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ORIGINAL RESEARCH

A Prospective Phase II Study of Safety and Efficacy of Sorafenib Followed by ^{90}Y Glass Microspheres for Patients with Advanced or Metastatic Hepatocellular Carcinoma

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Purpose: The most common cause of death in advanced/metastatic hepatocellular carcinoma (HCC) is liver failure due to tumor progression. While retrospective studies and meta-analyses of systemic therapy combined with liver-directed therapy have been performed, prospective studies of safety/efficacy of antiangiogenesis followed by intra-arterial therapies are lacking. We tested our hypothesis that sorafenib followed by yttrium 90 glass microspheres (^{90}Y GMs) is safe and that survival outcomes may improve by controlling hepatic tumors.

Methods: We enrolled 38 Child–Pugh A patients with advanced/metastatic HCC. In sum, 34 received sorafenib, followed after 4 weeks by ^{90}Y GMs. Analysis of safety and survival outcomes was performed to assess adverse events, median progression-free survival, and overall survival.

Results: A total of 34 patients were evaluable: 14 (41.2%) with chronic hepatitis, nine (26.5%) with vascular invasion, and eleven (32.4%) with extrahepatic diseases. Safety analysis revealed that the combination therapy was well tolerated. Grade III–IV adverse events comprised fatigue (n=3), diarrhea (n=2), nausea (n=1), vomiting (n=2), hypertension (n=4), thrombocytopenia (n=1), hyperbilirubinemia (n=1), proteinuria (n=1), hyponatremia (n=1), and elevated alanine or aspartate aminotransferase (n=5). Median progression-free and overall survival were 10.4 months (95% CI 5.8–14.4) and 13.2 months (95% CI 7.9–18.9), respectively. Twelve patients (35.3%) achieved partial responses and 16 (47.0%) stable disease. Median duration of sorafenib was 20 (3–90) weeks, and average dose was 622 (466–800) mg daily. Dosimetry showed similar mean doses between planned and delivered calculations to normal liver and tumor:normal liver uptake ratio, with no significant correlation with adverse events at 3 and 6 months post-^{90}Y treatment.

Conclusion: This is the first prospective study to evaluate sorafenib followed by ^{90}Y in patients with advanced HCC. The study validated our hypothesis of safety with encouraging efficacy signals of the sequencing treatment, and provides proof of concept for future combination modalities for patients with advanced or metastatic HCC.

Clinical Trial Registration Number: NCT01900002.

Keywords: HCC, sorafenib, yttrium 90, BCLC, hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) is the second-leading cause of cancer-related mortality worldwide and one of the fastest-growing causes of death in the US.[1,2] Curative treatment options include surgical resection, transplantation, and

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radiofrequency ablation; however, <30% of new HCC patients are eligible for these treatments based on Barcelona Clinic Liver Cancer (BCLC) stages of very early (0) or early (A).[3] A majority of HCC patients initially present with intermediate-stage (BCLC-B) or advanced-stage disease (BCLC-C), and their prognosis remains poor. Transarterial chemoembolization (TACE), transarterial embolization (TAE), and transarterial radioembolization (TARE) using yttrium-90 glass microspheres (^{90}Y GMs) are viable treatment options for patients with BCLC-B HCC. Frontline sorafenib, lenvatinib, atezolizumab plus bevacizumab, and second-line regorafenib, cabozantinib, ramucirumab, nivolumab with and without ipilimumab, and pembrolizumab systemic therapies are the FDA-approved systemic therapy options available for patients with advanced HCC.[4–12] Notably, the most common cause of death in patients with advanced or extrahepatic spread is intrahepatic progression of HCC, resulting in liver failure, even in metastatic disease.[13] However, the role of the combination of systemic and local therapies in advanced/metastatic HCC (BCLC-C) is not well established. Retrospective studies and meta-analyses of sorafenib combined with liver-directed therapy have been performed. However, there are no prospective studies available providing information on the feasibility and efficacy of antiangiogenic therapy followed by intra-arterial therapy in HCC, given the theoretical risk of altering vascularity of HCC tumors, which is necessary for intra-arterial agent delivery. In this single-arm phase II study, we tested our hypothesis that sorafenib followed by ^{90}Y is safe and that HCC survival outcomes may improve by controlling localized liver tumors in advanced/metastatic HCC. Our main study goal was to determine the safety and efficacy of sorafenib followed by ^{90}Y GMs in patients with advanced or metastatic HCC with BCLC C and Child–Pugh A class. We used dosimetry to compare calculated to delivered doses after the application of sorafenib (antiangiogenesis therapy) to normal liver and HCC tumors to predict adverse event (AE) rates and progression-free survival (PFS).

Methods

We conducted a single-arm, single-institution, phase II study to determine the safety and efficacy of sorafenib followed by ^{90}Y GMs in patients with advanced HCC. The study was approved by the University of Texas MD Anderson Cancer Center (Houston, Texas) Institutional Review Board and was deemed compliant with the Declaration of Helsinki. Written informed consent was obtained from each subject. Inclusion criteria were >18 years of age, Eastern Cooperative Oncology Group performance status 0 or 1, histologically or cytologically documented HCC (documentation of original biopsy for diagnosis was acceptable if tumor tissue were unavailable) or clinical diagnosis of HCC by American Association for the Study of Liver Diseases criteria in cirrhotic subjects, and Child–Pugh A.[14] Histological confirmation was mandatory for patients without cirrhosis. Patients were required to have at least one tumor lesion that could be accurately measured on at least one dimension according to the Response Evaluation Criteria in Solid Tumors (RECIST), and the target lesion must not have been previously treated with local therapy (such as radiation therapy, hepatic arterial therapy, TACE, RFA, percutaneous ethanol injection, or cryoablation). Patients who had received local therapy, such as radiation therapy, TAE, TACE, RFA, percutaneous ethanol injection, or cryoablation, were eligible if the previously treated lesions had progressed or recurred and could be identified as target lesions. Local therapy had to have been completed at least 4 weeks prior to the baseline scan. Patients were required to have serum creatinine <1.5× the upper limit of normal and prothrombin time 6 seconds above control. Exclusion criteria were prior ^{90}Y-GM treatment, prior radiation therapy to the liver, prior systemic therapy for HCC (including sorafenib), complete main portal vein thrombosis, tumor replacement of >70% of the total liver volume on the basis of a visual estimation by the investigator or tumor replacement of >50% of the total liver volume in the presence of albumin 3 mg/dL, eligibility for curative treatment (ablation, resection, or transplantation), contraindications to angiography and selective visceral arterial catheterization, any known contraindications to sorafenib, significant gastrointestinal bleeding within 30 days, metastatic brain disease, renal failure requiring dialysis, and any history of symptomatic pulmonary compromise, such as chronic obstructive pulmonary disease.

Study Medication and ^{90}Y-GM Administration

The starting dose of sorafenib was 400 mg twice a day, starting 4 weeks (± 1 week) before ^{90}Y-GM administration. Diagnostic hepatic angiography followed by transarterial injection of technetium-99m macroaggregated albumin (^{99m}TcMAA) was performed within 1 week of

study enrollment for ^{90}Y GM–treatment planning. Embolization of hepaticoenteric arterial branches was performed as per the interventional radiologist's discretion. Patients underwent planar and SPECT/CT imaging after administration of ^{99m}TcMAA for determination of lung shunt fraction and assessment of perfused liver volume intended for ^{90}Y-GM treatment. On a subsequent patient visit, ^{90}Y GMs (TheraSphere) were administered via transarterial infusion into the target territory. All tumors were treated in a single session. Retreatment with ^{90}Y was not allowed. Dosimetry was calculated according to the package insert (https://www.btg-im.com/getattachment/TheraSphere/Products/Indications/TheraSphere-Package-Insert_USA_Rev-14.pdf.aspx) with a target dose to the perfused tissue of 80–150 Gy at the discretion of the treating physician. Patients underwent SPECT/CT post-^{90}Y treatment imaging within 24 hours for qualitative treatment verification.

Dosimetry Methods and Analysis

Three-dimensional distributions of ^{99m}Tc-MAA and ^{90}YGMs within liver tissue were established with cross-sectional SPECT/CT imaging using previously published methods.[15,16] ^{99m}Tc-MAA and ^{90}Y SPECT/CT images were based on iterative reconstruction with attenuation and scatter corrections. The SPECT images were quantified using self-calibration[17] and converted to absorbed-dose maps based on a local-dose deposition algorithm for ^{90}Y.[18,19] Tumors and normal-liver volumes of interest were segmented by an interventional radiologist. An additional criterion for the dosimetric analysis in this work was that patients needed to have at least a single tumor >2.5 cm in size, due to the spatial resolution of ^{90}YSPECT. The largest eligible tumors were selected from each patient, and the number of tumors per patient was limited to three in order to minimize any bias in the results.

Assessment

The duration of each cycle was 4 weeks. During the study period, patients underwent clinical and laboratory evaluations every 4 weeks to determine the safety of the treatment. Tumor evaluations were performed initially after 12 weeks and then every 8 weeks either by magnetic resonance or computer tomography scans. We used RECIST 1.1[20] to assess response to treatment.

Statistical Methods and Analysis

The primary end point of this study was the safety of the combination of sorafenib and ^{90}Y GMs and rate of AEs (NCI-CTCAE version 5.0) for the first ten patients, and the protocol was amended to be extended to 40 patients with the primary end point of PFS. The secondary end points were overall survival (OS) and time to radiographic progression (TTRP). We employed Bayesian methods[21,22] to monitor toxicity and futility. Categorical variables are presented as frequencies, percentages, and 95% CIs, and continuous variables are summarized with descriptive statistics. PFS duration was calculated as the period from the study-registration date to the date of disease progression or death, whichever occurred first, or to the date of last follow-up for patients who were alive without disease progression. The TTRP was calculated as the period from the study-registration date to the date of radiographic disease progression. OS duration was calculated as the period from the date of study registration to the date of death or last follow-up for patients who were alive at the time of data collection. The Kaplan–Meier method was used to estimate the probability of survival, and the log rank-test was used to compare survival between subgroups of patients. SAS 9.4 (SAS Institute, Cary, NC, USA) and S-Plus 8.2 (Tibco, Palo Alto, CA, USA) were used for statistical analysis.

Results

Patient Characteristics

Among 40 patients assessed for eligibility, two declined therapy and four patients were ineligible for ^{90}Y-GM treatment, the latter receiving sorafenib only. A total of 34 patients received both sorafenib and 90Y GMs. In sum, 25 (73.5%) were male, 16 (47.0%) Caucasian, 20 (58.8%) had Eastern Cooperative Oncology Group performance status 1, 20 (58.8%) did not have chronic hepatitis, 20 (58.8%) had metabolic syndrome, and 22 (64.7%) had evidence of cirrhosis. Most patients (28, 82.3%) had multifocal tumors, 27 (79.4%) had ≤50% tumor involvement of the liver based on visual assessment, four (11.8%) metastasis, and 27 (79.4%) AFP ≥400 ng/mL at baseline. Patients' demographics and clinicopathological characteristics are shown in Table 1.

Treatment Details

The median duration of sorafenib treatment was 20 (3–90) weeks, and the average dose was 622 (466–800 mg) daily. Fifteen patients (44.1%) eventually discontinued sorafenib

Table 1 Baseline demographic and clinicopathological characteristics of patients (n=34)

		n
Sex	Female Male	9 (26.5%) 25 (73.5%)
Ethnicity	Asian African American Hispanic Missing Caucasian	4 (11.8%) 1 (2.9%) 5 (14.7%) 8 (23.5%) 16 (47.1%)
Pathology	Clear cell Moderately differentiated Moderately to poorly differentiated No biopsy Not stated Poorly differentiated Well differentiated Well to moderately differentiated	1 (2.9%) 12 (35.3%) 1 (2.9%) 11 (32.4%) 3 (8.8%) 2 (5.9%) 1 (2.9%) 3 (8.8%)
Hepatitis	Hepatitis B only Hepatitis B and C coinfection Hepatitis C only No virus infection	3 (8.8%) 4 (11.8%) 7 (20.6%) 20 (58.8%)
Smoking	Missing No Yes	2 (5.9%) 20 (58.8%) 12 (35.3%)
History of alcohol abuse	Missing No Yes	1 (2.9%) 15 (44.1%) 18 (52.9%)
Family history of cancer	Missing No Yes	1 (2.9%) 17 (50%) 16 (47.1%)
Family history of HCC	Missing No Yes	2 (5.9%) 31 (91.2%) 1 (2.9%)
History of cancer	No Yes	32 (94.1%) 2 (5.9%)
Hypertension	No Yes	7 (20.6%) 27 (79.4%)
Diabetes	No Yes	15 (44.1%) 19 (55.9%)
Hemochromatosis	No Yes	33 (97.1%) 1 (2.9%)
Autoimmune hepatitis	No	34 (100%)
Nonalcoholic fatty-liver disease	No Yes	29 (85.3%) 5 (14.7%)
Steatosis	No Yes	25 (73.5%) 9 (26.5%)
Evidence of cirrhosis	No Yes	12 (35.3%) 22 (64.7%)
Metabolic syndrome	No Yes	14 (41.2%) 20 (58.8%)
ECOG	0 1	14 (41.2%) 20 (58.8%)
Vascular invasion	No Yes	25 (73.5%) 9 (26.5%)
Portal vein thrombosis	No Yes	26 (76.5%) 8 (23.5%)
Number of nodules	1 2–3 >3	6 (17.6%) 8 (23.5%) 20 (58.8%)
Tumor nodularity	Multinodular Uninodular	28 (82.4%) 6 (17.6%)
Tumor volume	≤50% >50%	27 (79.4%) 7 (20.6%)
Metastasis	None Present	30 (88.2%) 4 (11.8%)
Lymph-node disease	None Present	27 (79.4%) 7 (20.6%)
Encephalopathy	Grade 1–2 None	1 (2.9%) 33 (97.1%)
Ascites	None Slight	30 (88.2%) 4 (11.8%)
Prior treatment	Local therapy (chemoembolization) No therapy Surgery or transplant	4 (11.8%) 28 (82.4%) 2 (5.9%)
Child–Pugh grade	A B	33 (97.1%) 1 (2.9%)

(*Continued*)

Table 1 (Continued).

		n
TNM	Stage I Stage II Stage IIIA Stage IIIB Stage IVA Stage IVB	4 (11.8%) 4 (11.8%) 11 (32.4%) 5 (14.7%) 6 (17.6%) 4 (11.8%)
CLIP	Stage 0–2 Stage 3 Stage 4–6	28 (82.4%) 5 (14.7%) 1 (2.9%)
Okuda	Stage I Stage II Stage III	23 (67.6%) 11 (32.4%) 0 (0%)
INR, Child–Pugh	1.7	34 (100%)
Albumin, Child–Pugh	2.8–3.5 g/dL >3.5 g/dL	4 (11.8%) 30 (88.2%)
Albumin, Okuda	>3 g/dL 3 g/dL	33 (97.1%) 1 (2.9%)
Bilirubin, Child–Pugh	2 mg/dL	34 (100%)
Bilirubin, Okuda	3 mg/dL	34 (100%)
AFP, CLIP	<400 ≥400	27 (79.4%) 7 (20.6%)
	n	**Mean ± SD, median (range)**
BMI	34	28.65±4.06, 27.86 (21.44–39.05)
Age at study enrollment	34	66.71±8.5, 66.5 (42–82)
Tumor size (cm)	34	8.85±4.7, 8.6 (2.3–21.3)

Abbreviations: CLIP, Cancer of the Liver Italian Program; INR, international normalized ratio; TNM, tumor–node–metastasis; ECOG, Eastern Cooperative Oncology Group; BMI, body-mass index.

due to disease progression, and 23 (67.6%) underwent dose reductions due to AEs (Supplementary Table 1).

A total of 34 patients were treated with ^{90}Y GMs: ten (29.4%) had whole-liver treatment, eleven (32.4%) lobar, eight (23.5%) lobar and concurrent contralateral segmental treatment, and five (14.7%) two or three segmental treatments. Four patients were excluded after diagnostic angiography for lack of tumor vascularity, gross arterial portal shunt with poor tumor enhancement, elevation of bilirubin, or noncompliance. The median hepatopulmonary shunt was 8.9% (3.3%–19%). The median period between diagnostic angiography and ^{90}Y radioembolization was 22 (10–41) days.

Toxicity Analysis

Grade III–IV AEs from the combination of sorafenib and ^{90}Y GMs comprised fatigue (n=3), diarrhea (n=2), nausea (n=1), vomiting (n=2), hypertension (n=4), thrombocytopenia (n=1), hyperbilirubinemia (n=1), proteinuria (n=1), hyponatremia (n=1), and elevated alanine or aspartate aminotransferase (n=5). Table 2 summarizes the AEs.

Response Analysis

Of the 34 patients who received both sorafenib and ^{90}Y GMs, 12 (35.3%) experienced partial response, 16 (47.0%) had stable disease, and four (11.8%) experienced disease progression on restaging CT at week 16 according to RECIST 1.1, while two (5.9%) came off the study due to toxicity. There was no complete response. Of all 38 patients (including the four who received sorafenib only), 12 (31.6%), 17 (44.7%), and four (10.5%) had partial response, stable disease, and disease progression, respectively, while five (13.2%) came off the study due to toxicity. Table 3 summarizes the responses.

Survival Outcomes

A total of 33 of the 34 patients who received both sorafenib and 90Y GMs had PFS events (disease progression or death, whichever occurred first). Median PFS was 10.3 (95% CI 5.8–14.4) months (Figure 1). Of 38 patients who received sorafenib only or both sorafenib and ^{90}Y GMs, 35 had known PFS events. Median PFS was 10.4 (95% CI 5.8–14.4) months. Log-rank tests indicated that PFS was significantly associated with hepatitis status (p=0.002), metabolic syndrome (p=0.044), portal vein thrombosis (p=0.028), number of nodules or tumor morphology (p=0.022), and metastatic status (p=0.015; Table 4). In sum 32 of the 34 patients died, with an estimated median OS of 13.2 (95% CI 7.9–18.9) months (Figure 2). The median OS of the 38 patients who received sorafenib only or both sorafenib and ^{90}Y GMs was 13.9 (95% CI 10.8–18.9) months. Log-rank tests indicated that OS was significantly associated with tumor nodularity (p=0.041), hepatitis status (p=0.010), and evidence of cirrhosis (p=0.005; Table 5). Table 6 presents the estimated median TTRP and 1- and 2-year PFS probability for 34 patients. The estimated median TTRP was 10.4 months (95% CI 5.8–18.8) months in both the 34 patients who received both sorafenib and ^{90}Y GMs and the 38 who received sorafenib only or both

Table 2 Adverse events

	Toxicity grade, n (%)		
	1–2	3	4
Constitutional events			
Fever without neutropenia	4 (11.8)	0	0
Fatigue	10 (29.4)	3 (8.8)	0
Weight Loss	5 (14.7)	1 (2.9)	0
Gastrointestinal events			
Anorexia	8 (23.5)	0	0
Nausea	11 (32.4)	1 (2.9)	0
Vomiting	3 (8.8)	2 (5.9)	0
Constipation	2 (5.9)	0	0
Diarrhea	12 (35.3)	2 (5.9)	0
Dermatological events			
Hyperhidrosis	2 (5.9)	0	0
Alopecia	3 (8.8)	0	0
Dry skin	3 (8.8)	0	0
Rash, acneiform	3 (8.8)	0	0
Rash, maculopapular	5 (14.7)	0	0
Palmar–plantar erythrodysesthesia	6 (17.6)	1 (2.9)	0
Skin ulceration	1 (2.9)	0	0
Gastrointestinal			
Nosebleed	1 (2.9)	0	0
Duodenal fistula	1 (2.9)	0	0
Bloating	2 (5.9)	0	0
Abdominal pain	3 (8.8)	0	0
Other			
Anemia	2 (5.9)	0	0
Elevated alanine aminotransferase	6 (17.6)	2 (5.9)	0
Elevated alkaline phosphatase	10 (29.4)	0	0
Elevated aspartate aminotransferase	6 (17.6)	3 (8.8)	1 (2.9)
Hyperbilirubinemia	10 (29.4)	1 (2.9)	0
Hyponatremia	0	1 (2.9)	0
Dry mouth	1 (2.9)	0	0
Hypertension	7 (20.6)	4 (11.8)	0
Hypomagnesemia	5 (14.7)	0	0
Elevated creatinine	1 (2.9)	0	0
Proteinuria	3 (8.8)	1 (2.9)	0
Decreased white blood cells (leukopenia)	1 (2.9)	0	0
Hypophosphatemia	0	1 (2.9)	0
Elevated INR	2 (5.9)	0	0
Hypocalcemia	1 (2.9)	0	0
Hypoalbuminemia	4 (11.8)	0	0
Neutropenia	5 (14.7)	0	0
Thrombocytopenia	8 (23.5)	1 (2.9)	0
Mucositis	0	1 (2.9)	0
Hoarseness of voice	2 (5.9)	0	0
Thromboembolic event	1 (2.9)	0	0
Injury, poisoning and procedural complications (other)	1 (2.9)	0	0
Cough	2 (5.9)	0	0

(*Continued*)

Table 2 (Continued).

	Toxicity grade, n (%)		
	1–2	3	4
Encephalopathy	0	1 (2.9)	0
Headache	3 (8.8)	0	0
Vertigo	1 (2.9)	0	0
Sore throat	1 (2.9)	0	0
Peripheral sensory neuropathy	2 (5.9)	0	0
Dysgeusia	3 (8.8)	0	0
Neoplasms — benign, malignant, and unspecified*	1 (2.9)	0	0
Investigations (other)	2 (5.9)	0	0
Skin and subcutaneous tissue disorders (other)	1 (2.9)	0	0

Note: *Melanoma (right upper skin lesion).
Abbreviation: INR, international normalized ratio.

Table 3 Responses in 34 patients who received both sorafenib and ^{90}Y

		n
CT at week 16	Off-study	2 (5.8%)
	PD	4 (11.8%)
	PR	12 (35.3%)
	SD	16 (47.1%)

Abbreviations: CT, computed tomography; PD, progression of disease; PR, partial response; SD, stable disease.

sorafenib and ^{90}Y GMs. Log-rank tests indicated that TTRP was significantly associated with hepatitis status (p=0.036), BCLC or TNM cancer stage (p=0.041 and 0.023), portal vein thrombosis (p=0.047), and metastasis (p=0.008). Supplementary Tables 2–4 present Cox model results and HRs for PFS, OS, and TTRP.

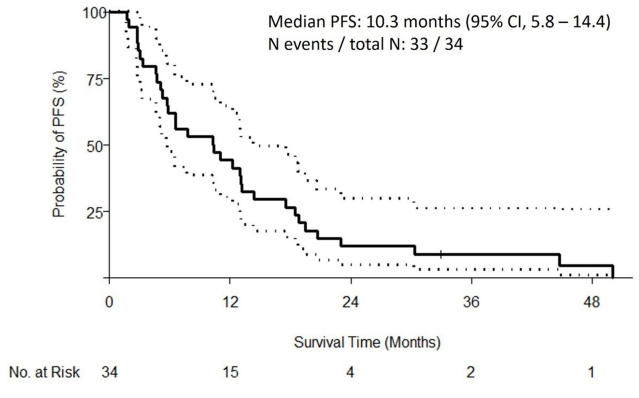

Figure 1 Progression-free survival (PFS).

Dosimetry Analysis

There was a total of 53 tumors from 34 patients for dosimetry analysis in this study. Thirteen patients were multitumor cases, with seven having two tumors and six having three. Tumors of 1–2.5 cm in size were segmented and included as nontarget tumors.

The population median treated-liver mean dose was similar between planned (120 [85–145] Gy) and delivered (115 [84–140] Gy) calculations. The population-averaged mean dose to normal liver was estimated at 80.9 Gy for planning MAA, similar to the posttreatment ^{90}Y SPECT/CT estimate of 84.6 Gy. AE grades for bilirubin, albumin, and ascites (AE criteria typically related to radioembolization) were evaluated at baseline and at 3 and 6 months postradioembolization. No statistically significant correlation was observed among mean absorbed doses to normal liver.

The tumor:normal-liver uptake ratio showed similar medians of 2.3 (0.3–8.4) and 2.1 (0.7–6.9) in planned ^{99m}Tc-MAA and delivered ^{90}Y-GM images; however, paired differences showed a wide 95% CI: −3 to 4. The population-averaged mean dose to tumors was estimated at 192 Gy, with median doses of 168 vs 144 Gy between responding vs nonresponding tumor subgroups. Higher median tumor-absorbed doses led to RECIST response, but this association was not statistically significant. Improved concordance between planned and delivered estimates of mean dose to tumors was observed when delivery catheters were within 1 cm and when a single (or >80% dominant) lesion was present.[16]

Table 4 Log-rank comparison of PFS among subgroups

		n	Event	Median PFS (95% CI)	1-year PFS (95% CI)	2-year PFS (95% CI)	*p*
	All patients	34	33	10.32 (5.78–14.36)	0.441 (0.302, 0.644)	0.118 (0.047, 0.295)	
Sex	Female	9	9	12.25 (5.72, NA)	0.556 (0.31, 0.997)	0.222 (0.065, 0.754)	
	Male	25	24	10.25 (5.22, 14.36)	0.4 (0.247, 0.646)	0.08 (0.021, 0.302)	0.175
Pathology	Missing	14	14	9.07 (5.72, 18.79)	0.357 (0.177, 0.721)		
	Poor	3	3	13.14 (3.29, NA)	0.667 (0.3, 1)	0.333 (0.067, 1)	
	Good/moderate	17	16	10.25 (4.66, 23.03)	0.471 (0.284, 0.779)	0.176 (0.063, 0.493)	0.296
Child–Pugh	A	33	32	10.25 (5.72, 14.36)	0.424 (0.285, 0.631)	0.121 (0.048, 0.304)	
	B	1	1	19.48 (NA, NA)	1 (1, 1)		0.591
BCLC	Stage B	9	9	14.36 (7.75, NA)	0.667 (0.42, 1)	0.222 (0.065, 0.754)	
	Stage C	25	24	6.54 (5.22, 13.14)	0.36 (0.213, 0.607)	0.08 (0.021, 0.302)	0.375
CLIP	Stage 0–2	28	27	11.32 (5.78, 18.5)	0.5 (0.345, 0.724)	0.143 (0.058, 0.354)	
	Stage 3	5	5	10.25 (3.06, NA)	0.2 (0.035, 1)		
	Stage 4–6	1	1	4.63 (NA, NA)			0.193
Okuda	Stage I	23	23	7.75 (5.72, 18.79)	0.435 (0.273, 0.693)	0.13 (0.045, 0.375)	
	Stage II	11	10	11.07 (5.03, NA)	0.455 (0.238, 0.868)	0.091 (0.014, 0.589)	0.916
AFP, CLIP	<400	27	26	11.07 (6.54, 18.5)	0.481 (0.326, 0.712)	0.148 (0.06, 0.366)	
	≥400	7	7	4.63 (2.76, NA)	0.286 (0.089, 0.922)		0.066
TNM	Stage I	4	4	22.36 (13.14, NA)	1 (1, 1)	0.5 (0.188, 1)	
	Stage II	4	4	9.4 (2.76, NA)	0.5 (0.188, 1)		
	Stage IIIA	11	11	12.98 (7.75, NA)	0.545 (0.318, 0.936)		0.114
	Stage IIIB	5	4	11.07 (5.22, NA)	0.4 (0.137, 1)	0.2 (0.035, 1)	
	Stage IVA	6	6	4.16 (3.06, NA)	0.167 (0.028, 0.997)	0.167 (0.028, 0.997)	
	Stage IVB	4	4	5.21 (1.71, NA)			
Hepatitis	Hepatitis B only	3	2	17.54 (5.78, NA)	0.667 (0.3, 1)	0.333 (0.067, 1)	0.002
	Hepatitis B and C coinfection	4	4	2.91 (2.73, NA)			
	Hepatitis C only	7	7	5.47 (5.03, NA)	0.167 (0.028, 0.997)		
	No virus infection	20	20	13.01 (10.38, 20.66)	0.6 (0.42, 0.858)	0.15 (0.053, 0.426)	
Smoking	Missing	2	1	17.89 (2.76, NA)	0.5 (0.125, 1)	0.5 (0.125, 1)	0.62
	No	20	20	6.16 (4.66, 18.5)	0.35 (0.193, 0.636)	0.15 (0.053, 0.426)	
	Yes	12	12	13.01 (7.75, NA)	0.583 (0.362, 0.941)		
Alcohol abuse	Missing	1	1	2.76 (NA, NA)			0.04
	No	15	14	10.38 (4.66, 23.03)	0.4 (0.215, 0.743)	0.133 (0.037, 0.484)	
	Yes	18	18	11.65 (5.78, 18.79)	0.5 (0.315, 0.794)	0.111 (0.03, 0.41)	
History of cancer	No	32	31	10.73 (5.72, 17.54)	0.469 (0.324, 0.678)	0.125 (0.05, 0.313)	0.328
	Yes	2	2	6.16 (5.78, NA)			

(*Continued*)

Table 4 (Continued).

		n	Event	Median PFS (95% CI)	1-year PFS (95% CI)	2-year PFS (95% CI)	p
Family history of HCC	Missing	2	2	5.22 (4.66, NA)			0.013
	No	31	30	11.07 (6.54, 18.5)	0.484 (0.336, 0.696)	0.129 (0.052, 0.322)	
	Yes	1	1	2.76 (NA, NA)			
Hypertension	No	7	7	6.54 (5.22, NA)			0.054
	Yes	27	26	12.98 (5.72, 18.79)	0.556 (0.396, 0.778)	0.148 (0.06, 0.366)	
Nonalcoholic fatty-liver disease	No	29	29	10.25 (5.78, 17.54)	0.483 (0.331, 0.704)	0.103 (0.035, 0.302)	0.938
	Yes	5	4	10.38 (4.66, NA)	0.2 (0.035, 1)	0.2 (0.035, 1)	
Steatosis	No	25	25	10.25 (5.78, 17.54)	0.44 (0.283, 0.685)	0.08 (0.021, 0.302)	0.667
	Yes	9	8	11.07 (3.06, NA)	0.444 (0.214, 0.923)	0.222 (0.065, 0.754)	
Evidence of cirrhosis	No	12	11	11.65 (5.78, NA)	0.5 (0.284, 0.88)	0.25 (0.094, 0.666)	0.09
	Yes	22	22	9.07 (5.03, 17.54)	0.409 (0.248, 0.676)	0.045 (0.007, 0.308)	
Metabolic syndrome	No	14	14	6.16 (3.29, 18.79)	0.214 (0.079, 0.584)		0.044
	Yes	20	19	13.01 (6.54, 20.66)	0.6 (0.42, 0.858)	0.2 (0.083, 0.481)	
Portal vein thrombosis	No	26	25	12.61 (6.54, 19.48)	0.538 (0.377, 0.769)	0.154 (0.062, 0.379)	0.028
	Yes	8	8	4.93 (3.06, NA)	0.125 (0.02, 0.782)		
Number of nodules	1	6	6	22.36 (13.14, NA)	0.833 (0.583, 1)	0.5 (0.225, 1)	0.022
	2–3	8	8	5.78 (4.66, NA)	0.25 (0.075, 0.83)		
	>3	20	19	9 (5.72, 18.79)	0.4 (0.234, 0.684)	0.05 (0.007, 0.338)	
Tumor nodularity	Multinodular	28	27	7.15 (5.22, 13.04)	0.357 (0.217, 0.587)	0.036 (0.005, 0.245)	0.032
	Uninodular	6	6	22.36 (13.14, NA)	0.833 (0.583, 1)	0.5 (0.225, 1)	
Tumor volume	≤50%	27	27	7.75 (5.72, 14.36)	0.444 (0.292, 0.678)	0.111 (0.038, 0.323)	0.728
	>50%	7	6	11.07 (4.63, NA)	0.429 (0.182, 1)	0.143 (0.023, 0.877)	
Tumor morphology	Massive/extension ≥50%	7	6	11.07 (4.63, NA)	0.429 (0.182, 1)	0.143 (0.023, 0.877)	0.049
	Multinodular and ≤50%	21	21	6.54 (5.03, 13.04)	0.333 (0.182, 0.61)		
	Uninodular and ≤50%	6	6	22.36 (13.14, NA)	0.833 (0.583, 1)	0.5 (0.225, 1)	
Metastasis	None	30	29	11.66 (6.54, 18.5)	0.5 (0.35, 0.715)	0.133 (0.054, 0.332)	0.015
	Present	4	4	5.21 (1.71, NA)			
Prior treatment	Local therapy (chemo/ radioembolization)	4	4	9.84 (2.83, NA)	0.5 (0.188, 1)		0.303
	No therapy	28	27	10.73 (5.72, 18.5)	0.464 (0.312, 0.691)	0.143 (0.058, 0.354)	
	Surgery or transplant	2	2	4.8 (3.06, NA)			
ECOG	0	14	14	7.15 (4.66, 30.35)	0.429 (0.234, 0.785)	0.143 (0.04, 0.515)	0.636
	1	20	19	10.73 (5.72, 18.79)	0.45 (0.277, 0.731)	0.1 (0.027, 0.372)	
Vascular invasion	No	25	25	12.25 (6.54, 18.5)	0.52 (0.357, 0.758)	0.12 (0.042, 0.347)	0.436
	Yes	9	8	5.22 (3.06, NA)	0.222 (0.065, 0.754)	0.111 (0.018, 0.705)	

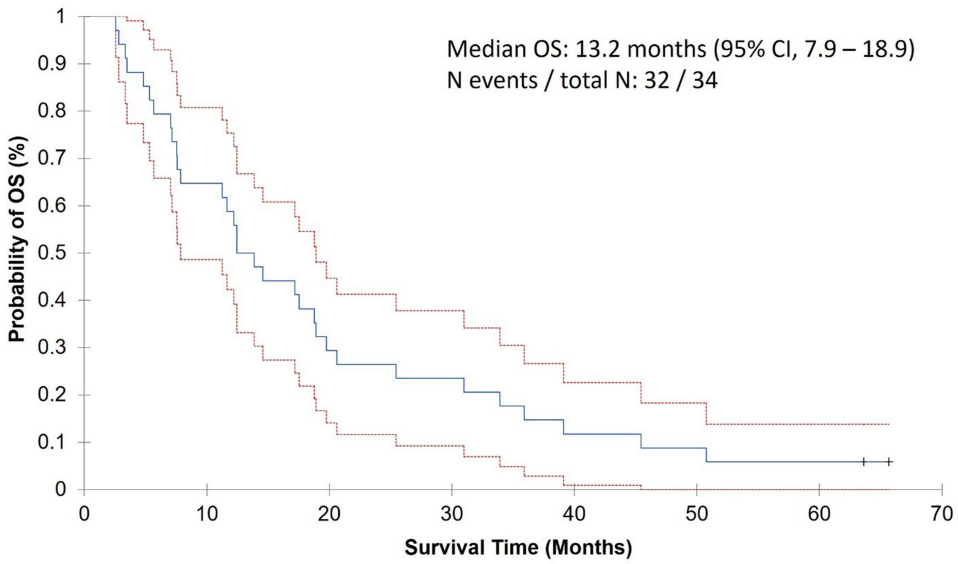

Figure 2 Overall survival (OS).

Discussion

Putative benefit from a combination of systemic antiangiogenesis therapy followed by liver-directed therapy including ^{90}Y GMs or TACE has not been validated in advanced or metastatic HCC. This is the first prospective study to evaluate sorafenib followed by ^{90}Y GMs in patients with advanced or metastatic HCC (BCLC stage C) with a prospective radiation-dosing plan and concurrent sorafenib and ^{90}Y GMs. The results of this study suggest that systemic antiangiogenesis (sorafenib) followed by intra-arterial therapy (^{90}Y GMs) in patients with advanced/metastatic HCC is safe. This study also suggests that the addition of ^{90}Y to systemic therapy could potentially provide survival benefits, with increased PFS and OS in patients with advanced HCC, although it was not a randomized clinical trial.

Patients enrolled in this study were initially categorized as having advanced disease (BCLC C) at presentation. The landmark randomized SHARP trial established the role of frontline therapy with sorafenib in advanced-HCC patients and indicated median OS of 10.7 months in its sorafenib arm (versus 7.9 months in the placebo arm) and median PFS of 5.5 months.[9] The use of ^{90}Y GMs in combination with systemic therapy for advanced HCC is still investigational, and the current study presents the safety and clinical benefit from sequencing this combination therapy in patients with advanced HCC. The principal-outcome measures of this study included median PFS of 10.4 months. This is a remarkable PFS benefit when compared to that shown with sorafenib in the SHARP study (5.5 months) and other systemic therapy regimens, including the new standard-of-care therapy of atezolizumab–bevacizumab, which has a median PFS of 6.8 months.[7] Median OS in 34 patients who received both sorafenib and ^{90}Y was 13.2 months, and that in 38 patients who either received sorafenib only or both sorafenib and ^{90}Y was 13.9 months. This observed median OS is longer than the OS of 10.7 months demonstrated in the SHARP trial, which included patients with BCLC B. The REFLECT study showed a median OS of 12.3 months, CheckMate 459 14.7 months, and IMbrave150 13.2 months in the sorafenib arm, including patients with BCLC A (IMbrave150) and BCLC B.[23–25] The DOSISPHERE trial showed OS of 26.6 months in its personalized dosimetry group and 10.7 months in the standard dosimetry group. However, this study included only patients with unresectable but locally advanced disease and excluded those with extrahepatic and metastatic diseases.[26] In this regard, our study suggests encouraging OS and potential survival benefit in patients with advanced HCC, as we included only patients with BCLC C. More importantly, sorafenib followed by ^{90}Y did not lead to alterations in tumor vascularity, which could have manifested on lower delivered ^{90}Y dose than calculated ^{90}Y dose. Additionally, our team and others have been adopting personalized dosimetry methodology as a new standard approach to ^{90}Y planning, and have found significant improvements in response rates in HCC. Therefore, future combined local and systemic therapy trials in HCC should follow a personalized dosimetry approach.

Notably, the role of local therapies for HCC has been established in intermediate-stage HCC (BCLC-B);[27] however,

Table 5 Log-rank comparison of OS among subgroups

		n	Events	Median OS (95% CI)	1-year OS (95% CI)	2-year OS (95% CI)	*p*
	All patients	34	32	12.25 (7.75, 19.48)	0.58 (0.435, 0.775)	0.244 (0.134, 0.446)	
Sex	Female	9	9	19.48 (12.25, NA)	0.778 (0.549, 1)	0.444 (0.214, 0.923)	0.055
	Male	25	23	12.02 (7.46, 18.63)	0.507 (0.342, 0.751)	0.169 (0.069, 0.412)	
Pathology	Missing	14	13	12.02 (7.75, NA)	0.55 (0.337, 0.897)	0.079 (0.012, 0.515)	0.167
	Poor	3	3	17.28 (3.29, NA)	0.667 (0.3, 1)	0.333 (0.067, 1)	
	Good/moderate	17	16	16.92 (7.46, 38.53)	0.588 (0.395, 0.876)	0.353 (0.185, 0.672)	
Child–Pugh	A	33	31	12.25 (7.75, 18.63)	0.567 (0.419, 0.767)	0.252 (0.139, 0.459)	0.818
	B	1	1	19.48 (NA, NA)	1 (1, 1)		
CLIP	Stage 0–2	28	26	12.25 (7.46, 25.07)	0.6 (0.442, 0.815)	0.3 (0.168, 0.535)	0.689
	Stage 3	5	5	11.47 (11.07, NA)	0.4 (0.137, 1)		
	Stage 4–6	1	1	13.67 (NA, NA)	1 (1, 1)		
Okuda	Stage I	23	22	14.36 (7.75, 30.55)	0.598 (0.426, 0.841)	0.322 (0.176, 0.592)	0.337
	Stage II	11	10	12.25 (7.42, NA)	0.545 (0.318, 0.936)	0.091 (0.014, 0.589)	
AFP, CLIP	<400	27	26	12.25 (7.75, 25.07)	0.593 (0.433, 0.81)	0.296 (0.166, 0.53)	0.283
	≥400	7	6	13.67 (3.42, NA)	0.536 (0.257, 1)		
TNM	Stage I	4	4	26.33 (14.36, NA)	1 (1, 1)	0.5 (0.188, 1)	0.777
	Stage II	4	4	9.86 (2.76, NA)	0.5 (0.188, 1)	0.25 (0.046, 1)	
	Stage IIIA	11	11	12.25 (7.75, NA)	0.636 (0.407, 0.995)	0.182 (0.052, 0.637)	
	Stage IIIB	5	4	11.07 (5.22, NA)	0.4 (0.137, 1)	0.2 (0.035, 1)	
	Stage IVA	6	6	9.44 (7.06, NA)	0.333 (0.108, 1)	0.167 (0.028, 0.997)	
	Stage IVB	4	3	13.67 (2.53, NA)	0.75 (0.426, 1)	0.375 (0.084, 1)	
Hepatitis	Hepatitis B only	3	1	NA (5.58, NA)	0.667 (0.3, 1)	0.667 (0.3, 1)	0.01
	Hepatitis B and C coinfection	4	4	7.44 (2.76, NA)			
	Hepatitis C only	7	7	7.41 (5.22, NA)	0.333 (0.108, 1)		
	No virus infection	20	20	17.89 (13.67, 33.44)	0.8 (0.643, 0.996)	0.35 (0.193, 0.636)	
Smoking	Missing	2	1	17.89 (2.76, NA)	0.5 (0.125, 1)	0.5 (0.125, 1)	0.756
	No	20	19	12.25 (7.06, 35.38)	0.589 (0.406, 0.855)	0.268 (0.127, 0.565)	
	Yes	12	12	13.3 (7.75, NA)	0.583 (0.362, 0.941)	0.167 (0.047, 0.591)	
Alcohol abuse	Missing	1	1	2.76 (NA, NA)			<0.001
	No	15	14	12.25 (11.07, NA)	0.6 (0.397, 0.907)	0.267 (0.115, 0.617)	
	Yes	18	17	14.36 (7.46, 25.07)	0.595 (0.403, 0.88)	0.238 (0.101, 0.559)	
History of cancer	No	32	31	12.96 (11.07, 19.48)	0.594 (0.446, 0.791)	0.25 (0.137, 0.456)	0.615
	Yes	2	1	7.46 (NA, NA)			

(*Continued*)

Table 5 (Continued).

		n	Events	Median OS (95% CI)	1-year OS (95% CI)	2-year OS (95% CI)	p
Family history of HCC	Missing	2	1	6.93 (NA, NA)			<0.001
	No	31	30	13.67 (11.07, 20.3)	0.613 (0.463, 0.811)	0.258 (0.142, 0.469)	
	Yes	1	1	2.76 (NA, NA)			
Hypertension	No	7	6	11.47 (7.75, NA)	0.343 (0.112, 1)	0.171 (0.029, 1)	0.688
	Yes	27	26	13.67 (7.46, 20.3)	0.63 (0.471, 0.841)	0.259 (0.137, 0.49)	
Nonalcoholic fatty liver disease	No	29	28	14.36 (7.75, 20.3)	0.613 (0.457, 0.822)	0.252 (0.133, 0.478)	0.534
	Yes	5	4	11.07 (6.93, NA)	0.4 (0.137, 1)	0.2 (0.035, 1)	
Steatosis	No	25	24	13.67 (7.75, 25.07)	0.63 (0.464, 0.855)	0.252 (0.126, 0.503)	0.956
	Yes	9	8	11.47 (5.22, NA)	0.444 (0.214, 0.923)	0.222 (0.065, 0.754)	
Evidence of cirrhosis	No	12	10	25.07 (16.92, NA)	0.917 (0.773, 1)	0.55 (0.322, 0.938)	0.003
	Yes	22	22	9.41 (7.06, 18.5)	0.409 (0.248, 0.676)	0.091 (0.024, 0.341)	
Metabolic syndrome	No	14	13	7.75 (5.58, NA)	0.321 (0.145, 0.712)	0.161 (0.045, 0.568)	0.1
	Yes	20	19	15.82 (12.25, 33.44)	0.75 (0.582, 0.966)	0.3 (0.154, 0.586)	
Portal vein thrombosis	No	26	24	14.36 (7.75, 30.55)	0.646 (0.484, 0.862)	0.323 (0.183, 0.57)	0.086
	Yes	8	8	11.27 (7.42, NA)	0.375 (0.153, 0.917)		
Number of nodules	1	6	6	26.33 (14.36, NA)	0.833 (0.583, 1)	0.5 (0.225, 1)	0.124
	2–3	8	8	12.14 (7.06, NA)	0.625 (0.365, 1)	0.25 (0.075, 0.83)	
	>3	20	18	11.47 (7.46, 20.3)	0.482 (0.303, 0.768)	0.161 (0.057, 0.452)	
Tumor nodularity	Multinodular	28	26	12.02 (7.46, 18.63)	0.524 (0.366, 0.75)	0.187 (0.085, 0.412)	0.041
	Uninodular	6	6	26.33 (14.36, NA)	0.833 (0.583, 1)	0.5 (0.225, 1)	
Tumor volume	≤50%	27	26	12.25 (7.75, 25.07)	0.583 (0.422, 0.806)	0.272 (0.145, 0.511)	0.771
	>50%	7	6	13.67 (7.42, NA)	0.571 (0.301, 1)	0.143 (0.023, 0.877)	
Tumor morphology	Massive/extension ≥50%	7	6	13.67 (7.42, NA)	0.571 (0.301, 1)	0.143 (0.023, 0.877)	0.121
	Multinodular and ≤50%	21	20	12.02 (7.06, 20.3)	0.508 (0.33, 0.781)	0.203 (0.085, 0.486)	
	Uninodular and ≤50%	6	6	26.33 (14.36, NA)	0.833 (0.583, 1)	0.5 (0.225, 1)	
Metastasis	None	30	29	12.25 (7.75, 19.48)	0.567 (0.414, 0.775)	0.233 (0.122, 0.446)	0.803
	Present	4	3	13.67 (2.53, NA)	0.75 (0.426, 1)	0.375 (0.084, 1)	
Prior treatment	Local therapy (chemo/ radioembolization)	4	4	12.37 (4.76, NA)	0.5 (0.188, 1)		0.677
	No therapy	28	26	12.25 (7.75, 19.48)	0.599 (0.44, 0.814)	0.262 (0.139, 0.494)	
	Surgery or transplant	2	2	25 (11.47, NA)	0.5 (0.125, 1)	0.5 (0.125, 1)	
ECOG	0	14	13	14.36 (7.75, NA)	0.55 (0.337, 0.897)	0.314 (0.14, 0.704)	0.799
	1	20	19	12.25 (7.46, 20.3)	0.6 (0.42, 0.858)	0.2 (0.083, 0.481)	
Vascular invasion	No	25	24	14.36 (7.75, 30.55)	0.632 (0.466, 0.856)	0.295 (0.158, 0.548)	0.442
	Yes	9	8	11.47 (7.42, NA)	0.444 (0.214, 0.923)	0.111 (0.018, 0.705)	

Abbreviations: CLIP, Cancer of the Liver Italian Program; TNM, tumor–node–metastasis; ECOG, Eastern Cooperative Oncology Group; NA, not applicable.

Table 6 Log-rank comparison of time to radiological progression (TTRP) among subgroups

		n	Events	Median TTRP (95% CI)	1-year PD-free rate (95% CI)	2-year PD-free rate (95% CI)	*p*
	All patients	34	22	10.38 (5.78, 18.79)	0.461 (0.298, 0.713)	0.068 (0.011, 0.418)	
Sex	Female	9	5	23.03 (5.72, NA)	0.508 (0.257, 1)		0.509
	Male	25	17	10.38 (5.78, 18.79)	0.457 (0.272, 0.766)	0.065 (0.01, 0.43)	
Pathology	Missing	14	8	10.38 (5.72, NA)	0.363 (0.136, 0.966)		0.777
	Poor	3	1	13.14 (NA, NA)	1 (1, 1)		
	Good/moderate	17	13	10.25 (4.66, NA)	0.438 (0.242, 0.794)	0.11 (0.02, 0.604)	
Child–Pugh	A	33	22	10.25 (5.78, 18.79)	0.437 (0.273, 0.7)	0.055 (0.008, 0.363)	0.195
	B	1	0	NA (NA, NA)	1 (1, 1)		
CLIP	Stage 0–2	28	17	12.98 (6.54, NA)	0.529 (0.348, 0.804)	0.088 (0.015, 0.53)	0.124
	Stage 3	5	4	6.65 (2.73, NA)	0.25 (0.046, 1)		
	Stage 4–6	1	1	4.63 (NA, NA)			
Okuda	Stage I	23	16	10.38 (5.78, 20.66)	0.484 (0.294, 0.797)	0.069 (0.011, 0.454)	0.751
	Stage II	11	6	10.25 (4.63, NA)	0.385 (0.145, 1)		
AFP, CLIP	<400	27	16	10.38 (6.54, NA)	0.486 (0.3, 0.789)	0.093 (0.015, 0.555)	0.148
	≥400	7	6	5.78 (3.06, NA)	0.343 (0.112, 1)		
TNM	Stage I	4	2	21.75 (13.14, NA)	1 (1, 1)	0.5 (0.125, 1)	0.023
	Stage II	4	2	13.04 (6.54, NA)	0.667 (0.3, 1)		
	Stage IIIA	11	8	12.98 (5.72, NA)	0.583 (0.34, 1)		
	Stage IIIB	5	2	18.79 (NA, NA)	0.8 (0.516, 1)		
	Stage IVA	6	4	5.03 (3.06, NA)			
	Stage IVB	4	4	5.21 (1.71, NA)			
Hepatitis	Hepatitis B only	3	2	11.66 (5.78, NA)	0.5 (0.125, 1)		0.036
	Hepatitis B and C coinfection	4	3	3.06 (2.73, NA)			
	Hepatitis C only	7	5	5.72 (5.03, NA)	0.278 (0.054, 1)		
	No virus infection	20	12	13.04 (10.25, NA)	0.599 (0.388, 0.926)	0.114 (0.019, 0.675)	
Smoking	Missing	2	0	NA (NA, NA)			0.736
	No	20	14	6.54 (4.66, NA)	0.293 (0.123, 0.696)	0.098 (0.016, 0.603)	
	Yes	12	8	13.04 (6.54, NA)	0.675 (0.43, 1)		
Alcohol abuse	Missing	1	0	NA (NA, NA)			0.85
	No	15	9	6.54 (4.63, NA)	0.365 (0.159, 0.837)		
	Yes	18	13	13.04 (5.78, NA)	0.529 (0.321, 0.87)	0.088 (0.014, 0.564)	
History of cancer	No	32	20	12.98 (5.72, 20.66)	0.504 (0.332, 0.764)	0.075 (0.012, 0.455)	0.283
	Yes	2	2	6.16 (5.78, NA)			

(*Continued*)

Table 6 (Continued).

		n	Events	Median TTRP (95% CI)	1-year PD-free rate (95% CI)	2-year PD-free rate (95% CI)	*p*
Family history of HCC	Missing	2	2	5.22 (4.66, NA)			0.261
	No	31	20	12.98 (6.54, 20.66)	0.501 (0.329, 0.762)	0.074 (0.012, 0.453)	
	Yes	1	0	NA (NA, NA)			
Hypertension	No	7	4	6.54 (5.78, NA)			0.147
	Yes	27	18	12.98 (5.72, 23.03)	0.555 (0.378, 0.815)	0.082 (0.014, 0.498)	
Nonalcoholic fatty-liver disease	No	29	19	12.98 (6.54, 20.66)	0.527 (0.354, 0.785)	0.078 (0.013, 0.474)	0.082
	Yes	5	3	4.66 (4.66, NA)			
Steatosis	No	25	19	10.38 (5.78, 20.66)	0.446 (0.275, 0.723)	0.074 (0.012, 0.454)	0.695
	Yes	9	3	13.14 (3.06, NA)	0.711 (0.433, 1)		
Evidence of cirrhosis	No	12	9	10.25 (5.72, NA)	0.379 (0.164, 0.873)		0.521
	Yes	22	13	12.98 (5.03, NA)	0.521 (0.32, 0.849)	0.13 (0.024, 0.694)	
Metabolic syndrome	No	14	9	6.54 (5.78, NA)	0.366 (0.152, 0.881)		0.484
	Yes	20	13	12.98 (5.72, NA)	0.521 (0.321, 0.844)	0.13 (0.024, 0.693)	
Portal vein thrombosis	No	26	16	12.98 (6.54, NA)	0.546 (0.361, 0.827)	0.091 (0.015, 0.547)	0.047
	Yes	8	6	4.63 (2.73, NA)	0.194 (0.035, 1)		
Number of nodules	1	6	3	13.14 (13.14, NA)	0.833 (0.583, 1)	0.417 (0.1, 1)	0.085
	2–3	8	7	5.78 (4.66, NA)	0.188 (0.036, 0.976)		
	>3	20	12	12.98 (5.78, NA)	0.503 (0.296, 0.855)		
Tumor nodularity	Multinodular	28	19	10.25 (5.72, 18.79)	0.397 (0.232, 0.68)		0.168
	Uninodular	6	3	13.14 (13.14, NA)	0.833 (0.583, 1)	0.417 (0.1, 1)	
Tumor volume	≤50%	27	18	10.38 (5.78, 23.03)	0.488 (0.311, 0.764)	0.081 (0.013, 0.492)	0.505
	>50%	7	4	10.25 (4.63, NA)	0.312 (0.067, 1)		
Tumor morphology	Massive/extension ≥50%	7	4	10.25 (4.63, NA)	0.312 (0.067, 1)		0.356
	Multinodular and ≤50%	21	15	6.54 (5.72, NA)	0.412 (0.23, 0.735)		
	Uninodular and ≤50%	6	3	13.14 (13.14, NA)	0.833 (0.583, 1)	0.417 (0.1, 1)	
Metastasis	None	30	18	12.98 (6.54, 23.03)	0.544 (0.364, 0.813)	0.081 (0.013, 0.489)	0.008
	Present	4	4	5.21 (1.71, NA)			
Prior treatment	Local therapy (chemo/ radioembolization)	4	4	9.84 (2.83, NA)	0.5 (0.188, 1)		0.259
	No therapy	28	16	10.38 (5.78, NA)	0.493 (0.306, 0.796)	0.094 (0.016, 0.562)	
	Surgery or transplant	2	2	4.8 (3.06, NA)			
ECOG	0	14	8	6.54 (4.66, NA)	0.45 (0.226, 0.898)	0.3 (0.104, 0.863)	0.827
	1	20	14	10.38 (6.54, NA)	0.476 (0.276, 0.821)		
Vascular invasion	No	25	16	12.98 (6.54, NA)	0.545 (0.36, 0.826)	0.091 (0.015, 0.546)	0.057
	Yes	9	6	4.63 (3.06, NA)	0.203 (0.037, 1)		

Abbreviations: CLIP, Cancer of the Liver Italian Program; TNM, tumor–node–metastasis; ECOG, Eastern Cooperative Oncology Group; NA, not applicable.

their role is less clear in advanced-stage HCC (BCLC C), although they can be used for local disease control in patients with adequate liver function and good performance status. Transarterial therapies, such as TACE and TARE (using ^{90}Y GMs), are frequently used for intermediate-stage HCC (BCLC B), with the main goal being local disease control. They are also used as a bridge to downsize HCC tumors for liver transplantation by delivering chemotherapeutic agents with vaso-occlusive materials to the arteries that feed HCC (TACE) or by delivering radioactive microspheres to the vascular territory of HCC (TARE).[28] In TACE, tumor injury is created by occluding the blood supply for hepatic tumors using an almost-exclusive hepatic arterial blood supply to the tumor tissue, as opposed to the main portal vein supply to the normal hepatic parenchyma. However, ^{90}Y GMs are not used for complete occlusion of the arterial supply, since oxygen is still needed for free-radical formation in the tumor tissue for radiation therapy.[29] Therefore, ^{90}Y therapy has a lower incidence of postembolization syndrome than TACE.

Sorafenib has been studied in combination with liver-directed therapy in patients with advanced-stage disease. In a recent meta-analysis of five studies that included two randomized clinical trials, a TACE–sorafenib combination resulted in longer time to progression (combined HR 0.61, 95% CI 0.39–0.95; p=0.031) than TACE alone or TACE plus placebo, with no OS benefit.[30] However, the SORAMIC study — a randomized trial of ^{90}Y radioembolization followed by sorafenib vs sorafenib monotherapy in advanced HCC — did not show OS benefit, with median OS of 12.1 months in the ^{90}Y + sorafenib arm and 11.4 months in the sorafenib arm (HR 1.01, 95% CI 0.81–1.25; p=0.953).[31] In a retrospective multicenter study of 325 patients by Sangro et al, ^{90}Y treatment yielded median OS duration of 10 (95% CI 7.7–10.9) months in BCLC C patients.[32] In a single-center, prospective, longitudinal cohort study of 291 patients by Salem et al, median OS was 7.3 (95% CI 6.5–10.1) in BCLC C patients, and patients with Child–Pugh class A had a median OS of 17.2 (95% CI 14.9–24.0) months.[33] Another single-center, retrospective, longitudinal cohort study of 74 (BCLC B and C) patients treated with ^{90}Y GMs and sorafenib found median OS of 12.4 (95% CI 9.1–15.6) months.[34] Additionally, the SARAH and SIRveNIB trials recently compared the safety and efficacy of ^{90}Y resin microspheres vs sorafenib for advanced-HCC patients.[35,36] Neither study demonstrated OS benefit for ^{90}Y resin microspheres vs sorafenib. Limitations in the ^{90}Y arms included a lack of ^{90}Y treatment in 22% and 29% of patients, respectively, and a lack of prospective radiation-dose planning. Notably, a subset analysis of the SARAH trial examined the relationship between the tumor-absorbed dose and survival, and demonstrated that increased tumor-absorbed doses yielded improved survival.[37] Patients with tumor-absorbed doses >100 Gy vs <100 Gy had significantly improved OS of 14.1 months vs 6.1 months. In addition, the probability of tumor control was directly related to tumor dose with a tumor-control probability of 90% at 150 Gy tumor-absorbed dose. Furthermore, some recent retrospective studies have demonstrated statistically significant difference in the mean tumor doses of responders vs nonresponders using GMs.[18,38,39] Reported tumor-dose thresholds have a wide range, mainly due to dose dependence on the imaging modality, dosimetry technique, and microsphere-specific activity at the time of treatment. For HCC with GMs, mean tumor doses of 342–353 Gy have been reported for responders by some,[26,39] while others have reported the threshold dose for tumor response as 160–220 Gy.[18,38] These dose-threshold values change to around 100 Gy when resin microspheres are used. Finally, as demonstrated in DOSISPHERE, all future studies would benefit from the use of personalized dosimetry for treatment planning.

Although our dosimetry studies confirmed the same trend of ^{90}Y dose–dependent tumor response, this was not statistically significant. However, this could be related to the small number of patients, the use of standard dosimetry, and the concurrent use of systemic therapy. Future studies using personalized dosimetry models in planning and treatment may more accurately determine the vascular effects of systemic therapy and lead to improved outcomes. The importance of dosimetry in ^{90}Y-GM treatments is reflected in recent ^{90}Y-dosimetry consensus publications by international multidisciplinary working groups.[40]

In conclusion, to date, there has been no evidence from prospective studies to suggest the safety or efficacy of anti-angiogenesis followed by intra-arterial therapies, such as ^{90}Y, in HCC. Remarkably, sorafenib pretreatment in our study did not preclude the ^{90}Y-GM procedure on the basis of vascularity changes or vascular injury. This has been the main concern with initiating sorafenib, which is an antiangiogenesis agent, before intra-arterial therapy. This is the first prospective study to illustrate the safety of sorafenib followed by ^{90}Y GMs in advanced HCC. Therefore, it provides proof of concept for future studies of similar sequencing of combined antiangiogenesis and intra-arterial therapies in HCC, including combinations of atezolizumab plus bevacizumab with ^{90}Y GMs or TACE.

Limitations of our study include being a single-institution, single-arm, phase II study, which may have posed institutional and investigator bias, the small sample, and the lack of a

control group. In particular, multivariate analyses were not feasible, due to the low number of patients. This added uncertainty in interpretation of survival-outcome data. However, we would like to highlight that our patients were all selected according to BCLC stage C, including patients with metastatic disease, a group with historically poor survival, yet median PFS was 10.5 months. Notably, the phase III STOP-HCC trial of ^{90}Y followed by sorafenib versus sorafenib alone in unresectable HCC excluded patients with extrahepatic disease (NCT01556490). Therefore, future studies with a larger number of patients are warranted to assess sequential systemic therapy and ^{90}Y in the metastatic disease setting to determine whether it can control local liver tumors, delay liver failure, and thus offer a survival advantage.

Translational Relevance

To date, there have been no published prospective studies of antiangiogenesis therapy followed by intra-arterial therapy in advanced HCC. Therefore, we tested our hypothesis of safety and efficacy of sorafenib followed after 4 weeks by ^{90}Y to better control hepatic tumors and delay deaths related to liver failure. We applied dosimetry methods to confirm similar "planned" to "delivered" ^{90}Y doses. Remarkably, sorafenib pretreatment did not preclude the ^{90}Y procedure based on vascularity changes or vascular injury, which has been the main concern with initiating sorafenib, which is an antiangiogenesis agent, before intra-arterial therapies. This study is the first prospective illustration of the safety of antiangiogenesis and sorafenib followed by ^{90}Y in HCC, and provides proof of concept for future studies of similar sequencing in HCC.

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References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359–386.
2. Mittal S, El-Serag HB. Epidemiology of hepatocellular carcinoma: consider the population. *J Clin Gastroenterol*. 2013;47 Suppl:S2–6.
3. Llovet JM, Di Bisceglie AM, Bruix J, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. *J Natl Cancer Inst*. 2008;100(10):698–711.
4. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med*. 2018;379(1):54–63.
5. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, Phase 3 trial. *Lancet*. 2017;389(10064):56–66.
6. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, Phase 1/2 dose escalation and expansion trial. *The Lancet*. 2017;389(10088):2492–2502.
7. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable Hepatocellular Carcinoma. *N Engl J Med*. 2020;382(20):1894–1905.
8. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet*. 2018;391(10126):1163–1173.
9. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359(4):378–390.
10. Yau T, Kang Y-K, Kim T-Y, et al. Nivolumab (NIVO) + ipilimumab (IPI) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): results from CheckMate 040. *J Clin Oncol*. 2019;37(15_suppl):4012.
11. Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label Phase 2 trial. *Lancet Oncol*. 2018;19(7):940–952.
12. Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20(2):282–296.
13. Couto OF, Dvorchik I, Carr BI. Causes of death in patients with unresectable hepatocellular carcinoma. *Dig Dis Sci*. 2007;52(11):3285–3289.
14. Bruix J, Sherman M; American Association for the Study of Liver D. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011;53(3):1020–1022.
15. Siman W, Mikell JK, Kappadath SC. Practical reconstruction protocol for quantitative (90)Y bremsstrahlung SPECT/CT. *Med Phys*. 2016;43(9):5093.
16. Thomas MA, Mahvash A, Abdelsalam M, Kaseb AO, Kappadath SC. Planning dosimetry for (90) Y radioembolization with glass microspheres: evaluating the fidelity of (99m) Tc-MAA and partition model predictions. *Med Phys*. 2020;7(10):5333–5342.

17. Balagopal A, Kappadath SC. Characterization of (90) Y-SPECT/CT self-calibration approaches on the quantification of voxel-level absorbed doses following (90) Y-microsphere selective internal radiation therapy. *Med Phys*. 2018;45(2):875–883.
18. Kappadath SC, Mikell J, Balagopal A, Baladandayuthapani V, Kaseb A, Mahvash A. Hepatocellular carcinoma tumor dose response after (90) Y-radioembolizationWith glass microspheres using (90) Y-SPECT/CT-BasedVoxel Dosimetry. *Int J Radiat Oncol Biol Phys*. 2018;102(2):451–461.
19. Mikell JK, Mahvash A, Siman W, Mourtada F, Kappadath SC. Comparing voxel-based absorbed dosimetry methods in tumors, liver, lung, and at the liver-lung interface for (90)Y microsphere selective internal radiation therapy. *EJNMMI Phys*. 2015;2(1):16.
20. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228–247.
21. Thall PF, Simon RM, Estey EH. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. *Stat Med*. 1995;14(4):357–379.
22. Thall PF, Wooten LH, Tannir NM. Monitoring event times in early phase clinical trials: some practical issues. *Clin Trials*. 2005;2(6):467–478.
23. Yamashita T, Kudo M, Ikeda K, et al. REFLECT-a phase 3 trial comparing efficacy and safety of lenvatinib to sorafenib for the treatment of unresectable hepatocellular carcinoma: an analysis of Japanese subset. *J Gastroenterol*. 2020;55(1):113–122.
24. Yau T, Park JW, Finn RS, et al. CheckMate 459: a randomized, multi-center phase III study of nivolumab (NIVO) vs sorafenib (SOR) as first-line (1L) treatment in patients (pts) with advanced hepatocellular carcinoma (aHCC). *Ann Oncol*. 2019;30:v874–v875.
25. Cheng AL, Qin S, Ikeda M, et al. LBA3 - IMbrave150: efficacy and safety results from a ph III study evaluating atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (Sor) as first treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC). *Ann Oncol*. 2019;30:ix186–ix187.
26. Garin E, Tselikas L, Guiu B, et al. Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. *Lancet Gastroenterol Hepatol*. 2021;6(1):17–29.
27. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet*. 2002;359(9319):1734–1739.
28. Kishore S, Friedman T, Madoff DC. Update on embolization therapies for Hepatocellular carcinoma. *Curr Oncol Rep*. 2017;19(6):40.
29. Pesapane F, Nezami N, Patella F, Geschwind JF. New concepts in embolotherapy of HCC. *Med Oncol*. 2017;34(4):58.
30. Wang G, Liu Y, Zhou SF, et al. Sorafenib combined with transarterial chemoembolization in patients with hepatocellular carcinoma: a meta-analysis and systematic review. *Hepatol Int*. 2016;10(3):501–510.
31. Ricke J, Klümpen HJ, Amthauer H, et al. Impact of combined selective internal radiation therapy and sorafenib on survival in advanced hepatocellular carcinoma. *J Hepatol*. 2019;71(6):1164–1174.
32. Sangro B, Carpanese L, Cianni R, et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. *Hepatology*. 2011;54(3):868–878.
33. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology*. 2010;138(1):52–64.
34. Teyateeti A, Mahvash A, Long JP, et al. Survival outcomes for Yttrium-90 transarterial radioembolization with and without sorafenib for unresectable Hepatocellular carcinoma patients. *J Hepatocell Carcinoma*. 2020;7:117–131.
35. Chow PKH, Gandhi M, Tan SB, et al. SIRveNIB: selective internal radiation therapy versus sorafenib in Asia-Pacific patients with hepatocellular carcinoma. *J Clin Oncol*. 2018;36(19):1913–1921.
36. Vilgrain V, Pereira H, Assenat E, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *Lancet Oncol*. 2017;18(12):1624–1636.
37. Hermann AL, Dieudonné A, Ronot M, et al. Relationship of tumor radiation-absorbed dose to survival and response in hepatocellular carcinoma treated with transarterial radioembolization with (90)Y in the SARAH study. *Radiology*. 2020;296(3):673–684.
38. Chan KT, Alessio AM, Johnson GE, et al. Prospective Trial using internal pair-production positron emission tomography to establish the Yttrium-90 radioembolization dose required for response of Hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys*. 2018;101(2):358–365.
39. Garin E, Lenoir L, Edeline J, et al. Boosted selective internal radiation therapy with 90Y-loaded glass microspheres (B-SIRT) for hepatocellular carcinoma patients: a new personalized promising concept. *Eur J Nucl Med Mol Imaging*. 2013;40(7):1057–1068.
40. Salem R, Padia SA, Lam M, et al. Clinical and dosimetric considerations for Y90: recommendations from an international multidisciplinary working group. *Eur J Nucl Med Mol Imaging*. 2019;46(8):1695–1704.