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Supplemental Methods

Participating centers

Clínica Universidad de Navarra, Pamplona, Spain.
Hospital Universitario 12 de Octubre, Madrid, Spain.
Hospital Universitario Donostia, San Sebastián, Spain.
Hospital Clínic, Barcelona, Spain.
Hospital Universitario Central de Asturias, Oviedo, Spain.
Hospital General Universitario Gregorio Marañón, Madrid, Spain.
Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain.
Hospital Universitario Ramón y Cajal, Madrid, Spain.
Hospital de Cruces, Baracaldo, Spain.

Inclusion and exclusion criteria

Inclusion Criteria

- Willing, able and mentally competent to provide written informed consent.
- Age 18 or more
- Diagnosis of HCC based on histology or non-invasive criteria if cirrhotics. Histological confirmation of hepatocellular carcinoma will be attempted prior to SIRT.
- Absence of extrahepatic disease (regional lymph nodes smaller than 2 cm in the short axis will not be considered extrahepatic disease).
- No suitability for liver resection, transplantation, or percutaneous ablation because of tumor location or size, age, comorbidities, or others
- Considered not good candidates for TACE based on:
  - Single tumors larger than 5 cm. Unsuitability for TACE in patients with single tumors of size between 5 and 10 cm will follow local practice.
  - Multiple tumors that cannot be targeted superselectively. These patients should be in the BCLC-B2 substage proposed by Bolondi et al (3). In summary, they should fall within the up-to-7 rule (the sum of the number of tumors and the maximal size of the largest lesion in cm should be higher than 7). Unsuitability for TACE will follow local practice.
  - Unilobar tumors with segmental or lobar portal vein thrombosis. Patients that have a small burden of disease (< 10% of the total tumor burden) in the contralateral lobe may be treated at the discretion of the site Principal Investigator
- Child-Pugh class A.
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1.
- Noninfected or active chronic HCV or HBV infection. Subjects with chronic HBV infection must have HBV DNA viral load < 500 IU/mL before SIRT and should be on effective antiviral therapy. If not on antiviral therapy at screening, then the subject must initiate treatment at the time of consent should have HBV DNA viral load < 1000 IU/mL before SIRT. All subjects enrolled in the HBV cohort must continue antiviral therapy through Follow-up Visit.
- At least one measurable lesion by RECIST 1.1 criteria.
  - Lesions previously treated by percutaneous ablation or TACE may be treated provided they have an active tumor volume that could be measured for tumor response evaluation (tumors with a rim of active contrast-enhanced tumor tissue are not considered measurable).
  - Tumor lesions should be ≥ 10 mm and malignant lymph nodes must be > 15 mm on short axis. Additional details are included in Appendix 3.
  - Bone metastases are not considered measurable lesions, unless there is a measurable soft tissue component per RECIST1.1.

- Subjects must consent to perform a tumor biopsy that allows the acquisition of a tumor sample for performance of correlative studies. If adequate tissue is not obtained during the first procedure then a repeat biopsy should be considered based on the investigator's assessment of clinical risk. However, a repeat biopsy is not required to meet eligibility.

Adequate organ and marrow function as evidenced by:

- WBC ≥ 2000/μL (stable, off any growth factor within 4 weeks of study drug administration)

  - Neutrophils ≥ 1000/μL (stable, off any growth factor within 4 weeks of study drug administration)
  - Platelets ≥ 60 x 103/μL (transfusion to achieve this level is not permitted)
  - Hemoglobin ≥ 9.0 g/dL (may be transfused to meet this requirement)
  - Creatinine CrCl >40 mL/min (Cockcroft-Gault formula)
  - AST and ALT ≤ 5 X ULN
  - Bilirubin ≤ 2 mg/dL
  - INR ≤ 1.8 (for patients under oral anticoagulants this criterion should be met while on LMWH)
  - Albumin ≥ 3.0 g/dL

- Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.
- Women must not be breastfeeding.
- Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug plus 90 days (duration of sperm turnover) for a total of 31 weeks post-treatment completion.
- Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, they must still undergo pregnancy testing as described in this section.
- WOCBP must agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with study drug plus 5 half-lives of study drug plus 30 days (duration of ovulatory cycle) for a total of 23 weeks post treatment completion.

Exclusion Criteria

- Subjects with suspected brain metastasis are excluded, unless a brain MRI/CT is negative for metastasis.
- Patients in the Child-Pugh classes B or C
- Any history of hepatic encephalopathy
- Any prior (within 6 months) clinically detected ascites or any current ascites, even if controlled with diuretics (a minor peri-hepatic rim of ascites detected at imaging is acceptable.)
- Any history of clinically meaningful variceal bleeding within the last three months.
- Active coinfection with both hepatitis B and C (as defined by detectable HBV-DNA and HCV-RNA).
- Hepatitis D infection in subjects with hepatitis B
- Occlusive main trunk portal vein thrombosis (malignant or benign) or absence of intrahepatic portal blood flow by Doppler-Ultrasound if patient carries a portocaval shunt (percutaneous or surgical).
- Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, prostate cancer without evidence of PSA progression or carcinoma in situ such as the following: gastric, prostate, cervix, colon, melanoma, or breast for example.
- Subjects with any active autoimmune disease that may require immunosuppresive therapy. Subjects with vitiligo, resolved childhood asthma/atopy, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Uncontrolled or clinically significant cardiac disease
- Known to be positive test for human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)
- Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways)
- Prior organ allograft or allogeneic bone marrow transplantation
- All toxicities attributed to prior anti-cancer therapy must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before SIRT. Subjects with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae are not permitted to enroll.

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- Active bacterial or fungal infections requiring systemic treatment within 7 days
- Use of other investigational drugs (drugs not marketed for any indication) within 28 days or at least 5 half-lives (whichever is longer) before SIRT.
- Known or underlying medical condition that, in the Investigator's opinion, would make the administration of study drug hazardous to the subjects or obscure the interpretation of toxicity determination or adverse events.
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
- Laboratory evidence of any underlying medical conditions that, in the Investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or adverse events.
- History of severe hypersensitivity reactions to other monoclonal antibodies.
- History of allergy to study drug components.
- WOCBP who are pregnant or breastfeeding

Women with a positive pregnancy test at enrollment or prior to administration of study medication

SIRT procedure

The entire SIRT procedure comprises a baseline mapping angiogram to determine the vascular anatomy of the liver, select the sites where SIR-Spheres will be released and coil-embolize gastrointestinal collaterals if needed. A nuclear medicine scan is performed after the injection of ^{99}mTc-macroaggregated albumin (MAA) injection in the selected sites. This scan allows to calculate the liver-to-lung shunting, detect extrahepatic deposition of radioactivity and assess the degree of preferential uptake of MAA by liver tumors as compared to non-tumoral liver. Lung-shunt in excess of 20% and extrahepatic deposition of MAA were considered a technical contraindication to SIRT. In the absence of technical contraindications, actual injection of SIR-Spheres was performed the same day, once the SIR-Spheres activity was calculated and prescribed. Sequential treatment was not permitted in this study.

The method used to calculate the activity of SIR-Spheres was based on the presentation of hepatic lesions, is explained in detail in the study protocol and is founded in prior experience [1,2]. SIRT was always performed as selectively as possible. If the tumor burden involved both lobes of the liver, either whole-liver or more selective SIRT were possible at the discretion of the team based on the vascular anatomy, and the decision was made on a case-by-case basis. For whole liver treatments, the BSA method was used to calculate the prescribed activity of SIR-Spheres Y-90 using the following formula: Dose activity [GBq] = (BSA − 0.2) + (Vtumor / VTotalLiver), where Vtumor = volume of tumor; VTotaLiver = total liver volume, including tumor. Selective catheterization of individual branches was always attempted instead of a single injection via the common hepatic artery, and the activity injected into each artery was proportional to the liver volume involved. For patients with measurable disease and additional small satellite tumors, activity calculation was based on the measurable disease.

When at least 2 liver segments were spared from treatment (typically, in a lobar approach), the Partition Model was used to determine the patient-specific prescribed activities of SIR-Spheres provided the patient had discrete and measurable tumors that could be delimited on the CT/MRI scan. When the patient was not cirrhotic and the amount of targeted volume was less than 60% of the total liver volume, the Model was used to calculate an activity that would result in the tumor absorbing 120 Gy irrespective of the dose delivered to the non-tumoral liver. Conversely, when the patient was cirrhotic or the amount of targeted volume (tumor plus non- tumoral liver) was equal to or more than 60% of the total liver volume, the Model was used to determine the activity that would result in the non-tumoral liver absorbing not more than 40 Gy.

Within 24 hours after the administration of SIR-Spheres, Y-90 PET/CT was performed to detect positron emission from the yttrium-90, in order to confirm the placement of SIR-Spheres in the targeted lesions, to exclude non-targeted delivery of SIR-Spheres, and to calculate the actual dose of radiation delivered to tumors and non-tumoral liver.

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Secondary study endpoints and additional sample size considerations

Secondary endpoints were overall response rate (ORR, percentage of patients whose best overall response [BOR] was complete or partial response), disease control rate (DCR, percentage of patients whose BOR was complete or partial response or stable disease), duration of response (DoR, time from SIRT to first documented tumor progression or death in patients with a BOR of complete or partial response), time to progression (TTP, time from SIRT to tumor progression), progression free survival (PFS, time from SIRT to tumor progression or death from any cause), and pattern of progression (proportion of patients with the event of tumor progression triggered by i) growth of existing tumor lesions only; ii) occurrence of new lesions inside the liver irrespective of previous criterion; and iii) occurrence of new lesions outside the liver irrespective of the two prior criteria). Exploratory objectives were overall survival (OS, time from SIRT to death); efficacy based on tumor- and blood-based biomarkers (baseline tumor cell programmed death ligand 1 (PD-L1) expression); impact of ALBI score on safety and efficacy; and health-related quality of life (HRQoL).

Although the primary objective was safety, the study should also inform eventual phase randomized clinical trial to explore the clinical benefit of combining nivolumab with transarterial therapies. With sufficient follow up for 40 subjects, this will allow to have a stable estimate of TTP. Considering an expected median TTP of 3 months with SIRT alone, a sample size was calculated with TTP as readout and the following statistical assumptions that reflect the hypothesis-generating nature of this trial: HR of 0.5 for TTP, 80% power to detect the difference in a 1-sided log-rank test and an error alpha of 0.05. This yielded a sample size of 72 patients that resulted in the need to have 36 patients treated with nivolumab and SIRT. Considering a 10% of screening failures due to technical contraindications for SIRT based on high lung shunt or unfavorable arterial vascularization, a sample size of 40 patients would allow to detect a relevant signal of incremental efficacy.

Requisites for continuing treatment with Nivolumab beyond progression.

In the absence of clinical deterioration, patients were allowed to continue study therapy after an initial investigator-assessed RECIST 1.1 defined progression as long as they met the following criteria:

- Investigator assessed clinical benefit
- Subject was tolerating nivolumab
- Treatment beyond progression did not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Subject provided written informed consent prior to receiving any additional nivolumab.

The decision to start or continue treatment with nivolumab beyond initial investigator-assessed progression was eventually discussed with the Principal Investigator and documented in the study records. Patients should discontinue nivolumab upon further evidence of further progression, defined as an additional 10% or greater increase in tumor burden from time of initial progression (including all target lesions and new measurable lesions). If progression occurred in the first evaluation after SIRT before nivolumab treatment had started, this increase should be 20% or greater for the first post-nivolumab evaluation and 10% or greater thereafter. Nivolumab treatment was discontinued permanently upon documentation of further progression.

For statistical analyses that include the investigator-assessed progression date, patients who continued treatment beyond initial investigator-assessed, RECIST 1.1- defined progression were considered to have investigator-assessed progressive disease at the time of the initial progression event.

References

[1] 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;112:1538–46. https://doi.org/10.1002/cncr.23339.
[2] Gil-Alzugaray B, Chopitea A, Iñarrairaegui M, Bilbao JI, Rodriguez-Fraile M, Rodriguez J, et al. Prognostic factors and prevention of radioembolization-induced liver disease. Hepatology 2013;57:1078–87. https://doi.org/10.1002/hep.26191.
[3] EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208. https://doi.org/10.1016/0168-8510(90)90421-9.
[4] Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 2007;5:70. https://doi.org/10.1186/1477-7525-5-70.

Supplemental Tables

Table S1. Characteristics of the SIRT procedure.

	All patients	BCLC-B2 substage	Unilobar tumors with portal vein invasion
Number of patients	42	31	11
Total tumor volume (ml), median (range)	182.5 (12 – 1950)	134 (65 – 336)	217 (50 – 484)
Total liver volume (ml), median (range)	1770 (110 – 2700)	1765 (1340 – 2014)	1775 (1487 – 2007)
Target liver volume (ml), median (range)	955 (170 – 2671)	970 (698 – 1505)	941 (650 – 1022)
Tumor involvement (%), median (range)	10.2 (1.0 – 74.7)	9.1 (1.0 – 74.7)	11.5 (2.3 – 41.0)
Coil-embolized arteries, n (%)	12 (28.6)	8 (25.8)	4 (36.4)
Flow redistribution, n (%)	10 (23.8)	7 (22.6)	3 (27.3)
MAA injection sites, n (%)			
1	18 (42.8)	14 (45.2)	4 (36.4)
2	18 (42.8)	12 (38.7)	6 (54.5)
3	6 (14.2)	5 (16.1)	1 (9.1)

Tumor MAA uptake, n (%)			
Good	28 (66.7)	20 (64.5)	8 (72.7)
Moderate	12 (28.6)	10 (32.3)	2 (18.2)
Poor	2 (4.8)	1 (3.2)	1 (9.1)
Tumor/NonTumor ratio, median (range)	2.2 (0.5 – 7.7)	2.3 (0.5 – 7.7)	1.8 (0.6 – 3.4)
Lung shunt fraction (%), median (range)	6 (2 – 18)	5 (4 – 9)	6 (2 – 18)
Activity calculation instrument, n (%)			
BSA method	10 (23.8)	8 (25.8)	2 (18.2)
Partition Model	32 (76.2)	23 (74.2)	9 (81.8)
Treatment Design, n (%)			
Sublobar	7 (16.7)	5 (16.1)	2 (18.2)
Right	18 (42.9)	13 (41.9)	5 (45.5)
Left	5 (11.9)	2 (6.5)	3 (27.3)
Right extended	3 (7.1)	3 (9.7)	-
Left extended	3 (7.1)	3 (9.7)	-
Whole liver	6 (14.3)	5 (16.1)	1 (9.1)
Injected Y90 activity (GBq)*, median (range)	1.3 (0.64 – 3.40)	1.2 (0.64 – 3.40)	1.5 (0.80 – 2.10)

Extrahepatic deposition of radioactivity on abdominal organs detected on Y90 PET-CT	0	0	0
Aim of Y90 activity calculation, n (%)			
Tumor-targeted dose	25 (59.5)	17 (54.8)	8 (72.7)
Liver-targeted dose	17 (40.5)	14 (45.2)	3 (27.3)

* More than 99% of the prescribed Y90 activity was actually injected in all patients.

Table S2. Individual events leading to nivolumab dose delays observed in 18 patients.

Event	SAE	Grade	Related to SIRT	Related to nivolumab (IMAE)
Metabolism and nutrition disorders				
Diabetes mellitus	Yes	3	No	Yes
Hyperosmolar nonketotic syndrome	Yes	3	No	Yes
Thyroiditis	No	1	No	Yes
Gastrointestinal disorders				
Ascites	No	3	No	No
Ascites	Yes	2	No	No
Diarrhea	Yes	3	No	Yes
Diarrhea	No	2	No	Yes
Diarrhea	No	1	No	No
Hematemesis	Yes	3	No	No
General disorders				
Pyrexia	Yes	2	No	No
Pyrexia	Yes	2	No	No
Dizziness	No	1	No	No
Hepatobiliary disorders				
Hyperbilirubinemia	No	3	Yes	No
ALT increased	No	3	No	Yes
ALT increased	No	2	No	Yes
ALT increased	No	1	No	No
AST increased	No	2	No	Yes
AST increased	No	2	No	No
Bilirubin increased	No	2	No	No
Bilirubin increased	No	1	Yes	No
Bilirubin increased	No	1	No	Yes
Hepatic function abnormal	Yes	2	No	No
Hepatic function abnormal	No	1	No	No
Hepatic encephalopathy	Yes	2	No	No
Hepatic encephalopathy	No	2	No	No

Infections and infestations				
Chlostridium bacteremia	Yes	3	No	No
Peritonitis bacterial	No	3	No	No
Urinary tract infection	Yes	2	No	No
Escherichia coli infection	No	1	No	No
Lower respiratory tract infection	No	1	No	No
Peritonitis	Yes	1	No	No
Pneumonia	No	1	No	No
Musculoskeletal and connective tissue disorders				
Rib fracture	No	1	No	No
Back pain	No	1	No	Yes
Renal and urinary disorders				
Renal impairment	Yes	3	No	Yes
Tubulointerstitial nephritis	Yes	3	No	Yes
Creatinine increased	No	2	No	Yes
Creatinine increased	No	1	No	Yes
Creatinine increased	No	1	No	No

SAE: serious adverse event. IMAE: immune-mediated adverse event. Some patients developed more than one AE leading to nivolumab dose delays.

Table S3. Individual adverse events that led to a permanent discontinuation of nivolumab in 6 patients.

AE	SAE	Grade	Related to SIRT	Related to Nivolumab (IMAE)
Liver abscess	Yes	3	Yes	No
Hyperbilirubinemia	No	2	Yes	No
Diarrhea	No	2	No	Yes
Postoperative wound infection	Yes	3	No	No
Bile duct obstruction	Yes	3	No	No
Hepatic encephalopathy	Yes	2	No	No
Liver abscess	No	3	No	No

IMAE: immune-mediated adverse event.

Table S4. Immune-mediated AEs (IMAE) requiring corticosteroids observed in 8 patients.

Patient	Organ class	AE	SAE	Grade
1	Endocrine	Diabetes mellitus	Yes	3
2	Endocrine	Hyperthyroidism	No	1
3	Endocrine	Hypothyroidism	No	1
	Endocrine	Thyroiditis	No	1
4	Hepatobiliary	Immune hepatitis	No	3
5	Gastrointestinal	Diarrhea	Yes	3
6	Hepatobiliary	AST & ALT increased	No	2
7	Hepatobiliary	AST & ALT increased	No	2
8	Hepatobiliary	ALT & Bilirubin increased	No	2

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Table S5. Response rate by investigator-assessed RECIST 1.1 criteria according to baseline characteristics.

		N	Responders	%
Subgroup	BCLC-B2	30	13	43.3
	Lobar PVI	11	4	36.4
ECOG	0	37	15	40.5
	1	4	2	50.0
Etiology	Uninfected	31	13	41.9
	Viral	10	4	40.0
Alpha-fetoprotein *	≤ 400 ng/ml	28	11	39.3
	> 400 ng/ml	12	6	50.0
Child-Pugh score	5	35	15	42.9
	6	6	2	33.3
ALBI grade	1	20	8	40.0
	2	21	9	42.9
Any prior treatment	No	21	10	47.6
	Yes	20	7	35.0
Prior TACE	No	30	14	46.7
	Yes	11	3	27.3
Prior Sorafenib	No	36	16	44.4
	Yes	5	1	20.0

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Activity calculation	Liver-targeted dose	17	4	23.5
	Tumor-targeted dose	24	13	54.2

* baseline values were not available for one patient

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Table S6. Time to progression and overall survival according to patient and treatment baseline characteristics.

		N	Time to progression, median (95% CI)	p	N	Progression-free survival, median (95% CI)	p	N	Overall survival, median (95% CI)	p
Tumor burden	BCLC-B2	30	10.61 (0.91 – 20.31)	0.120	30	10.61 (0.73 – 20.49)	0.115	31	22.04 (18.59 – 25.49)	0.765
	Lobar PVI	11	4.79 (0.29 – 9.29)		11	4.79 (0.29 – 9.29)		11	19.91 (1.74 – 38.07)	
Alpha-fetoprotein	≤ 400 ng/ml	28	9.16 (0.00 – 23.25)	0.038	28	9.16 (0.00 – 23.64)	0.060	29	22.57 (17.89 – 27.24)	0.023
	> 400 ng/ml	12	3.28 (0.94 – 5.62)		12	3.28 (0.94 – 5.62)		12	13.04 (1.27 – 24.81)	
ALBI grade	1	20	9.16 (5.10 – 13.22)	0.855	20	9.00 (5.20 – 12.79)	0.788	21	22.14 (17.05 – 27.22)	0.253
	2	21	7.81 (5.90 – 9.)		21	7.09 (3.06 – 11.12)		21	19.91 (9.26 – 30.55)	
Y90 activity calculation	Tumor-targeted dose	24	16.62 (0.00 - 35.93)	0.09	24	16.62 (0.00 – 36.22)	0.084	25	22.57 (18.32 – 26.82)	0.090
	Liver-targeted dose	17	6.89 (5.66 - 8.13)		17	6.89 (5.66 – 8.13)		17	17.24 (8.94 – 25.55)	

Supplemental figures

Figure S1. Waterfall plot showing maximum changes in tumor size of target lesions.
It is important to bear in mind when reading this figure that SIRT results in different doses of radiation absorbed by different tumor nodules.

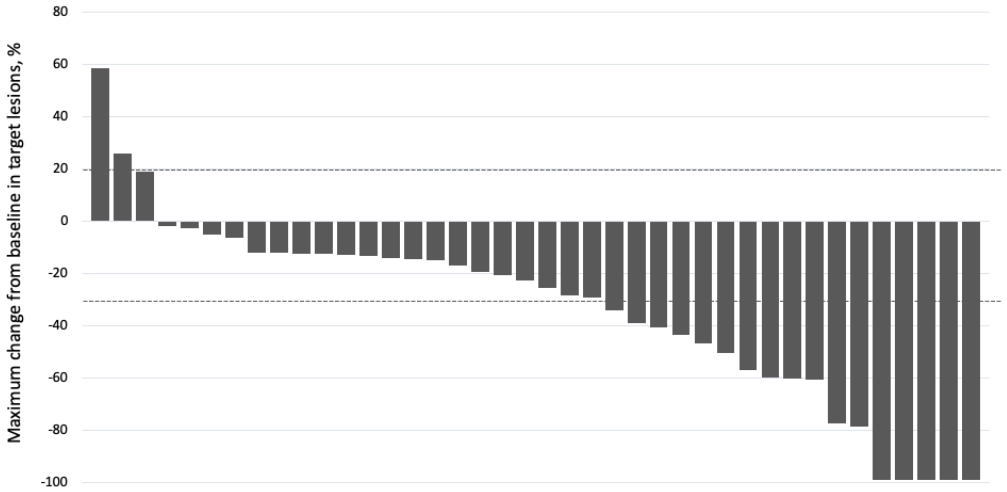
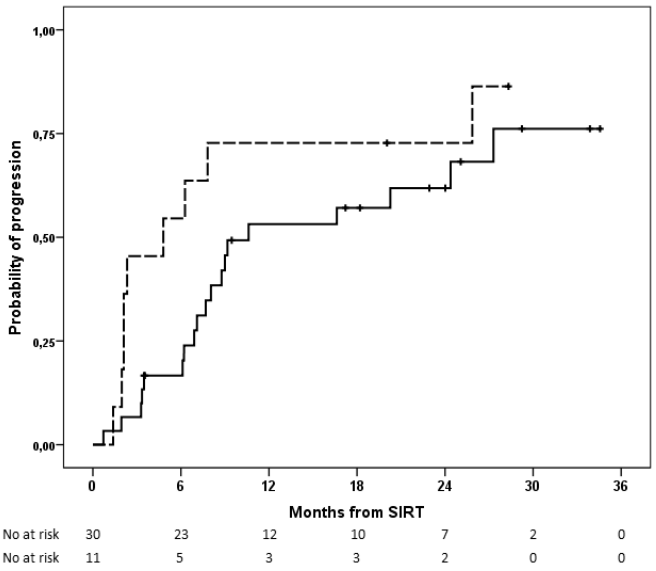


Figure S2. Time to progression per investigator assessment according to baseline tumor burden.
BCLC-B2 (median 10.6 months, 95%CI 0.9 – 20.3) vs. lobar PVI (median 4.8 months, 95%CI 0.3 – 9.3), p=0.12.



BCLC-B2	No at risk	30	23	12	10	7	2	0
Lobar PVI	No at risk	11	5	3	3	2	0	0

Figure S3. Time to progression per investigator assessment according to Y90 activity calculation.
Tumor-targeted dose (median 16.6 months, 95%CI 0.0 - 35.9) vs. liver-targeted dose (median 6.9 months, 95%CI 5.7 - 8.1), p=0.09.

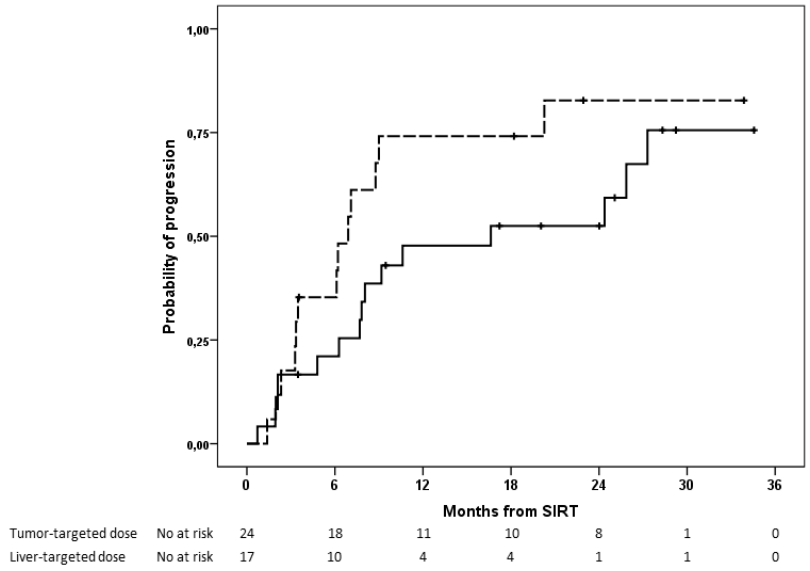
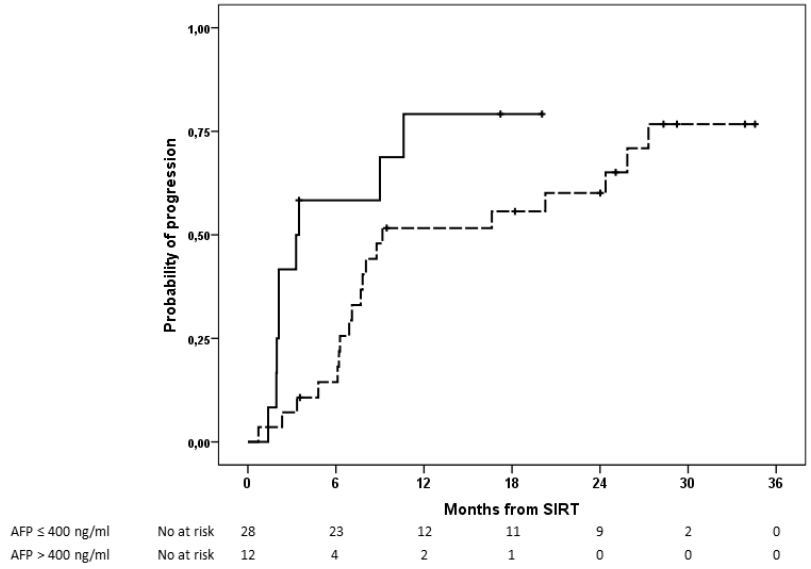


Figure S4. Time to progression per investigator assessment according to baseline AFP.
AFP ≤ 400 ng/ml (median 9.2 months, 95%CI 0.0 – 23.2) vs. AFP > 400 ng/ml (median 3.3 months, 95%CI 0.9 – 5.6), p=0.038.



AFP ≤ 400 ng/ml	No at risk	28	23	12	11	9	2	0
AFP > 400 ng/ml	No at risk	12	4	2	1	0	0	0

Figure S5. Progression-free survival per investigator assessment.
PFS rates at 1 and 2 years were 42% and 37%, respectively.

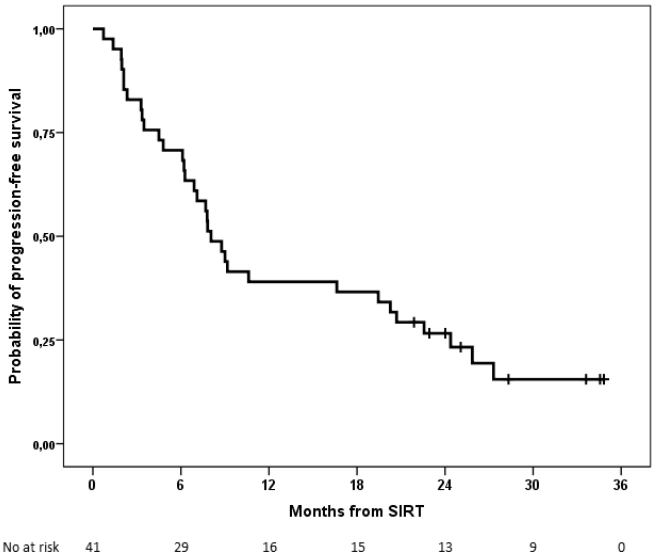
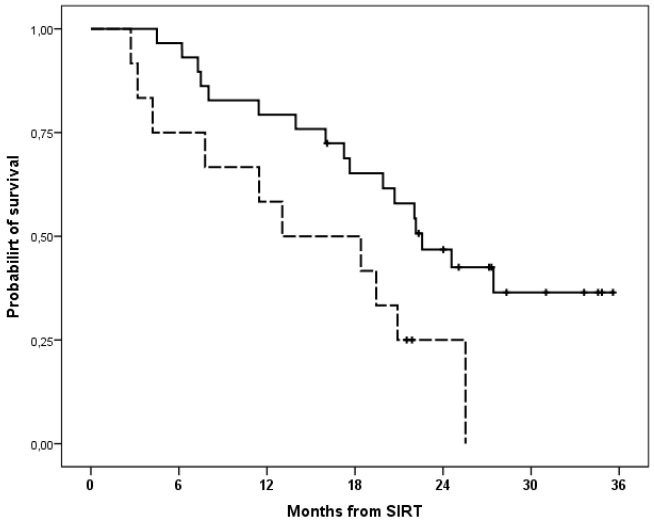
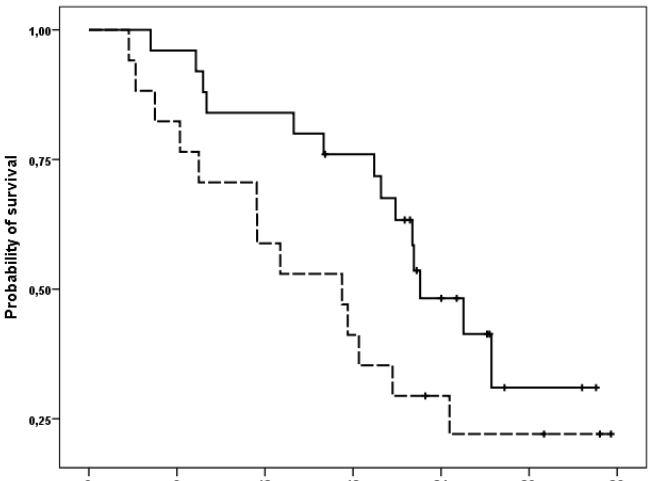


Figure S6. Overall survival according to baseline AFP levels.
AFP ≤ 400 ng/ml (median 22.6 months, 95%CI 17.9 – 27.2) vs. AFP > 400 ng/ml (median 13.0 months, 95%CI 1.3 – 24.8), p=0.023.



AFP ≤ 400 ng/ml	No at risk	29	28	23	18	12	5	0
AFP > 400 ng/ml	No at risk	12	9	7	6	1	0	0

Figure S7. Overall survival according to the aim of Y90 activity calculation.
Tumor-targeted dose (median 22.6 months, 95%CI 18.3 – 26.8) vs.
liver-targeted dose (median 17.2 months, 95%CI 8.9 – 25.5), p=0.09.



Tumor-targeted dose	No at risk	25	24	21	18	9	2	0
Liver-targeted dose	No at risk	17	14	10	7	4	3	0