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Nivolumab after selective internal radiation therapy for the treatment of hepatocellular carcinoma: a phase 2, single-arm study

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ABSTRACT

Purpose To evaluate the safety and efficacy of selective internal radiation therapy (SIRT) in combination with a PD-1 inhibitor in patients with unresectable hepatocellular carcinoma (uHCC) and liver-only disease ineligible for chemoembolization.

Patients and methods NASIR-HCC is a single-arm, multicenter, open-label, phase 2 trial that recruited from 2017 to 2019 patients who were naïve to immunotherapy and had tumors in the BCLC B2 substage (single or multiple tumors beyond the up-to-7 rule), or unilobar tumors with segmental or lobar portal vein invasion (PVI); no extrahepatic spread; and preserved liver function. Patients received SIRT followed 3 weeks later by nivolumab (240 mg every 2 weeks) for up to 24 doses or until disease progression or unacceptable toxicity. Safety was the primary endpoint. Secondary objectives included objective response rate (ORR), time to progression (TTP), and overall survival (OS).

Results 42 patients received SIRT (31 BCLC-B2, 11 with PVI) and were followed for a median of 22.2 months. 27 patients discontinued and 1 never received Nivolumab. 41 patients had any-grade adverse events (AE) and 21 had serious AEs (SAE). Treatment-related AEs and SAEs grade 3–4 occurred in 8 and 5 patients, respectively. Using RECIST 1.1 criteria, ORR reported by investigators was 41.5% (95% CI 26.3% to 57.9%). Four patients were downstaged to partial hepatectomy. Median TTP was 8.8 months (95% CI 7.0 to 10.5) and median OS was 20.9 months (95% CI 17.7 to 24.1).

Conclusions The combination of SIRT and nivolumab has shown an acceptable safety profile and signs of antitumor activity in the treatment of patients with uHCC that were fit for SIRT.

Trial registration number NCT03380130

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Selective internal radiation therapy (SIRT) using yttrium-90 microspheres and PD1 inhibitors are used to treat patients with liver cancer but there is very limited information about the safety and efficacy of the combination of both therapies.

WHAT THIS STUDY ADDS

⇒ In patients with hepatocellular carcinoma (HCC) who are not good candidates for TACE despite being free from extrahepatic metastasis, SIRT using SIR-Spheres resin microspheres followed by nivolumab produced no new signs of enhanced toxicity, with most patients receiving nivolumab as planned, and the observed time to progression and overall survival were encouraging.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The efficacy of the combination of SIRT and nivolumab deserves to be studied in prospective randomized clinical trials in this population of patients with HCC and large or multiple tumors or those with segmental or lobar portal vein invasion. The outcomes observed in this study provide the benchmark for the design of such trials.

INTRODUCTION

Liver cancer is the third-leading cause of cancer-related deaths worldwide, and hepatocellular carcinoma (HCC) accounts for more than 80% of cases.[1] Unresectable HCC patients are typically in the intermediate and advanced stages.[2] Intermediate means asymptomatic, multinodular liver-only disease while advanced means mild impairment of performance status, vascular invasion or extrahepatic spread. Intraarterial therapies are the mainstay of the treatment of the former while systemic therapy is mostly used for the latter. Immunotherapy with the combination of atezolizumab plus bevacizumab is widely recommended as first-line systemic therapy for advanced HCC.[3 4] Transarterial chemoembolization (TACE) is the most common

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intra-arterial therapy and ideal candidates for TACE are those with limited burden of disease that can be targeted by superselective embolization.[2]

Selective internal radiation therapy (SIRT) has been proposed as an alternative intra-arterial therapy for patients with a higher burden of disease including those with segmental or lobar portal vein invasion (PVI).[5] SIR-Spheres are resin microspheres containing yttrium-90, a pure beta-emitting isotope. Patients treated by SIRT using SIR-Spheres reach a median survival of 17 months if they are in the intermediate Barcelona Clinic Liver Cancer (BCLC) stage B and 10 months if they are in the advanced BCLC stage C with limited PVI.[6] Phase 3 clinical trials have not shown improved survival when SIRT alone[7 8] or in combination with sorafenib[9] were compared with sorafenib alone. The most common pattern of progression after SIRT is the onset of new tumor lesions inside or outside the liver,[10] an event that carries a poor prognosis. Therefore, the combination of SIRT with an effective, well-tolerated systemic therapy could result in improved efficacy and preserved quality of life.

Nivolumab is a fully human immunoglobulin G4 that selectively blocks the interaction between programmed death 1 (PD-1) expressed on activated T cells, with its ligands PD-L1/PD-L2 thus preventing T cells from being inactivated.[11] Nivolumab has demonstrated durable tumor responses with good tolerability in naïve and sorafenib-treated patients with advanced HCC.[12 13] SIRT increases the presence of activated CD8+T cells in the tumor microenvironment[14] and may therefore provide synergistic efficacy with Nivolumab. NASIR-HCC has assessed the combination of SIRT and immunotherapy in HCC patients with liver-only disease.

METHODS

Study design and population

NASIR-HCC (CA209-992) is a phase 2, multicenter, open-label, single-arm study of the safety and efficacy of Nivolumab in combination with SIRT using SIR-Spheres for the treatment of patients with HCC that are candidates for locoregional therapies. The study was conducted in nine academic centers in Spain (online supplemental file).

Eligible patients had unresectable HCC and were considered ineligible for TACE because either (i) they were in the BCLC-B2 substage,[15] which includes single tumors (BCLC-A stage) if they are >5 cm or multiple tumors (BCLC-B stage) if they fall beyond the up-to-7 rule (number of tumors plus size of the largest lesion in cm >7); or (ii) they were in BCLC-C stage due to predominantly unilobar tumors with segmental or lobar PVI. Additional eligibility criteria are provided in online supplemental file.

All SIRT evaluations and treatments were centrally performed at Clinica Universidad de Navarra as a single-day procedure. A detailed SIRT protocol is provided in online supplemental file. SIRT was performed selectively, eventually through multiple microspheres injections, to preserve the largest possible liver volume from receiving any amount of radiation. Activity calculation took into account the cirrhotic status of the liver and the amount of liver volume spared from irradiation, with the aim to maximize tumor absorbed dose when deemed safe.[16] Such individualized dosimetry was used whenever two liver segments were spared from radiation. Nivolumab (240 mg IV every 14 days) was started 3 weeks after SIRT visit and maintained until tumor progression, unacceptable toxicity or a maximum of 24 doses. Tumor response was assessed by investigators using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria[17] every 6 weeks for the first year, and then every 12 weeks thereafter until progression. Treatment with Nivolumab beyond progression was allowed under protocol-defined circumstances detailed in online supplemental file.

Outcomes

The primary endpoints were the rate and type of adverse events (AEs), serious AEs (SAEs), events of liver decompensation, and transient and permanent drug discontinuations due to toxicity. Immune-mediated adverse events (IMAE) related to nivolumab that were treated with corticosteroids were specifically recorded. Hepatic AEs (HAEs) were defined as those AE that have the liver as the target organ or represent usual complications of cirrhosis, including hepatobiliary events, liver-related investigations, thrombocytopenia, ascites, encephalopathy, spontaneous bacterial peritonitis and GI hemorrhage. Toxicity was graded according to Common Terminology Criteria for Adverse Events (CTCAE) V.4.0. Secondary endpoints are defined in detail in supplemental data and included overall response rate (ORR), disease control rate (DCR), duration of response (DoR), time to progression (TTP), progression-free survival (PFS), and pattern of progression. Exploratory objectives were overall survival (OS); efficacy based on tumor cell programmed death ligand 1 (PD-L1) expression and other tissue and blood biomarker; impact of the albumin-bilirubin (ALBI) score on safety and efficacy; and health related quality of life (HRQoL).

Statistical analyses

The primary objective was safety, but the study was considered key to explore the clinical benefit of combining nivolumab with SIRT. A sample size of 40 patients was determined adequate to provide safety information based on a 90% probability of observing at least one occurrence of any AE that might occur with a 5% incidence. At the time of study design, the estimated TTP after SIRT alone in a similar population was 3 months[18] and sample size of 40 patients receiving SIRT plus at least 3 doses of Nivolumab would therefore allow to detect a relevant signal of incremental efficacy as detailed in online supplemental file.

Safety analysis included all patients who received SIRT while efficacy analysis included those who received SIRT and one or more doses of nivolumab. All AEs were

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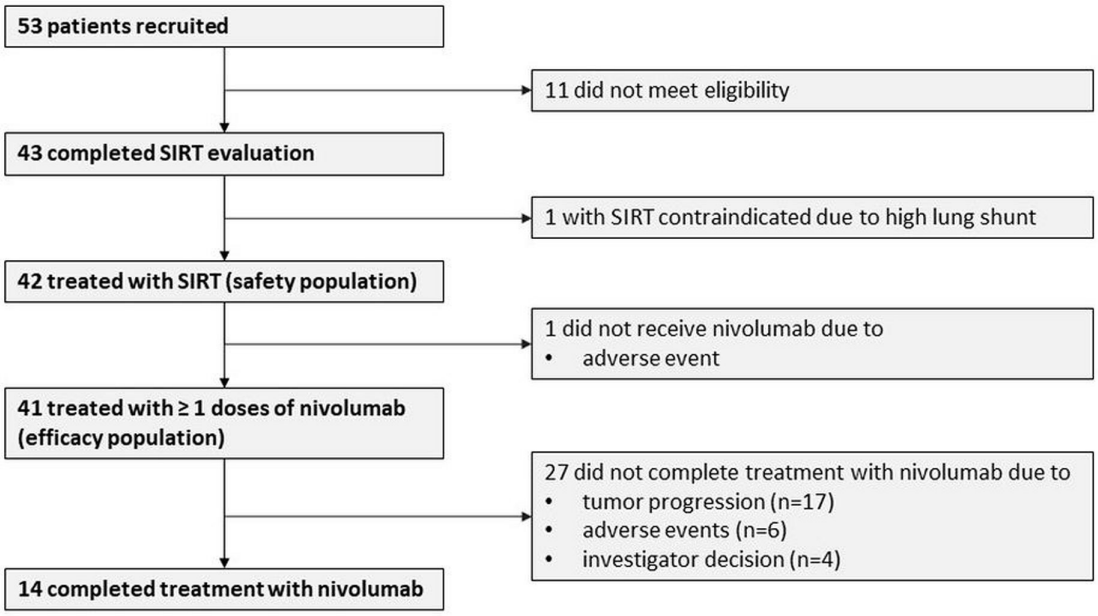

Figure 1 Flow chart. SIRT, selective internal radiation therapy.

summarized and reported by organ system, preferred term, and coded per the current version of the Medical Dictionary for Regulatory Activities. ORR and the corresponding 95% CI were calculated using the Clopper-Pearson method. The Kaplan-Meier method was used to analyze and plot time to events (TTP, DoR, PFS and OS) and median values were reported with 95% CI. The analysis of HRQoL will be reported separately.

RESULTS

Population and baseline characteristics

Forty-three patients were enrolled between January 2018 and April 2019 (figure 1). SIRT was contraindicated in one patient (2.3%) due to a hepatopulmonary shunt fraction >20%. The remaining 42 patients received SIRT and comprised the safety population. One patient with an incompetent ampulla of Vater developed liver abscesses after SIRT and never received Nivolumab, 27 discontinued Nivolumab during the study period mostly due to disease progression (n=17), and 14 patients received 24 doses of nivolumab as planned. Baseline demographic and clinical characteristics are listed in table 1. Six patients had received sorafenib, with a median of 10 weeks between the last dose of sorafenib and study entry.

Treatment

SIRT details are summarized in online supplemental table S1. The median time from informed consent to SIRT was 22 days (IQR 12 days). An effort was made to perform SIRT highly selectively. According to the volume of liver receiving any amount of radiation, SIRT was sublobar in 17%, lobar in 55%, and extended lobar or whole-liver in 28%, with multiple SIR-Spheres injections performed in 62% of patients. Activity was calculated using the partition model to maximize the dose delivered to the tumor compartment at >120 Gy in 25 patients (tumor-targeted dose group) while in the remaining 17 patients (liver-targeted dose group) either the partition model was used to restrict the dose delivered to the non-tumoral compartment to 40 Gy (n=9) or a modified BSA method was used to calculate the activity (n=8).

At database lock in February 2021, the median minimum follow-up was 22.2 months (range 2.7–35.6). The median time from SIRT to first dose of nivolumab was 3.1 weeks and 3 patients started nivolumab 4 weeks or more after SIRT (4.5, 4.8, and 6.1 weeks) due to AEs. Twenty-eight patients (66.6%) discontinued or never received nivolumab. The reason for treatment discontinuation was as per investigator's decision in 4 patients. In three of these cases tumors previously considered unresectable turned resectable after tumor regression and/or contralateral hypertrophy. One additional patient who interrupted nivolumab due to diarrhea was also considered resectable. Complete tumor resection was achieved in these 4 patients 26, 27, 37, and 46 weeks after SIRT, with no postoperative deaths recorded. Allfour patients were alive and recurrence-free 11, 16, 17 and 29 months after resection (22, 23, 24 and 35 months after SIRT).

Patients were on nivolumab for a median of 32.9 weeks (range 2.1–48.8 weeks). Fourteen patients (33.3%) completed nivolumab treatment as planned. Seven patients who reached the end of the treatment period with stable disease (n=4) or showing partial tumor response (n=3) were maintained on Nivolumab off-study based on local availability and investigator decision. Nine patients (21.9%) received tyrosine kinase inhibitors poststudy.

Safety

A summary of AEs is presented in table 2. AEs and SAEs grade 3–4 were observed in 19% and 26% of patients,

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Table 1 Patient demographics and baseline characteristics

	All patients	BCLC-B2 substage	Unilobar tumors with portal vein invasion
Patients (n, %)	42 (100)	31 (73.8)	11 (26.2)
Males (n, %)	36 (85.7)	27 (87.1)	9 (81.1)
Age in years (median, IQR)	65 (49–79)	65 (49–79)	65 (55–79)
Vascular invasion (n, %)	11 (26.2)	0	11 (100)
BCLC stage (n, %)			
A	3 (7.1)	3 (9.7)	0
B	25 (59.6)	25 (80.6)	0
C	14 (33.3)	3 (9.7)	11 (100)
Etiology (n, %)			
Uninfected	32 (76.2)	25 (80.6)	7 (63.6)
Hepatitis C	9 (21.4)	5 (16.1)	4 (36.4)
Hepatitis B	1 (2.4)	1 (3.2)	0
Alcohol consumption (n, %)	5 (11.9)	3 (9.6)	2 (18.1)
Arterial hypertension (n, %)	20 (47.6)	16 (51.6)	4 (36.4)
Diabetes (n, %)	10 (23.8)	7 (22.6)	3 (27.3)
Dyslipidemia (n, %)	9 (21.4)	8 (25.8)	1 (9.1)
ECOG performance status (n, %)			
0	38 (90.5)	28 (90.3)	10 (90.9)
1	4 (9.5)	3 (9.7)	1 (9.1)
Child-Pugh class (n, %)			
A5	36 (85.7)	27 (87.1)	9 (81.8)
A6	6 (14.3)	4 (12.9)	2 (18.2)
ALBI grade (n, %)			
1	21 (50)	17 (54.9)	4 (36.4)
2	21 (50)	14 (45.1)	7 (63.6)
Previous treatment (n, %)			
Liver resection	7 (16.7)	5 (16.1)	2 (18.2)
Percutaneous ablation	6 (14.3)	5 (16.1)	1 (9.1)
TACE	11 (26.2)	11 (35.5)	0
Sorafenib	6 (14.3)	5 (16.1)	1 (9.1)
Alpha-fetoprotein >400 ng/mL (n, %)	12 (29.3)	7 (23.3)	5 (45.5)
Platelet count, /pL (median, IQR)	141 (46–512)	139 (46–512)	145 (59–288)
Total bilirubin, mg/dL (median, IQR)	0.76 (0.20–1.89)	0.72 (0.20–1.89)	0.90 (0.40–1.40)
Albumin, g/dL (median, IQR)	3.95 (3.00–4.80)	4.00 (3.00–4.80)	3.83 (3.20–4.80)
Neutrophil to lymphocyte ratio (median, IQR)	2.69 (1.86–4.25)	2.61 (1.83–4.15)	3.38 (1.87–4.34)

ALBI, Albumin-Bilirubin; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; TACE, Transarterial chemoembolization.

respectively. No treatment-related deaths were reported. The incidence and type of SAEs was not different in patients in the BCLC-B2 substage versus those with lobar PVI. Treatment-related AE related to nivolumab (IMAE) or SIRT are detailed in table 3.

Eighteen patients (43.9%) had at least one nivolumab dose delay due to AEs (online supplemental table S2) and three patients (7.2%) had three or more dose delays. HAEs resulted in dose delays in 9 (21.4%) patients. Delays occurred less frequently after sublobar SIRT (14.2%) compared with lobar (52.1%) or lobar extended/whole-liver SIRT (25%). Nivolumab was discontinued due to AEs in six patients (online supplemental table S3). Two such AEs were considered related to SIRT (liver abscesses in a patient with incompetent ampulla of Vater despite antibiotic prophylaxis; and hyperbilirubinemia) and one

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Table 2 Summary of AEs

	Patients with adverse events, no (%)*	
	Any grade	Grade 3–4
All causality AEs	41 (98)	8 (19)
Treatment-related AEs	33 (79)	8 (19)
Related to SIRT	21 (50)	2 (5)
Related to nivolumab (IMAE)	27 (64)	6 (14)
All causality SAEs	21 (50)	11 (26)
Treatment-related SAEs	5 (12)	5 (12)
Related to SIRT	1 (2)	1 (2)
Related to Nivolumab (IMAE)	4 (9)	4 (9)
AEs of special interest with incidence >10%		
Hepatic	30 (71)	8 (19)
Blood	16 (38)	0
Gastrointestinal	16 (38)	3 (7)
Skin	12 (29)	0
Endocrine	10 (24)	2 (5)

*AEs and SAEs are reported separately.
AE, adverse event; SAEs, serious AEs; SIRT, selective internal radiation therapy.

was related to nivolumab (grade 3 diarrhea). Events of liver decompensation occurred in 18 (42.9%) patients during follow-up and were more frequent among patients receiving a liver-targeted dose (n=11, 61.1%) than a tumor-targeted dose (n=7, 38.9%), and correspondingly among patients receiving SIRT with a whole-liver or lobar extended design (n=8, 44.4%) vs a sublobar design (n=4, 16.6%).

Nine IMAEs requiring steroids were reported in eight patients and are listed in online supplemental table S4. One patient permanently discontinued Nivolumab due to diarrhea while the other patients with IMAEs were able to resume it. No patient required treatment with immunosuppressors other than corticosteroids.

HAEs that (A) were grade 3 or 4, (B) resulted in nivolumab dose delays or discontinuation, (C) were related to SIRT or to nivolumab, or (D) consisted in increased bilirubin or complications of cirrhosis, were observed more frequently in patients with ALBI grade 2 at baseline (table 4). As the volume of SIRT-targeted liver increased from sublobar to lobar or whole-liver SIRT, the proportion of patients with HAEs related to SIRT also increased, but the incidence of HAEs resulting in nivolumab dose delays or discontinuation was similar between subgroups. When treatment-related AEs of any class resulting in nivolumab dose delays were considered (and not only HAEs), a similar proportion of patients had baseline ALBI grades 1 and 2 (62% and 47%, respectively).

Table 3 Treatment-related adverse events related to SIRT or nivolumab

System organ class, preferred term	Patients with treatment-related adverse events, no (%)	
Event	Any grade	Grade 3-5
Related to SIRT		
Hepatobiliary disorders		
Hyperbilirubinemia	8 (19)	1 (2)
ALT increased	1 (2)	0
AST Increased	1 (2)	0
Blood and lymphatic system disorders		
Thrombocytopenia	7 (17)	0
Lymphopenia	1 (2)	0
Infections and infestations		
Liver abscess	1 (2)	1 (2)
Gastrointestinal disorders		
Ascites	1 (2)	0
General disorders		
Fever	1 (2)	0
Vascular disorders		
Hematoma	1 (2)	0
Related to nivolumab (IMAEs)		
Hepatobiliary disorders		
ALT increased	5 (12)	1 (2)
AST increased	6 (14)	1 (2)
Hyperbilirubinemia	2 (5)	0
Immune hepatitis	2 (5)	1 (2)
Endocrine disorders		
Hypothyroidism	4 (10)	0
Thyroiditis	2 (5)	0
Hyperthyroidism	1 (2)	0
Skin and subcutaneous tissue disorders		
Pruritus	4 (10)	0
Rash	3 (7)	0
Dermatitis	2 (5)	0
Gastrointestinal disorders		
Diarrhea	2 (5)	1 (2)
Blood and lymphatic system disorders		
Anemia	2 (5)	
Metabolism and nutrition disorders		
Diabetes mellitus	1 (2)	1 (2)
Hyperosmolar nonketotic syndrome	1 (2)	1 (2)
Renal and urinary disorders		
Renal impairment	1 (2)	1 (2)
Tubulointerstitial nephritis	1 (2)	1 (2)

Continued

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Table 3 Continued

System organ class, preferred term	Patients with treatment-related adverse events, no (%)	
Event	Any grade	Grade 3-5
Blood creatinine increased	1 (2)	0
Musculoskeletal and connective tissue disorders		
Back pain	1 (2)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; SIRT, selective internal radiation therapy.

Efficacy

As per investigator assessment, complete and partial responses were observed in 5 and 12 patients, respectively, accounting for an ORR of 41.5% (95% CI 26.3% to 57.9%). Stable disease was the best overall response in 21 patients accounting for a DCR of 92.7% (95% CI 80.1% to 98.5%). No patient or tumor baseline characteristic, including prior TACE or Sorafenib, was associated with relevant differences in ORR, although responses were more frequent when Y90 activity was calculated based on a tumor-targeted dose (online supplemental table S5). Median time to response was 9 weeks (range 1–50 weeks) and median DoR was 31 weeks (range 6–109 weeks). Eleven (26.8%) patients had ongoing responses at the time of analysis. The waterfall plot of changes in target lesions is shown in online supplemental figure S1.

During the follow-up, 28 patients experienced disease progression, and 27 patients died. First progression was in form of growth of pre-existing lesions in 9 patients, new intrahepatic lesions in 10, and new extrahepatic lesions in 9. Median TTP was 8.8 months (95% CI 7.0 to 10.5) (figure 2). There was tendency to a shorter TTP among patients with vascular invasion, alpha-fetoprotein (AFP)>400 ng/mL or liver-targeted dose that was statistically significant only for AFP >400 ng/mL (online supplemental table S6 and figures S2–S4). Median PFS was 9.0 months (95% CI 7.0 to 10.9) (online supplemental figure S5).

Median OS was 20.9 months (95% CI 17.7 to 24.1) (figure 3). A trend was observed toward shorter OS among patients with AFP >400 ng/mL or liver-targeted dose that was significant for the former (online supplemental table S6 and figure S6 and S7).

DISCUSSION

To our knowledge, this is the first full report of a prospective evaluation of the combination of SIRT and nivolumab in a cohort of patients with HCC free from extrahepatic metastasis. The combination showed a tolerable safety profile with no signs of synergistic toxicity, and promising ORR, TTP, and OS. SIRT has shown a favorable safety profile and antitumor activity in retrospective and prospective cohorts of patients with intermediate through advanced stage HCC including those with too many or too large tumors, a wide range of patterns of PVI, or in progression to TACE.[6 19 20] A recent publication has described the effects of this same combination in a more heterogenous and advanced group of HCC patients including a substantial number of patients with extrahepatic disease.[21] Indeed, authors concluded that the strategy should be further evaluated in patients with HCC ineligible for TACE and patients with advanced stage but without extrahepatic spread. In NASIR-HCC, we established such stringent patient selection criteria to help define the safety and potential efficacy of SIRT and nivolumab in a homogeneous population that could be the target for future controlled clinical trials, excluding those patients with limited tumor burden where SIRT would be a radical therapy, and also those with extrahepatic metastasis where a locoregional therapy will unlikely have any benefit. The similar safety profile and OS in the two subgroups of patients in the BCLC-B2 substage and limited PVI supports our choice as a reasonable target population.

Nivolumab has demonstrated a good safety profile and relevant activity in patients that were mostly in the advanced stage.[12 22] Yet, when tested against sorafenib as first-line therapy in advanced HCC a superior OS was not shown.[23] The safety of the combination with SIRT was acceptable and there were no signs of new or synergistic liver or lung toxicity, the main organs with overlapping AEs. This is in line with the finding that administration of an ICI within 90 days following external irradiation was not associated with an increased risk of SAEs.[24] The most frequent AEs were those expected from SIRT (thrombocytopenia, asthenia, and increased bilirubin) or nivolumab (diarrhea, asthenia, increased transaminases, or pruritus). SIRT-related AEs caused nivolumab discontinuation in only two patients. Patients with worse liver functional reserve in ALBI grade 2 at baseline had higher rates of HAEs but not AEs of any class resulting in Nivolumab delays or discontinuation.

Regarding efficacy, data from prospective trials using SIRT in HCC can provide a reasonable perspective to assess the outcomes observed in this trial. Reported median PFS and OS in trials including patients considered unsuitable for TACE were 4.1 and 8.0 months, respectively, in the SARAH trial,[25] and 5.8 and 8.8 months SIRVENIB trial.[8] In randomized trials comparing SIRT versus TACE among patients suited for TACE, median PFS and OS ranged from 3.6 and <12 months in the SIRTACE trial[18] to 6 and 19.7 months in a German trial.[26] Median PFS at 9 months and median OS at 20.9 months in NASIR-HCC are consistently higher and suggest enhanced activity of the combination of SIRT with nivolumab. When considering only the BCLC-B2 substage, again the 10.6 months median PFS observed in this trial compares well with the 6.2 months reported in a multicenter retrospective series of SIRT-treated patients.[27] Response to SIRT is usually delayed for several months[28] and the median time to

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Table 4 Patients with hepatic adverse events of all causality, including hepatobiliary events, liver-related investigations, liver-related infections, thrombocytopenia, ascites, encephalopathy, bacterial peritonitis and GI hemorrhage

	All patients (n=42)		ALBI grade at baseline				SIRT design						Tumor burden			
			1 (n=21)		2 (n=21)		Sublobar (n=7)		Lobar (n=23)		Whole-liver (n=12)		BCLC-B2 (n=31)		Unilobar PVI (n=11)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any grade	32	76.2	16	76.2	16	76.2	5	71.4	15	65.2	12	100.0	25	80.6	7	63.6
Grade 3–4	9	21.4	2	9.5	7	33.3	2	28.6	4	17.4	3	25.0	7	22.6	2	18.2
Resulting in nivolumab dose delay	11	26.2	1	4.8	10	47.6	2	28.6	5	21.7	4	33.3	8	25.8	3	27.3
Related to SIRT	14	33.3	6	28.6	8	38.1	1	14.3	6	26.1	7	58.3	13	41.9	1	9.1
Related to nivolumab	7	16.7	2	9.5	5	23.8	1	14.3	3	13.0	3	25.0	6	19.4	1	9.1
Type of event																
Increased AST/ALT*	18	42.9	9	42.9	9	42.9	4	57.1	6	26.1	8	66.7	16	51.6	2	18.2
Increased bilirubin†	16	38.1	4	19.0	12	57.1	0	0.0	8	34.8	8	66.7	14	45.2	2	18.2
Thrombocytopenia	12	28.6	7	33.3	5	23.8	1	14.3	7	30.4	4	33.3	11	35.5	1	9.1
Ascites	4	9.5	0	0.0	4	19.0	0	0.0	3	13.0	1	8.3	2	6.5	2	18.2
Bacterial peritonitis	3	7.1	0	0.0	3	14.3	0	0.0	3	13.0	0	0.0	1	3.2	2	18.2
Encephalopathy	3	7.1	0	0.0	3	14.3	0	0.0	2	8.7	1	8.3	3	9.7	0	0.0
Hepatic function abnormal	2	4.8	0	0.0	2	9.5	0	0.0	1	4.3	1	8.3	0	0.0	2	18.2
Liver abscess	2	4.8	1	4.8	1	4.8	1	14.3	1	4.3	0	0.0	2	6.5	0	0.0
Hematemesis	1	2.4	0	0.0	1	4.8	0	0.0	0	0.0	1	8.3	1	3.2	0	0.0
Hepatitis immune	1	2.4	1	4.8	0	0.0	0	0.0	0	0.0	1	8.3	1	3.2	0	0.0
Increased GGT	1	2.4	1	4.8	0	0.0	0	0.0	0	0.0	1	8.3	1	3.2	0	0.0
Non-tumoral portal vein thrombosis	1	2.4	1	4.8	0	0.0	0	0.0	1	4.3	0	0.0	1	3.2	0	0.0

*Includes events of 'increased AST', 'increased ALT' or 'hypertransaminasemia'.
†Includes events of 'increased bilirubin' or 'hyperbilirubinemia'.
ALBI, Albumin-Bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; GGT, Gamma-glutamyl transpeptidase; GI, gastrointestinal; PVI, portal vein invasion; SIRT, selective internal radiation therapy.

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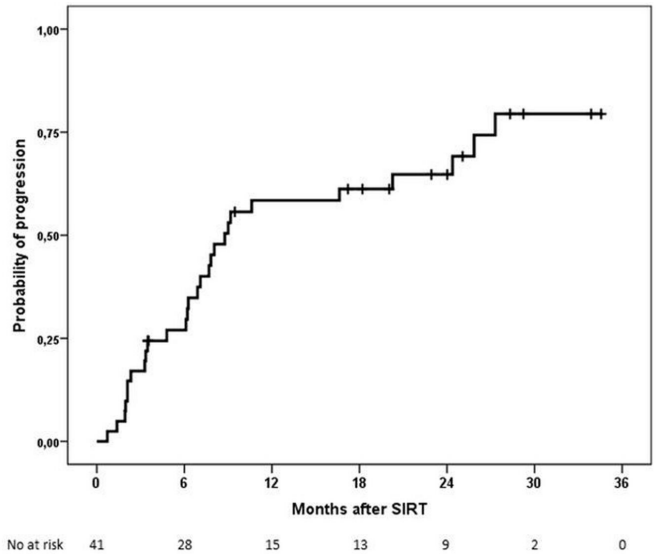

Figure 2 Kaplan-Meier plot of time to progression (TTP) per Investigator assessment. TTP rates at 1 and 2 years were 58% and 65%, respectively. SIRT, selective internal radiation therapy.

response of 9 weeks observed in this study is certainly shorter than what would be expected from SIRT alone. The high DCR at 93% was strongly influenced by the first evaluation of tumor response 3 weeks after SIRT, an early time point when most tumors are expected to remain stable.

Several studies have demonstrated that delivering a high dose of radiation to the tumor compartment is key to obtain a good long-term outcome after SIRT.[20 29] The data from NASIR-HCC point in the same direction and highlight the importance of treatment design and activity calculation in maximizing the effectiveness of SIRT.

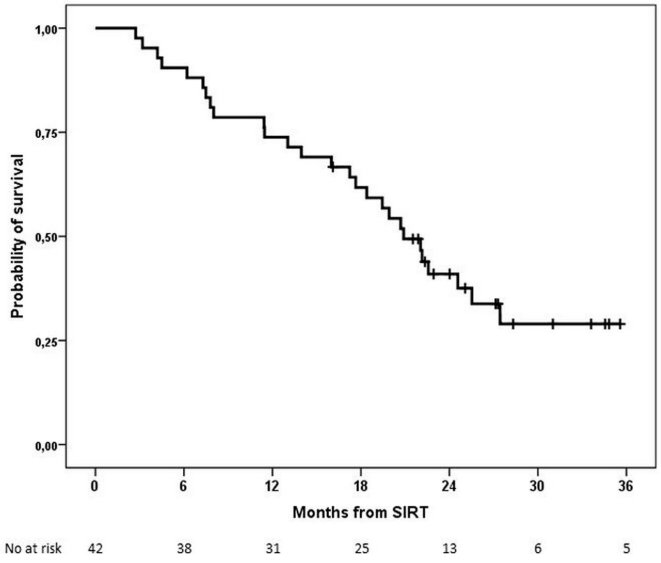

Figure 3 Kaplan-Meier plot of overall survival (OS). OS rates at 1 and 2 years were 74% and 41%, respectively. SIRT, selective internal radiation therapy.

Immune checkpoint inhibitors in combination with other therapies may provide a clinical benefit for advanced HCC patients naïve to systemic therapy. Atezolizumab plus bevacizumab has become a standard of care[3] after proving superior OS and PFS compared with sorafenib.[30] Improved OS and PFS benefits with the anti-PD-1 Sintilimab plus a Bevacizumab biosimilar was also shown in HBV-associated HCC.[31] More recently, tremelimumab plus durvalumab has shown superior OS and PFS[32] versus sorafenib. However, combinations come with more strict inclusion criteria compared with anti-PD-1/PD-L1 monotherapies, particularly for patients with cardiovascular comorbidities. SIRT plus nivolumab could be a valuable alternative for this subgroup of patients lacking an evidence-based recommended therapy.

Limitations

The single-arm design of the study should prompt caution in the interpretation of results compared with other prospective and retrospective cohorts, in particular with those large randomized trials that included patients in more advanced stages like SARAH, SIRveNIB and SORAMIC.[8 25 33] Performing all SIRT procedures in a single center minimizes the effect of different levels of expertize across centers but may impact the reproducibility of the results.

Conclusions

The NASIR-HCC trial has shown that the combination of SIRT with SIR-Spheres resin microspheres, followed by nivolumab was safe and active as first-line therapy of patients with locally advanced HCC ineligible for TACE, where SIRT alone has failed to prove superiority over the standard of care. The high DCR, prolonged TTP, and encouraging OS suggest that the combination could be an option for this population and should be tested in a phase 3 controlled trial.

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Patient consent for publication Consent obtained directly from patient(s).

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Correction: *Nivolumab after selective internal radiation therapy for the treatment of hepatocellular carcinoma: a phase 2, single-arm study*

Manuel de la Torre-Aláez M, Matilla A, Varela M, *et al*. Nivolumab after selective internal radiation therapy for the treatment of hepatocellular carcinoma: a phase 2, single-arm study. *Jr ImmunoTher Cancer* 2022;10:e005457. doi: 10.1136/jitc-2022-005457.

This article has been corrected since it was first published. A previous revision of the manuscript was published in error. Supplementary Table S2 is now incorporated in the main article as Table 3, and a new Figure S1 has been included in the supplementary material.

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Supplemental Materials

Supplemental Methods **2**
Participating centers 2
Inclusion and exclusion criteria 2

SIRT procedure **4**

Secondary study endpoints and additional sample size considerations **5**

Requisites for continuing treatment with Nivolumab beyond progression. **5**

References **5**

Supplemental Tables **7**
Table S1. Characteristics of the SIRT procedure. 7
Table S2. Individual events leading to nivolumab dose delays observed in 18 patients. 9
Table S3. Individual adverse events that led to a permanent discontinuation of nivolumab in 6 patients. 11
Table S4. Immune-mediated AEs (IMAE) requiring corticosteroids observed in 8 patients. 12
Table S5. Response rate by investigator-assessed RECIST 1.1 criteria according to baseline characteristics. 13
Table S6. Time to progression and overall survival according to patient and treatment baseline characteristics. 15

Supplemental figures **16**
Figure S1. Waterfall plot showing maximum changes in tumor size of target lesions. 16
Figure S2. Time to progression per investigator assessment according to baseline tumor burden. 17
Figure S3. Time to progression per investigator assessment according to Y90 activity calculation. 18
Figure S4. Time to progression per investigator assessment according to baseline AFP. 19
Figure S5. Progression-free survival per investigator assessment. 20
Figure S6. Overall survival according to baseline AFP levels. 21
Figure S7. Overall survival according to the aim of Y90 activity calculation. 22

de la Torre-Aláez M, *et al. J Immunother Cancer* 2023; 10:e005457. doi: 10.1136/jitc-2022-005457

Supplemental Methods

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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.

de la Torre-Aláez M, *et al. J Immunother Cancer* 2023; 10:e005457. doi: 10.1136/jitc-2022-005457

- 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.

de la Torre-Aláez M, *et al. J Immunother Cancer* 2023; 10:e005457. doi: 10.1136/jitc-2022-005457

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.

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Cancer 2008;112:1538–46. https://doi.org/10.1002/cncr.23339.
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[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

de la Torre-Aláez M, *et al. J Immunother Cancer* 2023; 10:e005457. doi: 10.1136/jitc-2022-005457

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

de la Torre-Aláez M, *et al. J Immunother Cancer* 2023; 10:e005457. doi: 10.1136/jitc-2022-005457

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.

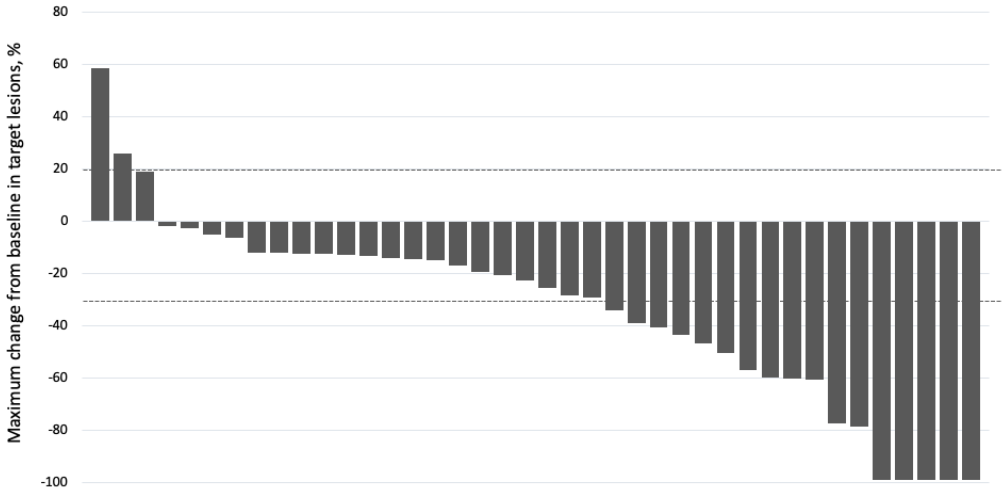
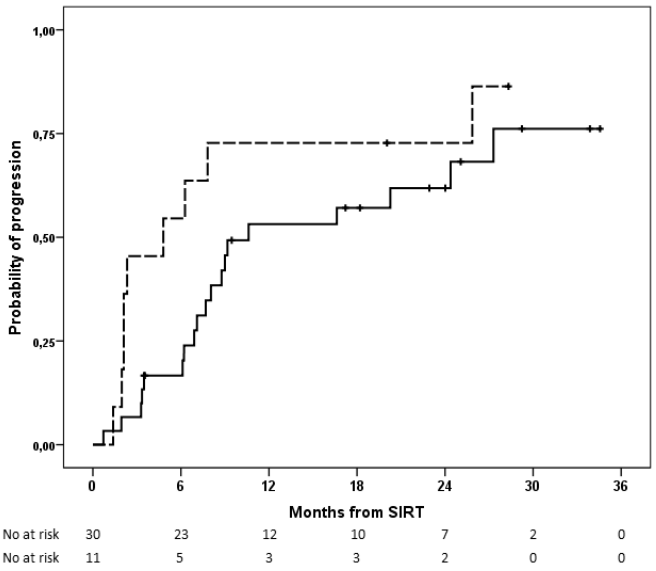


Figure S2. Time to progression per investigator assessment according to baseline tumor burden.
BCLC-B2 (median 10.6 months, 95%CI 0.9 – 20.3) vs. lobar PVI (median 4.8 months, 95%CI 0.3 – 9.3), p=0.12.



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.

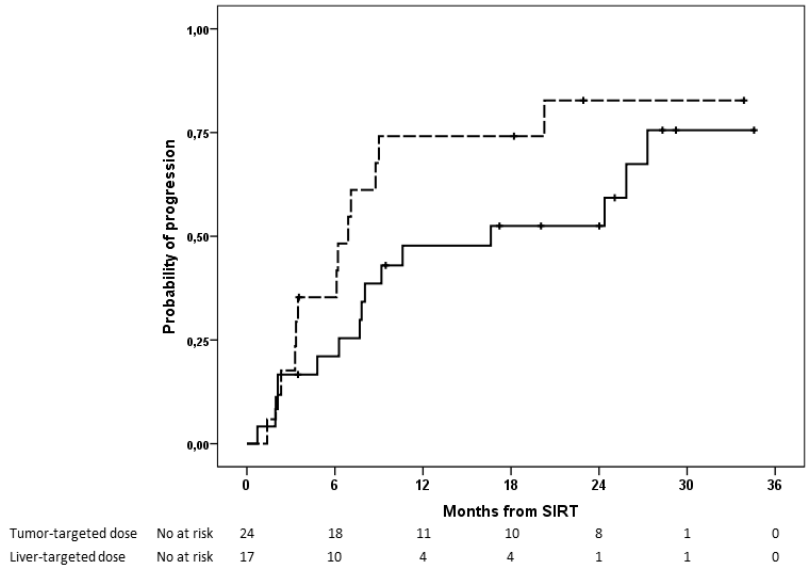
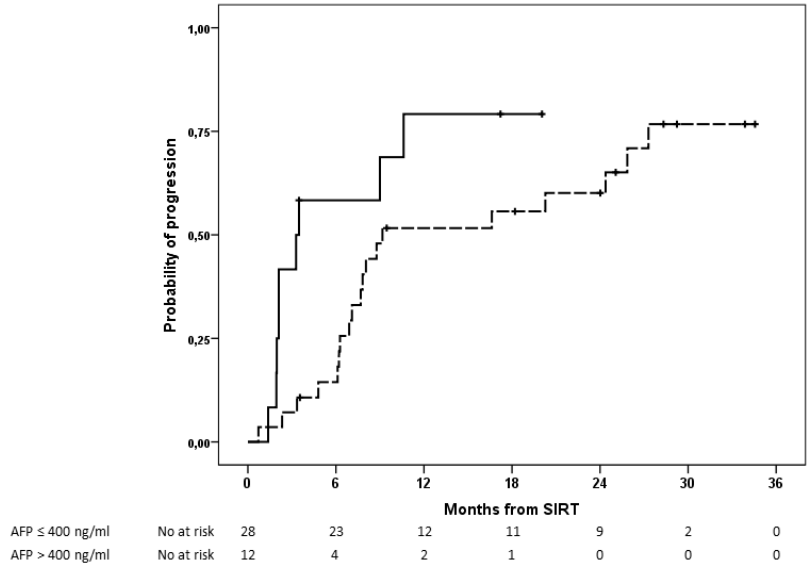


Figure S4. Time to progression per investigator assessment according to baseline AFP.
AFP ≤ 400 ng/ml (median 9.2 months, 95%CI 0.0 – 23.2) vs. AFP > 400 ng/ml (median 3.3 months, 95%CI 0.9 – 5.6), p=0.038.



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.

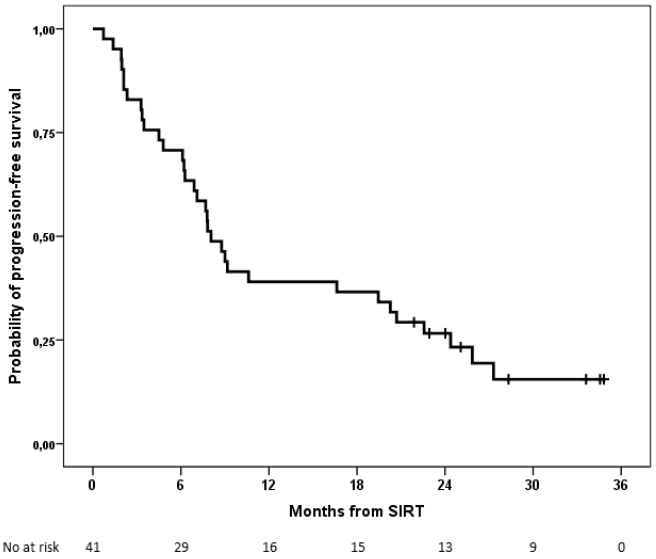
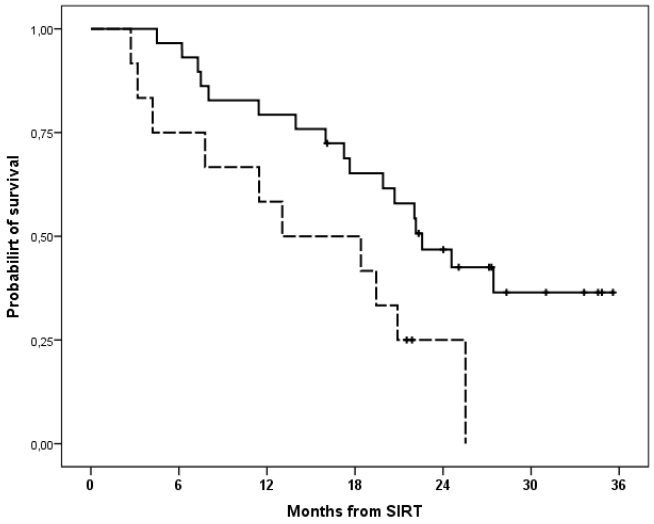
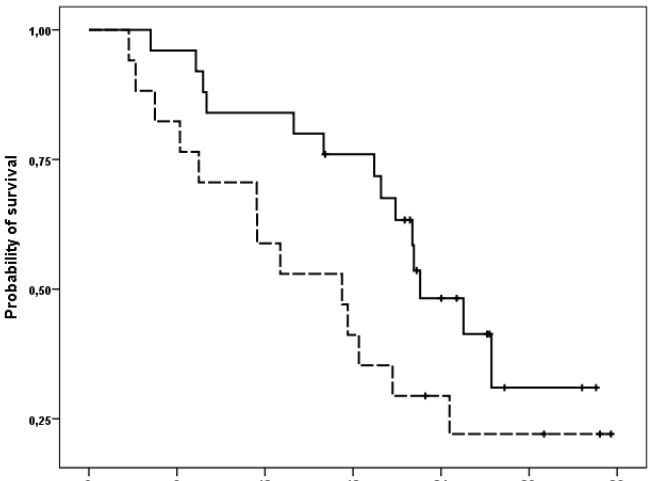


Figure S6. Overall survival according to baseline AFP levels.
AFP ≤ 400 ng/ml (median 22.6 months, 95%CI 17.9 – 27.2) vs. AFP > 400 ng/ml (median 13.0 months, 95%CI 1.3 – 24.8), p=0.023.



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