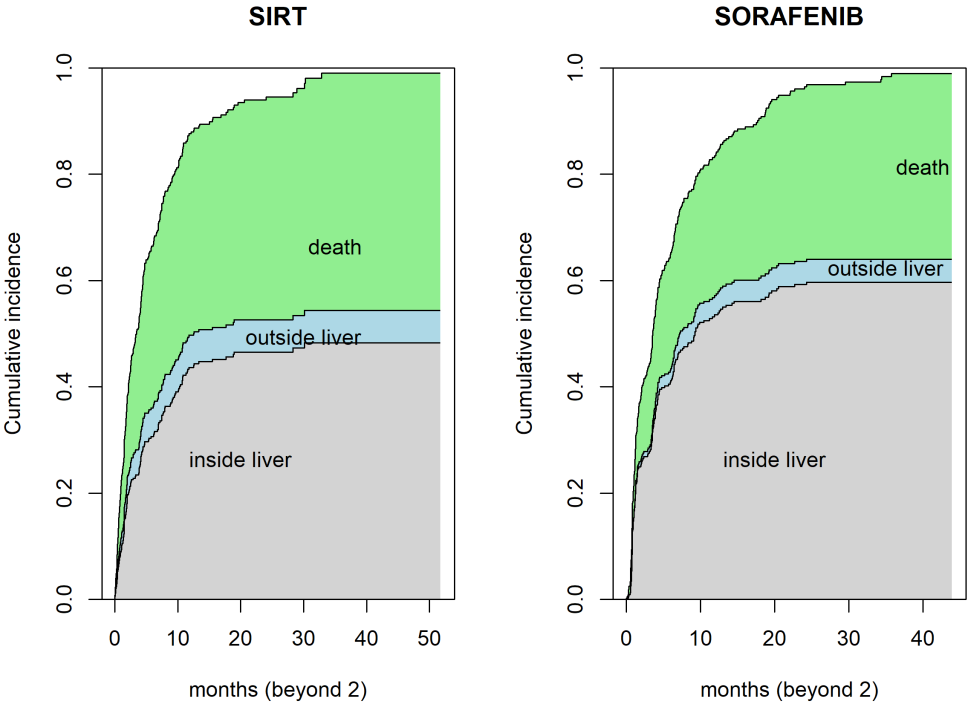


Figure 10: Cumulative incidence of progression (>2 months) by treatment and type (ITT Population)



6.3.4 Tumour response rate and Disease control rate

Table 16: Response rate (ITT Population)

Characteristic	*Level*	*SARAH (N=459)*	*SIRveNIB (N=360)*	*Both groups (N=819)*	*Sorafenib (N=400)*	*SIRT (N=419)*
Evaluable for response	No	71 (15.5%)	135 (37.5%)	206 (25.2%)	80 (20.0%)	126 (30.1%)
	Yes	388 (84.5%)	225 (62.5%)	613 (74.8%)	320 (80.0%)	293 (69.9%)
Best overall Response	CR	7 (1.5%)		7 (0.9%)	2 (0.5%)	5 (1.2%)
	PR	52 (11.3%)	33 (9.2%)	85 (10.4%)	24 (6.0%)	61 (14.6%)
	SD	224 (48.8%)	119 (33.1%)	343 (41.9%)	204 (51.0%)	139 (33.2%)
	PD	104 (22.7%)	73 (20.3%)	177 (21.6%)	90 (22.5%)	87 (20.8%)
	Missing	72 (15.7%)	135 (37.5%)	207 (25.3%)	80 (20.0%)	127 (30.3%)
Response Rate	Missing	72 (15.7%)	135 (37.5%)	207 (25.3%)	80 (20.0%)	127 (30.3%)
	CR+PR	59 (12.9%)	33 (9.2%)	92 (11.2%)	26 (6.5%)	66 (15.8%)
	SD+PD	328 (71.5%)	192 (53.3%)	520 (63.5%)	294 (73.5%)	226 (53.9%)
Disease Control Rate	PD	104 (22.7%)	73 (20.3%)	177 (21.6%)	90 (22.5%)	87 (20.8%)
	CR+PR+SD	283 (61.7%)	152 (42.2%)	435 (53.1%)	230 (57.5%)	205 (48.9%)
	Missing	72 (15.7%)	135 (37.5%)	207 (25.3%)	80 (20.0%)	127 (30.3%)

6.3.5 Adverse events

Reported are the number of patients who experienced a worst grade of at least this level. P-values compare patients Grade≥3 (vs <3) between treatment arms.

Table 17: Worst overall toxicity per patient (ITT Population)

	SARAH (N=459)	*SIRveNIB (N=360)*	*Sorafenib (N=400)*	*SIRT (N=419)*	*P-Value*
No Toxicity Reported	27(5.88%)	144(40%)	53(13.25%)	118(28.16%)	
Grade 1	17(3.7%)	47(13.06%)	28(7%)	36(8.59%)	
Grade 2	78(16.99%)	56(15.56%)	63(15.75%)	71(16.95%)	
Grade 3	195(42.48%)	83(23.06%)	161(40.25%)	117(27.92%)	
Grade 4	14(3.05%)	27(7.5%)	28(7%)	13(3.1%)	
Grade 5	128(27.89%)	3(0.83%)	67(16.75%)	64(15.27%)	
Grade≥3	337(73.42%)	113(31.39%)	256(64%)	194(46.3%)	<.0001

Table 18: Specific adverse event by worst grade by treatment (ITT Population)

		SARAH (N=459)	*SIRveNIB (N=360)*	*Sorafenib (N=400)*	*SIRT (N=419)*	*P-Value*
Abdominal pain	No Toxicity Reported	332(72.33%)	316(87.78%)	310(77.5%)	338(80.67%)	
	Grade 1	45(9.8%)	22(6.11%)	32(8%)	35(8.35%)	
	Grade 2	50(10.89%)	15(4.17%)	35(8.75%)	30(7.16%)	
	Grade 3	28(6.1%)	7(1.94%)	21(5.25%)	14(3.34%)	
	Grade 5*	4(0.87%)		2(0.5%)	2(0.48%)	
	Grade≥3	32(6.97%)	7(1.94%)	23(5.75%)	16(3.82%)	0.1798

		SARAH (N=459)	*SIRveNIB (N=360)*	*Sorafenib (N=400)*	*SIRT (N=419)*	*P-Value*
Alopecia	No Toxicity Reported	424(92.37%)	344(95.56%)	349(87.25%)	419(100%)	
	Grade 1	21(4.58%)	13(3.61%)	34(8.5%)		
	Grade 2	14(3.05%)	3(0.83%)	17(4.25%)		N/A
Anorexia	No Toxicity Reported	341(74.29%)	327(90.83%)	304(76%)	364(86.87%)	
	Grade 1	50(10.89%)	21(5.83%)	43(10.75%)	28(6.68%)	
	Grade 2	47(10.24%)	11(3.06%)	39(9.75%)	19(4.53%)	
	Grade 3	21(4.58%)	1(0.28%)	14(3.5%)	8(1.91%)	
	Grade≥3	21(4.58%)	1(0.28%)	14(3.5%)	8(1.91%)	0.1445
Ascites	No Toxicity Reported	374(81.48%)	330(91.67%)	352(88%)	352(84.01%)	
	Grade 1	14(3.05%)	11(3.06%)	12(3%)	13(3.1%)	
	Grade 2	28(6.1%)	7(1.94%)	17(4.25%)	18(4.3%)	
	Grade 3	29(6.32%)	10(2.78%)	13(3.25%)	26(6.21%)	
	Grade 4	1(0.22%)	2(0.56%)	1(0.25%)	2(0.48%)	
	Grade 5	13(2.83%)		5(1.25%)	8(1.91%)	
	Grade≥3	43(9.37%)	12(3.33%)	19(4.75%)	36(8.59%)	0.0298
Cardiac failure congestive	No Toxicity Reported	358(78%)	322(89.44%)	346(86.5%)	334(79.71%)	
	Grade 1	37(8.06%)	23(6.39%)	18(4.5%)	42(10.02%)	
	Grade 2	38(8.28%)	8(2.22%)	16(4%)	30(7.16%)	
	Grade 3	24(5.23%)	6(1.67%)	19(4.75%)	11(2.63%)	
	Grade 5	2(0.44%)	1(0.28%)	1(0.25%)	2(0.48%)	
	Grade≥3	26(5.66%)	7(1.94%)	20(5%)	13(3.1%)	0.1574

		SARAH (N=459)	*SIRveNIB (N=360)*	*Sorafenib (N=400)*	*SIRT (N=419)*	*P-Value*
Diarrhoea	No Toxicity Reported	268(58.39%)	312(86.67%)	207(51.75%)	373(89.02%)	
	Grade 1	71(15.47%)	33(9.17%)	82(20.5%)	22(5.25%)	
	Grade 2	71(15.47%)	8(2.22%)	65(16.25%)	14(3.34%)	
	Grade 3	37(8.06%)	7(1.94%)	37(9.25%)	7(1.67%)	
		12(2.61%)		9(2.25%)	3(0.72%)	
	Grade≥3	49(10.68%)	7(1.94%)	46(11.5%)	10(2.39%)	<.0001
Dry skin	No Toxicity Reported	416(90.63%)	354(98.33%)	355(88.75%)	415(99.05%)	
	Grade 1	17(3.7%)	6(1.67%)	20(5%)	3(0.72%)	
	Grade 2	20(4.36%)		19(4.75%)	1(0.24%)	
	Grade 3	5(1.09%)		5(1.25%)		
		1(0.22%)		1(0.25%)		
	Grade≥3	6(1.31%)		6(1.5%)		0.0729
Fatigue	No Toxicity Reported	173(37.69%)	321(89.17%)	216(54%)	278(66.35%)	
	Grade 1	87(18.95%)	27(7.5%)	62(15.5%)	52(12.41%)	
	Grade 2	111(24.18%)	4(1.11%)	66(16.5%)	49(11.69%)	
	Grade 3	80(17.43%)	7(1.94%)	49(12.25%)	38(9.07%)	
	Grade 4	1(0.22%)	1(0.28%)	2(0.5%)		
	Grade 5	7(1.53%)		5(1.25%)	2(0.48%)	
	Grade≥3	88(19.17%)	8(2.22%)	56(14%)	40(9.55%)	0.0329
Fever	No Toxicity Reported	415(90.41%)	331(91.94%)	357(89.25%)	389(92.84%)	
	Grade 1	22(4.79%)	25(6.94%)	30(7.5%)	17(4.06%)	

		SARAH (N=459)	*SIRveNIB (N=360)*	*Sorafenib (N=400)*	*SIRT (N=419)*	*P-Value*
	Grade 2	16(3.49%)	3(0.83%)	8(2%)	11(2.63%)	
	Grade 3	6(1.31%)	1(0.28%)	5(1.25%)	2(0.48%)	
	Grade≥3	6(1.31%)	1(0.28%)	5(1.25%)	2(0.48%)	0.2230
Gi bleeding	No Toxicity Reported	406(88.45%)	340(94.44%)	361(90.25%)	385(91.89%)	
	Grade 1	10(2.18%)	4(1.11%)	8(2%)	6(1.43%)	
	Grade 2	4(0.87%)	5(1.39%)	5(1.25%)	4(0.95%)	
	Grade 3	22(4.79%)	4(1.11%)	13(3.25%)	13(3.1%)	
	Grade 4	2(0.44%)	6(1.67%)	5(1.25%)	3(0.72%)	
	Grade 5	15(3.27%)	1(0.28%)	8(2%)	8(1.91%)	
	Grade≥3	39(8.5%)	11(3.06%)	26(6.5%)	24(5.73%)	0.6181
Gi ulceration	No Toxicity Reported	452(98.47%)	357(99.17%)	398(99.5%)	411(98.09%)	
	Grade 1	2(0.44%)	1(0.28%)	2(0.5%)	1(0.24%)	
	Grade 2	2(0.44%)			2(0.48%)	
	Grade 3	3(0.65%)	2(0.56%)		5(1.19%)	
	Grade≥3	3(0.65%)	2(0.56%)		5(1.19%)	0.0287
Hand foot skin reaction	No Toxicity Reported	412(89.76%)	292(81.11%)	287(71.75%)	417(99.52%)	
	Grade 1	12(2.61%)	25(6.94%)	36(9%)	1(0.24%)	
	Grade 2	24(5.23%)	16(4.44%)	40(10%)		
	Grade 3	10(2.18%)	24(6.67%)	33(8.25%)	1(0.24%)	
	Grade 4		3(0.83%)	3(0.75%)		
	Grade 5	1(0.22%)		1(0.25%)		

		SARAH (N=459)	*SIRveNIB (N=360)*	*Sorafenib (N=400)*	*SIRT (N=419)*	*P-Value*
	Grade≥3	11(2.4%)	27(7.5%)	37(9.25%)	1(0.24%)	<.0001
Haemorrhage (non gi)	No Toxicity Reported	417(90.85%)	354(98.33%)	370(92.5%)	401(95.7%)	
	Grade 1	12(2.61%)	3(0.83%)	12(3%)	3(0.72%)	
	Grade 2	10(2.18%)	1(0.28%)	6(1.5%)	5(1.19%)	
	Grade 3	14(3.05%)	2(0.56%)	11(2.75%)	5(1.19%)	
	Grade 4	1(0.22%)			1(0.24%)	
	Grade 5	5(1.09%)		1(0.25%)	4(0.95%)	
	Grade≥3	20(4.36%)	2(0.56%)	12(3%)	10(2.39%)	0.5606
Hyperbilirubinemia	No Toxicity Reported	357(77.78%)	301(83.61%)	322(80.5%)	336(80.19%)	
	Grade 1	37(8.06%)	14(3.89%)	31(7.75%)	20(4.77%)	
	Grade 2	29(6.32%)	17(4.72%)	24(6%)	22(5.25%)	
	Grade 3	31(6.75%)	20(5.56%)	19(4.75%)	32(7.64%)	
	Grade 4	2(0.44%)	8(2.22%)	4(1%)	6(1.43%)	
	Grade 5	3(0.65%)			3(0.72%)	
	Grade≥3	36(7.84%)	28(7.78%)	23(5.75%)	41(9.79%)	0.0317
Hypertension	No Toxicity Reported	417(90.85%)	336(93.33%)	344(86%)	409(97.61%)	
	Grade 1	9(1.96%)	5(1.39%)	13(3.25%)	1(0.24%)	
	Grade 2	18(3.92%)	16(4.44%)	31(7.75%)	3(0.72%)	
	Grade 3	14(3.05%)	3(0.83%)	11(2.75%)	6(1.43%)	
	Grade 5	1(0.22%)		1(0.25%)		
	Grade≥3	15(3.27%)	3(0.83%)	12(3%)	6(1.43%)	0.1190

		SARAH (N=459)	*SIRveNIB (N=360)*	*Sorafenib (N=400)*	*SIRT (N=419)*	*P-Value*
Hyponatremia	No Toxicity Reported	373(81.26%)	356(98.89%)	354(88.5%)	375(89.5%)	
	Grade 1	60(13.07%)		32(8%)	28(6.68%)	
	Grade 2	7(1.53%)		4(1%)	3(0.72%)	
	Grade 3	16(3.49%)	2(0.56%)	8(2%)	10(2.39%)	
	Grade 4	1(0.22%)	2(0.56%)	2(0.5%)	1(0.24%)	
	Grade 5	2(0.44%)			2(0.48%)	
	Grade≥3	19(4.14%)	4(1.11%)	10(2.5%)	13(3.1%)	0.6202
Increased creatinine level	No Toxicity Reported	288(62.75%)	331(91.94%)	308(77%)	311(74.22%)	
	Grade 1	67(14.6%)	13(3.61%)	35(8.75%)	45(10.74%)	
	Grade 2	59(12.85%)	12(3.33%)	32(8%)	39(9.31%)	
	Grade 3	28(6.1%)	3(0.83%)	15(3.75%)	16(3.82%)	
	Grade 4	1(0.22%)	1(0.28%)	2(0.5%)		
	Grade 5	16(3.49%)		8(2%)	8(1.91%)	
	Grade≥3	45(9.8%)	4(1.11%)	25(6.25%)	24(5.73%)	0.7065
Liver dysfunction	No Toxicity Reported	247(53.81%)	339(94.17%)	284(71%)	302(72.08%)	
	Grade 1	31(6.75%)	7(1.94%)	13(3.25%)	25(5.97%)	
	Grade 2	40(8.71%)	3(0.83%)	24(6%)	19(4.53%)	
	Grade 3	76(16.56%)	8(2.22%)	49(12.25%)	35(8.35%)	
	Grade 4	8(1.74%)	3(0.83%)	4(1%)	7(1.67%)	
	Grade 5	57(12.42%)		26(6.5%)	31(7.4%)	
	Grade≥3	141(30.72%)	11(3.06%)	79(19.75%)	73(17.42%)	0.3029

		SARAH (N=459)	*SIRveNIB (N=360)*	*Sorafenib (N=400)*	*SIRT (N=419)*	*P-Value*
Nausea vomiting	No Toxicity Reported	352(76.69%)	333(92.5%)	330(82.5%)	355(84.73%)	
	Grade 1	38(8.28%)	18(5%)	27(6.75%)	29(6.92%)	
	Grade 2	42(9.15%)	5(1.39%)	25(6.25%)	22(5.25%)	
	Grade 3	21(4.58%)	4(1.11%)	13(3.25%)	12(2.86%)	
	Grade 5	6(1.31%)		5(1.25%)	1(0.24%)	
	Grade≥3	27(5.88%)	4(1.11%)	18(4.5%)	13(3.1%)	0.2744
Other increased liver values	No Toxicity Reported	247(53.81%)	283(78.61%)	263(65.75%)	267(63.72%)	
	Grade 1	59(12.85%)	19(5.28%)	40(10%)	38(9.07%)	
	Grade 2	52(11.33%)	25(6.94%)	29(7.25%)	48(11.46%)	
	Grade 3	85(18.52%)	30(8.33%)	60(15%)	55(13.13%)	
	Grade 4	4(0.87%)	3(0.83%)	5(1.25%)	2(0.48%)	
	Grade 5	12(2.61%)		3(0.75%)	9(2.15%)	
	Grade≥3	101(22%)	33(9.17%)	68(17%)	66(15.75%)	0.5871
Pruritus	No Toxicity Reported	417(90.85%)	355(98.61%)	373(93.25%)	399(95.23%)	
	Grade 1	12(2.61%)	3(0.83%)	6(1.5%)	9(2.15%)	
	Grade 2	15(3.27%)	2(0.56%)	11(2.75%)	6(1.43%)	
	Grade 3	11(2.4%)		7(1.75%)	4(0.95%)	
	Grade 4	1(0.22%)		1(0.25%)		
	Grade 5	3(0.65%)		2(0.5%)	1(0.24%)	
	Grade≥3	15(3.27%)		10(2.5%)	5(1.19%)	0.1497
Pulmonary embolism	No Toxicity Reported	451(98.26%)	358(99.44%)	393(98.25%)	416(99.28%)	

		SARAH (N=459)	*SIRveNIB (N=360)*	*Sorafenib (N=400)*	*SIRT (N=419)*	*P-Value*
	Grade 1	1(0.22%)	1(0.28%)	1(0.25%)	1(0.24%)	
	Grade 2	2(0.44%)		2(0.5%)		
	Grade 4	3(0.65%)		2(0.5%)	1(0.24%)	
	Grade 5		1(0.28%)	1(0.25%)		
	Grade≥3	2(0.44%)		1(0.25%)	1(0.24%)	0.3727
Radiation hepatitis	No Toxicity Reported	459(100%)	358(99.44%)	400(100%)	417(99.52%)	
	Grade 4		1(0.28%)		1(0.24%)	
	Grade 5		1(0.28%)		1(0.24%)	
	Grade≥3		2(0.56%)		2(0.48%)	0.1614
Radiation pneumonitis	No Toxicity Reported	458(99.78%)	360(100%)	400(100%)	418(99.76%)	
	Grade 5	1(0.22%)			1(0.24%)	
	Grade≥3	1(0.22%)			1(0.24%)	0.3331
Rash or desquamation	No Toxicity Reported	427(93.03%)	359(99.72%)	375(93.75%)	411(98.09%)	
	Grade 1	14(3.05%)	1(0.28%)	10(2.5%)	5(1.19%)	
	Grade 2	11(2.4%)		10(2.5%)	1(0.24%)	
	Grade 3	5(1.09%)		3(0.75%)	2(0.48%)	
	Grade 5	2(0.44%)		2(0.5%)		
	Grade 3	7(1.53%)		5(1.25%)	2(0.48%)	0.2190
Weight loss	No Toxicity Reported	390(84.97%)	352(97.78%)	345(86.25%)	397(94.75%)	

	SARAH (N=459)	*SIRveNIB (N=360)*	*Sorafenib (N=400)*	*SIRT (N=419)*	*P-Value*
Grade 1	20(4.36%)	5(1.39%)	17(4.25%)	8(1.91%)	
Grade 2	29(6.32%)	3(0.83%)	21(5.25%)	11(2.63%)	
Grade 3	16(3.49%)		14(3.5%)	2(0.48%)	
Grade 5	4(0.87%)		3(0.75%)	1(0.24%)	
Grade≥3	20(4.36%)		17(4.25%)	3(0.72%)	0.0008

**Note on Abdominal pain (grade 5 event): The patient who died from this adverse event had also tumour progression (assessed on the CT scan) that could explain the fatal outcome.*

7 SUBGROUP ANALYSES

- Age (<65 years, ≥65 years)
- Gender
- BCLC stage (A, B, C)
- BCLC sub-stage (B1, B2, B3, B4) (Using Bolondi Criteria)
- ECOG performance status (0 , 1)
- Hepatitis status (B, C, Both)
- Prior HCC treatment (yes, no)
- Presence or absence of portal vein thrombosis
- Tumour burden (≤ 50% of liver, > 50% of liver)
- Unilobar vs Bilobar
- Single focal vs multifocal
- Serum alpha-feto protein level (≤100 ng/ml versus >100 ng/ml)

Table 19: Overall survival – subgroup analysis (ITT Population)

Subgroup		N	Events	Median SORAF	Median SIRT	SIRveNIB	SARAH	Combined	Stratified Log rank	Interaction
Age	<65	453	351	9.7	7.5	1.22(0.91,1.64)	1.27(0.94,1.71)	1.25(1.01,1.54)	0.040	0.263
	≥65	366	288	10.9	9.7	1.01(0.66,1.54)	1.06(0.80,1.40)	1.04(0.83,1.31)	0.731	
Gender	M	712	557	10.0	8.6	1.04(0.80,1.35)	1.19(0.96,1.48)	1.13(0.95,1.33)	0.158	0.810
	F	107	82	8.7	8.2	1.58(0.84,2.94)	0.82(0.42,1.58)	1.16(0.73,1.82)	0.498	
BCLC stage	A	22	15	22.3	16.6	-	1.32(0.46,3.80)	-	0.610	0.678
	B	317	229	13.9	13.1	1.14(0.81,1.62)	0.96(0.65,1.43)	0.98(0.76,1.27)	0.657	
	C	479	394	8.0	6.5	1.00(0.71,1.40)	1.22(0.95,1.56)	1.16(0.83,1.61)	0.199	
BCLC sub-stage	B1	72	50	16.3	19.3	0.31(0.03,2.83)	1.06(0.58,1.94)	0.97(0.54,1.74)	0.865	0.0189
	B2	206	152	12.8	9.6	1.18(0.80,1.74)	1.21(0.69,2.12)	1.19(0.86,1.63)	0.289	
	B3	15	11	34.9	7.8	7.33(0.83,64.4)	1.03(0.09,11.5)	3.05(0.60,15.3)	0.083	
	B4	2	2	45.8	2.4	-	-	-	0.317	
ECOG	0	560	421	11.8	9.5	1.14(0.86,1.50)	1.30(1.00,1.69)	1.22(1.01,1.48)	0.043	0.136
	1	258	217	7.3	6.2	0.97(0.60,1.56)	0.93(0.67,1.28)	0.94(0.72,1.23)	0.640	
Hepatitis Status	B	224	168	8.6	9.3	0.98(0.71,1.35)	0.70(0.29,1.67)	0.94(0.69,1.27)	0.684	0.717
	C	148	113	13.1	9.1	2.02(1.00,4.06)	1.63(1.03,2.56)	1.73(1.19,2.53)	0.004	
	Both	10	7	12.3	9.1	0.92(0.18,4.75)	-	-	0.923	
	None	356	292	9.7	7.5	1.06(0.61,1.83)	1.03(0.80,1.33)	1.03(0.80,1.32)	0.759	
Prior HCC treatments	No	626	501	9.6	7.8	1.10(0.84,1.45)	1.09(0.87,1.37)	1.10(0.92,1.31)	0.305	0.61
	Yes	193	138	12.3	13.1	1.18(0.71,1.94)	1.31(0.83,2.07)	1.25(0.89,1.75)	0.195	
Portal vein thrombosis	No	622	471	11.4	10.5	1.11(0.83,1.49)	1.09(0.87,1.37)	1.10(0.92,1.31)	0.318	0.539
	Yes	197	168	5.7	5.3	1.07(0.71,1.62)	1.39(0.88,2.19)	1.21(0.89,1.64)	0.224	
Tumour burden within liver	>50%	137	120	4.8	5.7	0.80(0.50,1.28)	1.05(0.59,1.87)	0.89(0.62,1.28)	0.537	0.091
	≤50%	682	519	11.8	9.5	1.22(0.92,1.61)	1.19(0.96,1.48)	1.20(1.01,1.43)	0.036	
Unilobar/Bilobar	Unilobar	518	403	10.3	8.9	1.50(1.01,2.21)	1.16(0.93,1.46)	1.12(0.90,1.39)	0.032	0.259
	Bilobar	252	201	9.5	7.8	1.06(0.74,1.50)	1.09(0.69,1.73)	1.31(0.97,1.76)	0.649	
Unifocal/multifocal	Unifocal	305	233	11.3	8.3	1.29(0.80,2.06)	1.18(0.87,1.61)	1.11(0.84,1.47)	0.146	0.6093

	Multifocal	465	371	9.6	8.3	1.16(0.85,1.59)	1.12(0.86,1.47)	1.16(0.92,1.47)	0.211	
Alpha-feto protein	<100ng/ml	336	240	14.2	11.8	1.02(0.65,1.60)	1.31(0.96,1.78)	1.21(0.93,1.56)	0.150	0.4754
	≥100ng/ml	435	360	7.7	6.7	1.14(0.86,1.52)	0.94(0.70,1.27)	1.04(0.84,1.28)	0.713	

Table 20: PFS analysis – Subgroup analysis (ITT Population)

Subgroup		N	Events	Median SORAF	Median SIRT	SIRveNIB	SARAH	Combined	Stratified Log rank	Interaction
Age	<65	453	396	4.0	4.3	1.03 (0.78,1.36)	1.02 (0.77,1.35)	1.02 (0.84,1.25)	0.83	0.88
	≥65	366	325	4.8	4.0	0.72 (0.48,1.08)	1.07 (0.83,1.4)	0.96 (0.77,1.19)	0.70	
Gender	M	712	626	4.3	4.3	0.81(0.63,1.04)	1.1(0.89,1.34)	0.97(0.83,1.14)	0.72	
	F	107	95	4.6	3.3	1.38(0.78,2.45)	0.56(0.3,1.04)	0.91(0.6,1.39)	0.71	
BCLC stage	A	22	20	6.4	7.6	-	1.12 (0.44,2.86)	-	0.81	
	B	317	269	5.9	5.6	0.88 (0.64,1.21)	0.96 (0.67,1.38)	0.91 (0.71,1.16)	0.46	
	C	479	431	3.7	3.3	0.86 (0.62,1.2)	1.04 (0.82,1.31)	-	0.79	
BCLC sub-stage	B1	72	64	3.8	5.8	0.30(0.03,2.63)	0.90(0.53,1.53)	0.85(0.51,1.42)	0.480	0.39
	B2	206	174	5.7	6.1	0.89(0.62,1.27)	1.07(0.62,1.85)	0.94(0.70,1.27)	0.689	
	B3	15	13	8.7	5.3	4.57(0.52,40.4)	5.89(0.5,69.02)	5.11(1.00,26.1)	0.038	
	B4	2	2	2.3	2.4	0.30(0.03,2.63)	0.90(0.53,1.53)	0.85(0.51,1.42)	0.317	
ECOG	0	560	487	5.0	5.3	0.9 (0.69,1.17)	1.17 (0.91,1.49)	1.04 (0.87,1.24)	0.70	
	1	258	233	3.9	3.2	0.84 (0.52,1.33)	0.8 (0.59,1.1)	0.81 (0.63,1.05)	0.11	
Hepatitis Status	B	224	192	5.3	4.1	0.75 (0.55,1.02)	0.69 (0.31,1.56)	0.74 (0.56,0.99)	0.044	
	C	148	132	4.9	5.4	1.3 (0.66,2.59)	1.4 (0.92,2.13)	1.37 (0.96,1.96)	0.086	
	Both	10	7	9.1	2.8	0.83 (0.13,5.21)	-	0.83 (0.13,5.21)	0.85	
	None	356	324	4.2	3.9	0.95(0.56,1.61)	0.93(0.73,1.19)	0.93(0.73,1.18)	0.56	
Prior HCC treatments	No	626	558	4.3	4.1	1.06(0.82,1.39)	1.04(0.84,1.29)	1.05(0.89,1.24)	0.58	
	Yes	193	163	4.9	4.3	0.55(0.34,0.87)	1.04(0.68,1.59)	0.77(0.56,1.06)	0.11	
Portal vein thrombosis	No	622	545	4.8	5.2	0.86(0.65,1.14)	1.01(0.82,1.25)	0.95(0.8,1.13)	0.57	
	Yes	197	176	3.5	2.9	0.94(0.62,1.41)	1.14(0.73,1.8)	1.02(0.76,1.38)	0.87	

Tumour burden within liver	>50%	137	122	3.1	3.0	0.88(0.56,1.38)	0.84(0.46,1.54)	0.86(0.6,1.24)	0.43
	≤50%	682	599	4.6	5.1	0.9(0.69,1.17)	1.08(0.88,1.32)	1.01(0.86,1.18)	0.94
Unilobar/Bilobar	Unilobar	518	462	4.4	4.1	0.99(0.69,1.43)	1.02(0.83,1.27)	0.96(0.79,1.18)	0.85
	Bilobar	252	219	4.0	4.3	-	-	-	
Unifocal/multifocal	Unifocal	305	269	4.3	4.3	1.12(0.71,1.75)	0.99(0.75,1.32)	0.9(0.69,1.16)	0.82
	Multifocal	465	412	4.2	4.2	-	-	-	
Alpha-feto protein	<100ng/ml	336	294	6.0	6.0	0.75(0.5,1.13)	1.1(0.83,1.45)	0.97(0.77,1.22)	0.81
	≥100ng/ml	435	383	4.0	3.3	0.99(0.75,1.31)	0.86(0.65,1.16)	0.93(0.76,1.14)	0.48

Table 21: PFS in the liver - Subgroup analysis (ITT Population)

Subgroup		**N**	**Events**	**Median SORAF***	**Median SIRT***	**SIRveNIB**	**SARAH**	**Combined**	**Stratified Log rank**	**Interaction**
Age	<65	453	210	10.3	-	0.40(0.26,0.62)	0.66(0.45,0.95)	0.53(0.40,0.71)	0.77	0.077
	≥65	366	174	16.6	-	0.62(0.36,1.09)	0.80(0.57,1.14)	0.75(0.56,1.01)	0.86	
Gender	M	712	337	10.8	-	0.41(0.28,0.60)	0.76(0.58,0.99)	0.62(0.50,0.77)	0.86	0.93
	F	107	47	11.4	-	0.88(0.39,1.98)	0.45(0.20,1.02)	0.64(0.36,1.13)	0.80	
BCLC stage	A	22	13	21.3	32.2	-	1.33(0.47,3.80)	-	0.86	
	B	317	152	10.3	-	0.44(0.28,0.69)	0.73(0.46,1.14)	0.61(0.44,0.86)	0.47	0.62
	C	479	219	10.8	-	0.51(0.31,0.83)	0.69(0.50,0.95)	0.63(0.48,0.82)	0.97	
BCLC sub-stage	B1	72	47	10.4	10.4	-	0.85(0.47,1.55)	0.16(0.09,0.29)	0.472	0.054
	B2	206	93	10.3	-	0.47(0.29,0.75)	0.44(0.20,1.00)	0.46(0.30,0.70)	0.710	
	B3	15	5	11.4	-	0.25(0.03,2.04)	2.12(0.21,21.9)	0.65(0.14,3.09)	0.038	
	B4	2	1	2.3	-	-	-	-	0.317	
ECOG	0	560	275	11.1	-	0.48(0.33,0.70)	0.84(0.62,1.15)	0.67(0.53,0.85)	0.67	0.29
	1	258	109	10.8	-	0.45(0.21,0.94)	0.57(0.37,0.88)	0.54(0.37,0.78)	0.16	
Hepatitis Status	B	224	97	11.1	-	0.49(0.31,0.78)	1.03(0.41,2.56)	0.57(0.38,0.86)	0.033	
	C	148	77	11.1	-	0.35(0.16,0.79)	0.80(0.48,1.36)	0.63(0.41,0.98)	0.062	
	Both	10	1	10.3	-	-	-	-	0.85	0.73
	None	356	173	16.3	-	0.44(0.22,0.90)	0.67(0.48,0.93)	0.38(0.28,0.53)	0.84	
	No	626	36	13.6	-	0.49(0.33,0.72)	0.75(0.56,1.00)	0.65(0.51,0.82)	0.49	0.42

Prior HCC treatments	Yes	193	287	10.3	-	0.43(0.23,0.79)	0.67(0.39,1.16)	0.55(0.37,0.83)	0.12	
Portal vein thrombosis	No	622	97	11.1	-	0.46(0.31,0.67)	0.83(0.63,1.09)	0.68(0.54,0.85)	0.71	0.11
	Yes	197	307	11.7	-	0.52(0.28,0.98)	0.39(0.21,0.74)	0.45(0.29,0.71)	0.91	
Tumour burden within liver	>50%	137	48	-	-	1.08(0.53,2.19)	0.43(0.16,1.17)	0.79(0.44,1.41)	0.46	0.41
	≤50%	682	336	10.3	-	0.36(0.25,0.53)	0.75(0.57,0.97)	0.59(0.48,0.74)	0.82	
Unilobar/Bilobar	Unilobar	518	21	11.9	-	0.42(0.24,0.73)	0.77(0.58,1.01)	0.72(0.55,0.94)	0.73	0.44
	Bilobar	252	248	10.3	-	0.55(0.34,0.88)	0.55(0.31,0.99)	0.48(0.32,0.72)	0.56	
Unifocal/multifocal	Unifocal	305	115	20.1	-	0.57(0.30,1.11)	0.84(0.57,1.23)	0.74(0.53,1.05)	0.77	0.17
	Multifocal	465	21	10.3	-	0.45(0.29,0.69)	0.65(0.46,0.90)	0.63(0.47,0.85)	0.77	
Alpha-feto protein	<100ng/ml	336	187	10.3	15.3	0.53(0.32,0.88)	0.70(0.50,0.99)	0.64(0.48,0.85)	0.87	
	≥100ng/ml	435	173	21.6	-	0.45(0.29,0.71)	0.70(0.46,1.05)	0.57(0.42,0.77)	0.39	0.46

*Median is the time where risk of liver failure is 50%.