

## Phase II Trial of Sorafenib Combined With Concurrent Transarterial Chemoembolization With Drug-Eluting Beads for Hepatocellular Carcinoma

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### ABSTRACT

#### Purpose

To evaluate safety and efficacy of combined transarterial chemoembolization (TACE) with doxorubicin-eluting beads (DEB) and sorafenib in patients with advanced hepatocellular carcinoma (HCC).

#### Patients and Methods

A prospective single-center phase II study was undertaken involving patients with unresectable HCC. The protocol involved sorafenib 400 mg twice per day combined with DEB-TACE. Safety and response were assessed.

#### Results

DEB-TACE in combination with sorafenib was successfully administered in 35 patients: mean age, 63 years; Child's A, 89%; Barcelona Clinic Liver Cancer stage C, 64%; Eastern Cooperative Oncology Group performance status of 0 and 1, 46% and 54%, respectively; and mean index tumor size, 7.7 cm (standard deviation,  $\pm$  4.2 cm). Patients underwent 128 cycles of therapy (sorafenib plus DEB-TACE, 60 cycles; sorafenib alone, 68 cycles). Median number of cycles per patient was two (range, one to five cycles); median number of days treated with sorafenib was 71 (range, 4 to 620 days). The most common toxicities during cycle one were fatigue (94%), anorexia (67%), alterations in liver enzymes (64%), and dermatologic adverse effects (48%). Although most patients experienced at least one grade 3 to 4 toxicity, most toxicities were minor (grade 1 to 2, 83% v grade 3 to 4, 17%). Toxicity during cycle two was decreased. Over the course of the study, there were 40 sorafenib dose interruptions and 25 sorafenib dose reductions. Sorafenib plus DEB-TACE was associated with a disease control rate of 95% (Response Evaluation Criteria in Solid Tumors Group)/100% (European Association for the Study of the Liver [EASL]), with an objective response of 58% (EASL).

#### Conclusion

The combination of sorafenib and DEB-TACE in patients with unresectable HCC is well tolerated and safe, with most toxicities related to sorafenib. Toxicity is manageable with dose adjustment of sorafenib. Preliminary efficacy data are promising.

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### INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide.<sup>1</sup> Although treatment of HCC includes ablation, resection, and transplantation, many patients present with advanced disease and are therefore not candidates for these therapeutic options. Survival of patients with unresectable advanced HCC is poor, with 1-, 3-, and 5-year survival rates of 29%, 8%, and 0%, respectively.<sup>2</sup> Sorafenib has been shown to improve overall survival among patients with advanced

HCC.<sup>3,4</sup> Sorafenib inhibits angiogenesis by targeting the vascular endothelial growth factor receptor 2 (VEGFR2) and platelet-derived growth factor receptor (PDGFR) pathway while also blocking cell proliferation by targeting the Ras/mitogen-activated protein kinase signaling pathway. In the SHARP (Sorafenib HCC Assessment Randomized Protocol) trial, sorafenib therapy resulted in survival of 10.7 versus 7.9 months for patients who received placebo.<sup>3</sup> Although a similar relative survival benefit associated with sorafenib was found in the subsequent Asia-Pacific trial

(hazard ratio, 0.68), survival among patients was still less than 1 year.<sup>4</sup>

Intra-arterial therapy, usually in the form of conventional transarterial chemoembolization (cTACE), can increase survival in selected patients with inoperable intermediate HCC (Barcelona Clinic Liver Cancer [BCLC] stage B),<sup>5,6</sup> with 1-, 2- and 3-year survival of 75%, 47% and 26%, respectively.<sup>5</sup> Recently, drug-eluting bead (DEB)-TACE has emerged as a method to enhance drug delivery and reduce systemic drug exposure compared with conventional cTACE.<sup>7,8</sup> Several clinical trials have shown that DEB-TACE yielded response rates in the range of 70% to 80% and decreased adverse effects when compared with cTACE.<sup>9,10</sup> One limitation of TACE, however, has been the high incidence of recurrence. An increase in plasma VEGF levels after TACE has been well documented and may be a potential cause of recurrent disease.<sup>11,12</sup> After TACE, the tumor microenvironment becomes deranged with increased hypoxia, leading to an upregulation in hypoxia inducible factor-1 $\alpha$ , which in turn upregulates VEGF and PDGFR and increases tumor angiogenesis.<sup>11-13</sup> This upregulation of angiogenesis may have adverse pro-tumor consequences, and elevations in serum VEGF are a poor prognostic indicator in patients with HCC.<sup>14-16</sup> As a result, there has been interest in combining antiangiogenic targeted agents with TACE to decrease post-TACE angiogenesis and improve the efficacy of locoregional therapy as well as possibly decreasing the incidence of systemic disease. In fact, preclinical models combining bland transarterial embolization with antiangiogenic agents have noted a reduction in tumor volume and vessel density, as well as a prolongation in survival compared with transarterial embolization alone.<sup>17</sup>

Whether combining sorafenib with DEB-TACE is safe, well tolerated, and efficacious remains unknown, with no prospective clinical data currently available. We therefore conducted a prospective single-center, single-arm phase II trial to evaluate the safety and efficacy of sorafenib combined with DEB-TACE in patients with unresectable HCC. The primary study end point was toxicity. Secondary study end points were objective response and disease control rate.

## PATIENTS AND METHODS

### Study Population and Eligibility

Patients (age 18 years or older) with a diagnosis of unresectable HCC based on histology obtained by needle biopsy or a hypervascular lesion on cross-sectional imaging and  $\alpha$ -fetoprotein level of 200 ng/mL or greater were evaluated. Eligibility criteria included: Eastern Cooperative Oncology Group performance status of 0 to 1; adequate bone marrow (leukocyte count  $> 3,000$  cells/ $\mu$ L, absolute neutrophil count  $\geq 1,500/\mu$ L, platelet count  $\geq 50,000/\mu$ L), renal (creatinine  $\leq 2.0$  mg/dL), and cardiac (left ventricular ejection fraction  $\geq 45\%$ ) function; and life expectancy of more than 12 weeks. Eligible patients had Child-Pugh liver function of A to B7, with ALT and AST less than eight times upper limit of normal, as well as total bilirubin of less than 3 mg/dL and albumin greater than 2.0 mg/dL. Exclusion criteria included: hepatic tumor burden of more than 70%, presence of extrahepatic disease, complete occlusion of the entire portal venous system, uncontrolled hypertension ( $\geq 150/100$  mm/Hg), evidence of bleeding diathesis or coagulopathy, concomitant HIV infection, and second primary malignancy. Patients who had undergone embolization, hepatic radiation, or systemic therapy were also excluded; however, previous therapy with sorafenib was allowed if treatment was fewer than 3 months in duration.

The study was approved by the US Food and Drug Administration with a physician-sponsored investigational new drug as well as the Johns Hopkins Hospital institutional review board. The study was conducted in accordance

with the principles of the Declaration of Helsinki, and all patients provided written informed consent.

### Study Design

Patients were treated on a 6-week cycle regimen, in which one cycle consisted of sorafenib (400 mg twice daily, initiated 1 week before DEB-TACE) administered continuously and DEB-TACE performed during week 2 (ie, 1 week after initiation of sorafenib). Clinical examinations were performed every week, with laboratory assessment in weeks 3 and 5 and imaging in week 5. For the first 11 patients in the study, a sorafenib dose interruption (3 days before and after DEB-TACE) was utilized, because no clinical data were available on the safety of combination therapy. An interim analysis demonstrated a good safety profile of combination therapy with no increase in grade 3 to 4 toxicity as compared with existing data on patients treated with DEB-TACE or sorafenib alone.<sup>3,4,7,8</sup> As a result, all subsequent patients were allowed to receive sorafenib continuously throughout the treatment cycles. During subsequent cycles (ie, cycle two and beyond), all patients received continuous sorafenib, DEB-TACE in week 2 (when indicated), and laboratory assessment during week 5. Up to four DEB-TACE treatments were allowed in 6 months. Treatment continued until occurrence of unacceptable toxicities, sorafenib interruption exceeding 30 days, or disease progression.

Dose reductions (ie, 400 mg once daily, 400 mg every other day) and drug interruptions were allowed for toxicities. If additional dose reductions were required, patient participation in the study was discontinued. The DEB-TACE procedure has been described more fully elsewhere.<sup>10</sup> Briefly, DEB-TACE was administered in a superselective manner with a maximum of 100 mg doxorubicin per procedure loaded onto 100 to 300  $\mu$ m LC beads (one vial of LC beads containing 2 mL, 100-300  $\mu$ m [BioCompatibles, Farnham, United Kingdom] was loaded with 50 mg of doxorubicin hydrochloride, 25 mg/mL [Pharmacia-UpJohn, London, United Kingdom]). Total dose delivered was determined by size of lesion(s) to be treated.

### Study End Points and Data Analysis

The primary end points were safety and toxicity associated with combined sorafenib plus DEB-TACE in patients with unresectable HCC. All patients who

**Table 1.** Patient Baseline Demographics and Clinical Characteristics (n = 35)

Variable	No.	%
Age, years		
Mean	63	
Range	31-88	
Male	26	74
Etiology		
Hepatitis B infection	2	6
Hepatitis C infection	13	37
Alcohol	8	23
Hemochromatosis	1	3
Cryptogenic cirrhosis/other	11	31
Child-Pugh class		
A	31	89
B	4	11
ECOG performance status		
0	16	46
1	19	54
BCLC stage		
B	12	34
C	23	64
Portal vein thrombosis	11	31
Index tumor size, cm		
Mean	7.7	
SD	$\pm 4.2$	

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

received one or more doses of sorafenib were included in the evaluation and assessed using National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Efficacy was the secondary end point. All patients who underwent DEB-TACE were included in the efficacy evaluation. Tumor response of the targeted lesions was evaluated with contrast-enhanced and diffusion-weighted magnetic resonance imaging. As previously described,<sup>18</sup> response was assessed by size (Response Evaluation Criteria in Solid Tumors Group [RECIST]),<sup>19,20</sup> enhancement (European Association for the Study of the Liver [EASL] criteria),<sup>21</sup> and tumor apparent diffusion coefficient values. Complete response, partial response, stable disease, and progressive disease were calculated using both RECIST and EASL criteria.

Toxicity profiles were grouped by cycle (cycle one  $v \geq$  two) and severity (grade 1 to 2  $v$  3 to 4). Assessment of liver function was stratified by whether the patient had a sorafenib treatment break and baseline bilirubin. Comparisons were made using paired *t* tests, and all statistical tests were two sided. *P* values were reported, with a *P* value less than .05 considered statistically significant.

RESULTS

Patient Characteristics

Of the 55 patients who consented from March 2009 through January 2011, 14 were determined ineligible on additional screening, three lacked insurance approval, and three ultimately declined participation. Thirty-five patients were therefore enrolled (Table 1). The study population was predominantly male (74%), and etiology of cirrhosis was not related to hepatitis B or C in most patients (57%). Most patients (89%) were Child's A, and 64% were BCLC stage C; 31% of patients had portal vein thrombosis, and the mean index tumor size was 7.7 cm.

Safety and Treatment Toxicity

The 35 patients enrolled onto the study were treated with a total of 128 cycles of therapy (sorafenib plus DEB-TACE, 60 cycles; sorafenib alone, 68 cycles; Fig 1). Median number of cycles per patient was two (range, one to five cycles), and median number of days treated with sorafenib was 71 (range, 4 to 620 days). Ten patients remained on sorafenib as of February 1, 2011, and were censored at that time point. Median number of DEB-TACE treatments per patient was one (range, one to five treatments). Mean dose of doxorubicin decreased with each subsequent DEB-TACE cycle (cycle one, 75 mg; two, 60 mg; three, 49 mg).

During week 1 of cycle one (sorafenib only), 91% of patients experienced some toxicity. Two patients were intolerant to sorafenib and were withdrawn from the study during week 1 (severe rash, fatigue, encephalopathy). Eleven patients were treated with sorafenib during week 1 of cycle one with a 3-day sorafenib break before and after DEB-TACE. Eight (73%) of these 11 patients experienced grade 3 to 4 toxicity during cycle one, consistent with the toxicity seen previously with DEB-TACE alone at our institution.<sup>10</sup> Subsequent patients were treated with continuous sorafenib with no breaks before or after DEB-TACE (*n* = 22). The most common toxicities during week 1 of cycle one included fatigue (50%), hand-foot-skin reaction (HFSR; 30%), rash (20%), and right upper quadrant pain (18%; Fig 2A). Most toxicities during week 1 of cycle one were grade 1 to 2 (92%) rather than 3 to 4 (8%; Table 2). Uncommon grade 3 to 4 toxicities seen in week 1 of cycle one were elevated lipase (3%) and encephalopathy (3%).

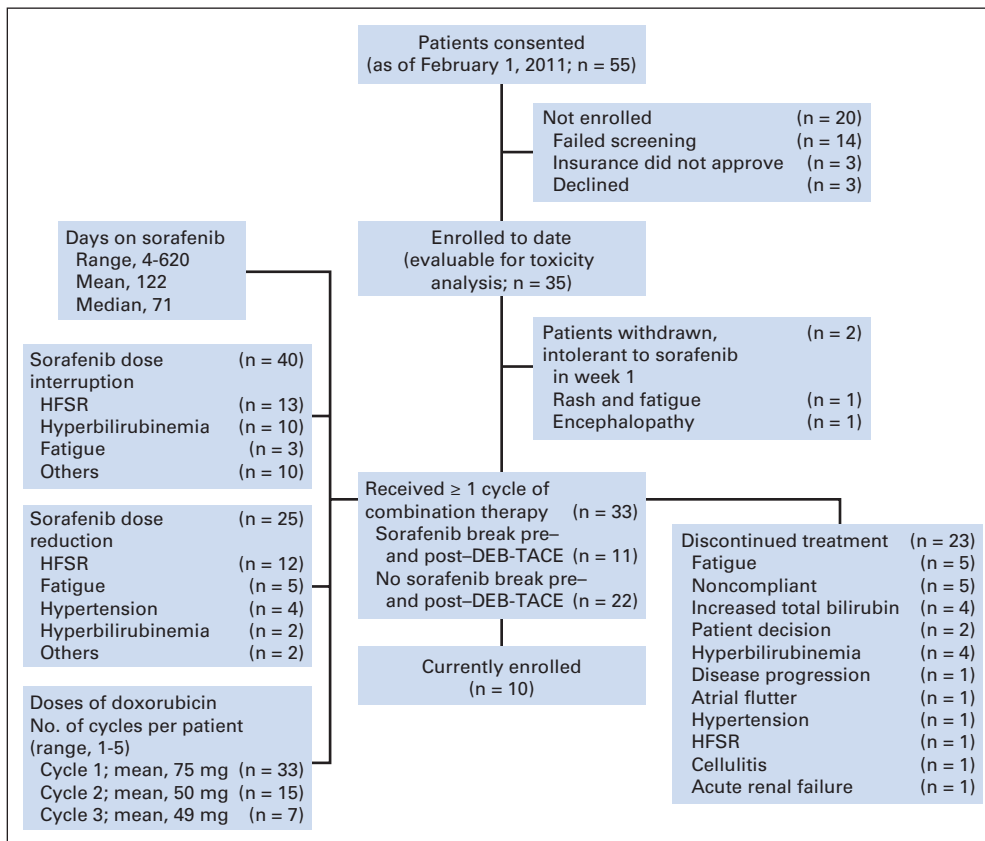
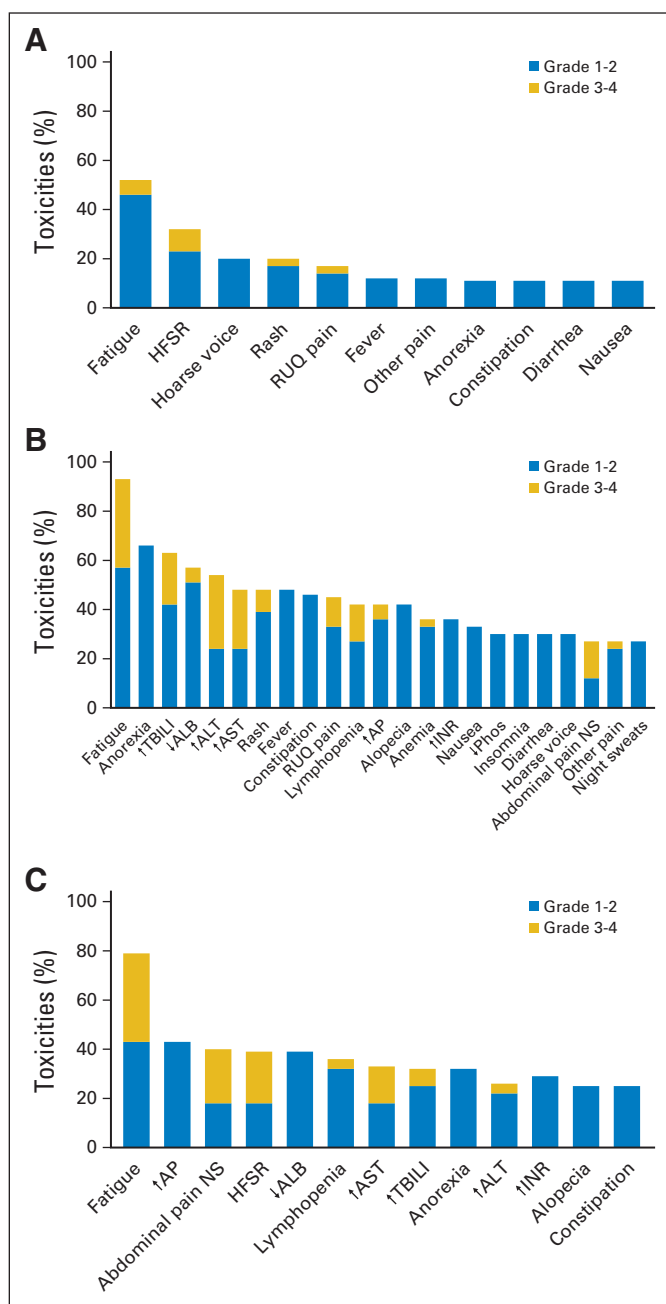


Fig 1. Flow chart of phase II trial of sorafenib plus doxorubicin-eluting beads (DEB) transarterial chemoembolization (TACE) in patients with advanced hepatocellular carcinoma outlining patient accrual, treatment, and clinical course during trial. HFSR, hand-foot-skin reaction.



**Fig 2.** Bar graph depicting toxicities stratified by (A) week 1, cycle one (sorafenib only; > 10% toxicity occurrence); (B) cycle one (sorafenib plus doxorubicin-eluting beads-transarterial chemoembolization; ≥ 25% toxicity occurrence); and (C) cumulative toxicity (≥ 25% toxicity occurrence) associated with two or more to six cycles. ALB, albumin; AP, activator protein; HFSR, hand-foot-skin reaction; INR, international normalized ratio; NS, nonspecific; Phos, phosphorous; RUQ, right upper quadrant; TBILI, total bilirubin.

Each patient experienced at least one toxicity during subsequent weeks of cycle one (sorafenib plus DEB-TACE). The most common toxicities consisted of fatigue (94%), anorexia (67%), alterations in liver (64%) and hematologic (42%) function tests, dermatologic adverse effects (48%), and pain (45%; Fig 2B). During cycle one, 30 of 33 patients experienced at least one grade 3 to 4 toxicity associated with sorafenib plus DEB-TACE. However, only 17% of all reported toxicities were grade 3 to 4, with most reported toxicities being grade 1 to 2 (83%). More common

grade 3 to 4 toxicities included fatigue (36%), elevated ALT (30%), and elevated AST (24%), and uncommon grade 3 to 4 toxicities were hypertension (6%); encephalopathy (6%); and infection, skeletal pain, chest pain, dyspnea, and pulmonary embolus (all 3%).

Twenty-eight patients were treated with two or more cycles of therapy. In contrast to cycle one, toxicity was lower after cycle two. Only 15 (54%) of 28 patients experienced grade 3 to 4 toxicity. Cumulative incidence of all complications after two or more cycles was comparable to toxicity seen after cycle one alone: fatigue (79%), alterations in liver (43%) and hematologic (37%) function tests, dermatologic adverse effects (39%), and pain (50%; Fig 2C). Among all reported toxicities, incidence of grade 3 to 4 toxicity after two or more cycles of therapy was similar to grade 3 to 4 toxicity noted after cycle one (16% v 17%). The most common grade 3 to 4 toxicity after two or more cycles was fatigue (36%), and infrequent grade 3 to 4 toxicities included arrhythmia, rash, elevated amylase, infection, liver abscess, encephalopathy, and right upper quadrant pain (all 4%; Table 2).

Figure 3 shows liver function tests at baseline and after therapy. Those patients who had a sorafenib treatment break before and after DEB-TACE tended to have lower total bilirubin (median, 0.87 mg/dL) after DEB-TACE compared with those who did not have a sorafenib break (median, 1.5 mg/dL;  $P = .32$ ). Patients with hyperbilirubinemia at baseline (> 2 mg/dL) who did not have a sorafenib break had higher total bilirubin and lower albumin 3 weeks after DEB-TACE compared with those who had normal initial bilirubin (total bilirubin: 5.84 v 0.96 mg/dL [ $P = .003$ ]; albumin: 2.9 v 3.4 mg/dL [ $P = .07$ ]).

Over the course of the study, there were 40 sorafenib dose interruptions, most commonly for HFSR ( $n = 13$ ). There were 25 sorafenib dose reductions, again most commonly for HFSR ( $n = 12$ ). Twenty-three patients were discontinued from the study (Fig 1). The most common reasons were patient decision/noncompliance ( $n = 6$ ), hyperbilirubinemia ( $n = 4$ ), and disease progression ( $n = 4$ ). One patient died as a result of disease progression within 30 days of receiving treatment during the study.

### Efficacy

Fifty-six targeted lesions among 33 patients were evaluated for treatment response (Table 3). After cycle one of sorafenib plus DEB-TACE, there was a 4% decrease in tumor size (from 6.0 to 5.8 cm;  $P = .05$ ). In contrast, assessment of tumor necrosis revealed a more marked response. Specifically, after combined treatment, there was a 50% decrease in tumor enhancement (from 90% to 45%;  $P < .001$ ) and 23% increase in ADC values (from 1.27 to 1.53;  $P < .05$ ). The disease control rate as evaluated per lesion was 92% by RECIST criteria; using EASL criteria, the objective response rate was 58%, and the disease control rate was 100%.

## DISCUSSION

Although not the first study to investigate cTACE plus angiogenic therapy, the current study is the first prospective phase II study to our knowledge to examine the combination of sorafenib and DEB-TACE in patients with unresectable HCC. We established that the combination of sorafenib and DEB-TACE was well tolerated and safe. Specifically, toxicities were manageable, because most were grade 1 to 2, and there were no treatment-related deaths. In addition, preliminary analysis revealed favorable efficacy as demonstrated by a disease-control

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Table 2. Treatment Toxicities Stratified by Cycle

Toxicity	Grade																	
	Week 1, Cycle One (sorafenib only; n = 35)						Cycle One (n = 33)						Cycles Two and Beyond (n = 28)					
	Any		1 to 2		3 to 4		Any		1 to 2		3 to 4		Any		1 to 2		3 to 4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Any	32	91	30	86	9	26	33	100	33	100	30	91	28	100	28	100	21	75
Blood/bone marrow suppression																		
Anemia				12	36	11	33	1	3	8	29	8	29					
Leukocytopenia				6	18	6	18		5	18	5	18						
Lymphopenia				14	42	9	27	5	15	10	37	9	33	1	4			
Neutropenia				1	3	1	3		1	4	1	4						
Thrombocytopenia	1	3	1	3		7	21	7	19		5	18	5	18				
Cardiac events																		
Arrhythmia				3	9	3	9		1	4		1	4					
Hypertension	4	12	4	12		4	12	2	126	2	6	1	4	1	4			
Cardiovascular system																		
Edema				9	27	8	24	1	3	1	4	1	4					
Coagulation																		
Elevated INR				12	36	12	36		8	29	8	29						
Constitutional symptoms																		
Fatigue	18	52	16	46	2	6	31	94	19	57	12	36	22	79	12	43	10	36
Fever	4	12	4	12		16	48	16	48		4	14	4	14				
Insomnia	1	3	1	3		10	30	10	30		4	15	4	15				
Night sweats	2	6	2	6		9	27	9	27		3	11	3	11				
Weight loss				1	3	1	3		3	11	3	11						
Dermatologic events																		
Alopecia	1	3	1	3		14	42	14	42		7	25	7	25				
Dry skin	1	3	1	3		2	6	2	6		3	11	3	11				
HSFR	11	32	8	23	3	9	16	48	10	30	6	18	11	39	5	18	6	21
Mucositis	2	6	2	6		5	15	5	15		1	4	1	4				
Pruritis	2	6	2	6		6	18	6	18		2	8	1	4	1	4		
Rash	7	20	6	17	1	3	16	48	13	39	3	9						
GI events																		
Ascites				3	9	3	9											
Anorexia	4	11	4	11		22	67	22	66		9	32	9	32				
Constipation	4	11	4	11		15	46	15	45		7	25	7	25				
Diarrhea	3	9	3	9		10	30	10	30		6	21	6	21				
Dry mouth	3	9	3	9		3	9	3	9		1	40	1	4				
Early satiety	1	3	1	3		1	3	1	3		1	4	1	4				
Gastritis/heartburn/indigestion	3	9	3	9		4	12	4	12		1	4	1	4				
Nausea	4	11	4	11		11	33	11	33		5	18	5	18				
Taste alteration				4	12	4	12		2	8	2	8						
Vomiting	2	6	2	6		6	18	6	18		1	4	1	4				
Hemorrhage/bleeding	1	3	1	3		1	3	1	3		2	7	2	7				
Hepatic/pancreatic function																		
Elevated ALT	1	3	1	3		18	55	8	24	10	30	7	26	6	22	1	4	
Elevated AST				16	48	8	24	8	24	9	33	5	18	4	15			
Elevated AP				14	42	12	36	2	6	15	43	15	43					
Elevated amylase				6	18	6	18		3	11	2	7	1	4				
Elevated lipase	1	3		1	3	11	33	7	21	4	12	5	18	5	18			
Hyperbilirubinemia	1	3	1	3		21	64	14	42	7	21	9	32	7	25	2	7	
Hypoalbuminemia				19	58	17	51	2	6	11	40	11	40					
Hypophosphatemia				10	30	10	30		2	7	2	7						
Infection				4	12	3	9	1	3	2	8	1	4	1	4			
Liver abscess							1	4		1	4							
Musculoskeletal																		
Cramping	2	6	2	6		3	9	3	9		2	7	2	7				
Skeletal pain	2	6	2	6		6	18	5	15	1	3	2	8	1	4	1	4	

(continued on following page)

**Table 2.** Treatment Toxicities Stratified by Cycle (continued)

Toxicity	Grade																	
	Week 1, Cycle One (sorafenib only; n = 35)						Cycle One (n = 33)						Cycles Two and Beyond (n = 28)					
	Any		1 to 2		3 to 4		Any		1 to 2		3 to 4		Any		1 to 2		3 to 4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Neurologic symptoms/events																		
Ataxia	1	3	1	3														
Cognitive impairment	1	3	1	3	1	3	1	3										
Dizziness	1	3	1	3	2	6	2	6										
Headache	3	9	3	9	4	12	4	12										
Encephalopathy	1	3	1	3	2	6	2	6	1	4	1	4						
Pain																		
Abdominal nonspecific	2	6	2	6	9	27	4	12	5	15	11	50	5	18	6	24		
Chest				3	15	2	6	1	3	1	4	1	4					
Epigastric				1	3	1	3		2	7	2	7						
Right upper quadrant	5	17	4	14	1	3	15	45	11	33	4	12	4	15	3	11	1	4
Other	4	12	4	12		9	27	8	24	1	3							
Pulmonary																		
Cough	1	3	1	3	5	15	5	15		1	4	1	4					
Dyspnea				2	6	1	3	1	3	3	11	3	11					
Dyspnea on exertion				3	9	3	9											
Pulmonary embolus/coagulopathy				1	3		1	3	3	11	3	11						
Raspy voice/sore	7	20	7	20	10	30	10	30										
Renal																		
Elevated creatinine				1	3	1	3		4	14	4	14						
Acute renal failure				2	6	2	6											
Urinary frequency/incontinence	2	6	2	6	3	9	3	9										
Sexual																		
Decreased libido	1	3	1	3	2	6	2	6										

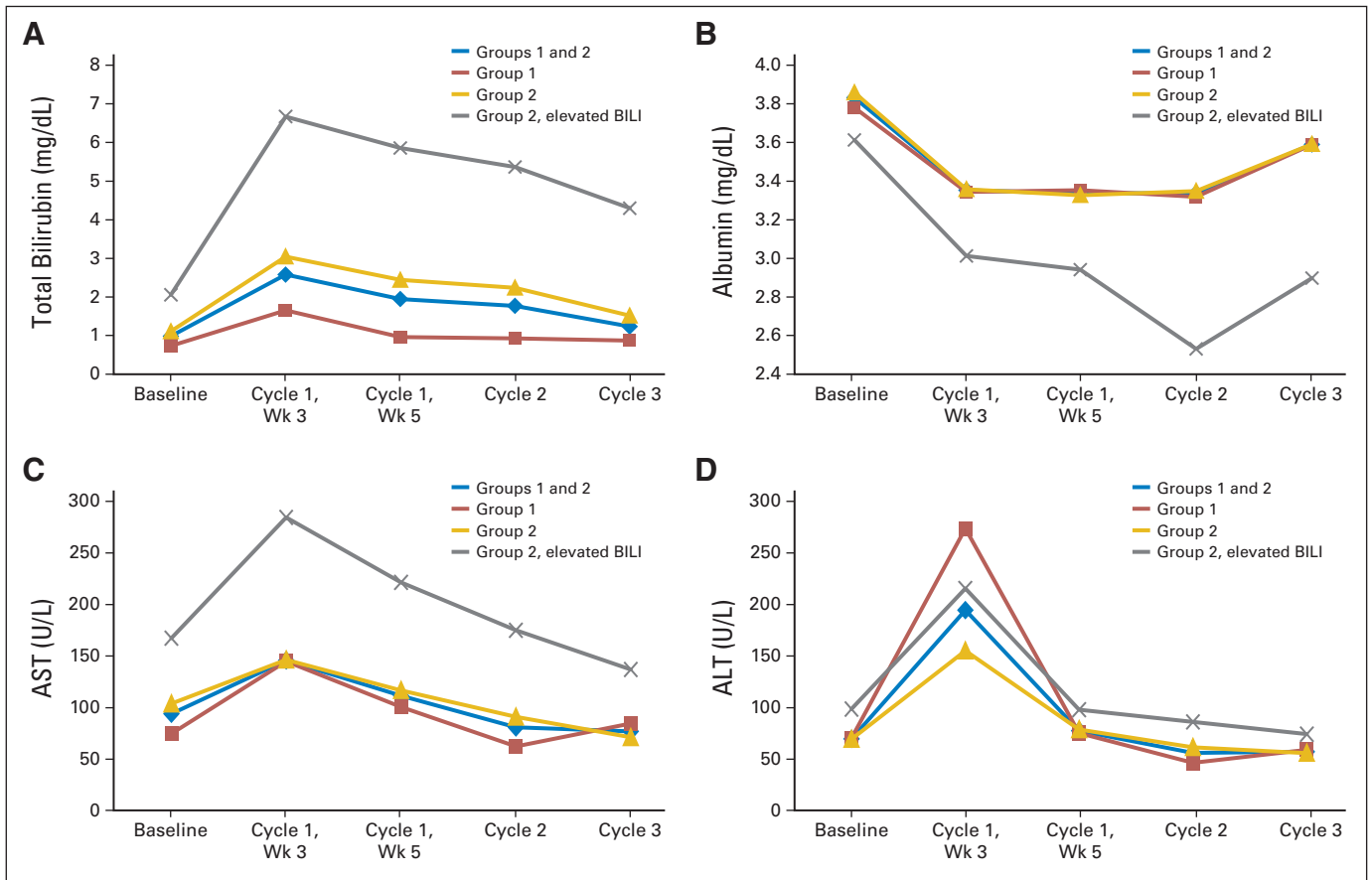
Abbreviations: AP, activator protein; HFSR, hand-foot-skin reaction; INR, international normalized ratio.

rate of 90% to 100% and objective response of 58% based on EASL criteria. These data are important, because most patients with HCC present with advanced disease and have limited therapeutic options. Although cTACE is a modality frequently utilized, recent data have suggested that DEB-TACE may be a better locoregional approach, because DEB-TACE may allow for better drug delivery, reduced systemic drug exposure, and decreased adverse effects.<sup>7-9</sup> However, both cTACE and DEB-TACE can be associated with postprocedure elevations in VEGF and PDGR and increased tumor angiogenesis.<sup>11-13</sup> As such, there has been interest in combining TACE with antiangiogenic systemic therapy. Sorafenib targets several angiogenesis pathways and therefore is potentially an attractive agent to combine with TACE.

The fact that plasma VEGF and other angiogenic factors increase soon after TACE therapy provided the rationale for initiating sorafenib 1 week before DEB-TACE. Given that the half-life of sorafenib is only 24 to 48 hours, providing a run-in with sorafenib therapy theoretically should help better mitigate the effects of post-TACE hypoxia-induced angiogenesis. In addition, treatment with sorafenib alone allowed us to monitor and assess the toxicity of monotherapy before initiating a combined modality approach. During the first week of sorafenib therapy, two patients were discontinued from the trial because of drug intolerance. Although all other patients also experienced toxicity during the first week of sorafenib, these toxicities were manageable. The most common toxicities were fatigue, dermatologic adverse effects (HFSR and rash), and right upper quadrant pain, most of which were grade 1 to 2 (Fig 2A). This toxicity

profile was similar to those reported in the SHARP<sup>3</sup> and Asia-Pacific<sup>4</sup> trials, which noted diarrhea, HFSR, anorexia, and alopecia as the more common toxicities.

A possible natural synergy between sorafenib and systemic doxorubicin, or summation of dose intensity, has been reported previously.<sup>22</sup> However, the safety of combined sorafenib and doxorubicin delivered via DEB-TACE has not. The primary objective of the current phase II trial, therefore, was to ascertain whether the combination of these two agents delivered in this manner would have added toxicity. Although 30 of 33 patients treated with combined sorafenib and intra-arterial doxorubicin had grade 3 to 4 toxicity, these toxicities were manageable. The toxicity profile of sorafenib plus DEB-TACE was similar to that of sorafenib alone, with fatigue, anorexia, and dermatologic adverse effects among the most common. Although it is difficult to discern between DEB-TACE- and sorafenib-related toxicities, it is interesting to note that the toxicity profile for sorafenib plus DEB-TACE was similar to those noted in the SHARP and Asia-Pacific sorafenib-only trials (constitutional and dermatologic). Over the course of the study, there were 40 sorafenib dose interruptions as well as 25 dose reductions, most commonly for HFSR. By reducing the dose of sorafenib, subsequent emergent toxicity was lower. In fact, only 15 of 28 patients experienced grade 3 to 4 toxicity during cycle two, and cumulative incidence of all grade 3 to 4 toxicities after two or more cycles (16%) was equal to that after just cycle one (17%). Toxicity directly attributable to DEB-TACE seemed to be uncommon; only one patient experienced a liver



**Fig 3.** Line graphs depicting baseline and temporal changes in (A) total bilirubin (BILI), (B) albumin, (C) AST, and (D) ALT after sorafenib plus doxorubicin-eluting beads (DEB)-transarterial chemoembolization (TACE) therapy. Data stratified by whether patients had sorafenib break and by baseline total BILI levels (groups one and two, entire cohort; group one, sorafenib break plus DEB-TACE; group two, no sorafenib break plus DEB-TACE; group two, no sorafenib break plus DEB-TACE with baseline total BILI > 2 mg/dL).

abscess. In aggregate, our data strongly suggest that sorafenib combined with DEB-TACE is a safe and relatively well-tolerated therapy, although dose reduction of sorafenib is frequently required.

Another interesting aspect of the current study was the effect of combined sorafenib plus DEB-TACE on liver function. Combined modality therapy with sorafenib plus DEB-TACE did not seem to affect AST, ALT, or total bilirubin levels in most patients. Among those patients with normal baseline bilirubin level who had no sorafenib break, bilirubin levels after therapy remained stable. However, patients who had elevated baseline total bilirubin (> 2 mg/dL) and no sorafenib treatment break before or after DEB-TACE were found to have marked and persistent elevated total bilirubin after DEB-TACE (Fig 3). Of note, previous studies investigating either sorafenib alone<sup>3,4</sup> or DEB-TACE alone<sup>8-10</sup> have failed to note similar elevation in total bilirubin post therapy. Although DEB-TACE may confer some protection against liver toxicity over cTACE,<sup>9</sup> our data suggest that use of combined sorafenib plus DEB-TACE may need to be considered more cautiously in those patients who present with elevated bilirubin.

In addition to demonstrating the safety of sorafenib plus DEB-TACE, our data suggest that such therapy may also be efficacious. Although few lesions had a reduction in tumor size based on RECIST criteria, most targeted lesions had a decrease in tumor enhancement (Table 3). In addition, the disease control rate as evaluated per lesion was 92% to 100%, with an objective response rate of 58%. These data on efficacy are preliminary; however, results from the current study provide a

basis for future studies aimed at evaluating the therapeutic impact of sorafenib plus DEB-TACE.

In summary, the combination of sorafenib and DEB-TACE in patients with unresectable HCC was well tolerated and safe. Most toxicities seemed to be related to sorafenib, because the toxicity profile largely mirrored those previously reported in the sorafenib monotherapy SHARP and Asia-Pacific trials. These toxicities were manageable with dose adjustment of sorafenib. Preliminary efficacy results for combined sorafenib and DEB-TACE were promising, as demonstrated by an excellent disease control rate. Results from the current trial provide safety and preliminary efficacy data in support of ongoing randomized, multicenter trials such as the SPACE (Sorafenib or Placebo in Combination With TACE)<sup>23</sup> and ECOG (Eastern Cooperative Oncology Group) 1208 cTACE/DEB-TACE sorafenib versus placebo trials.<sup>24</sup> Collectively, data from our study and these other emerging trials should help determine whether the combination of sorafenib plus DEB-TACE will become the standard of care for patients with unresectable HCC.

**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were

**Table 3.** Efficacy of Combined Sorafenib Plus DEB-TACE Based on Tumor Response

Feature/Response	Response by Imaging (n = 33; 56 lesions)			
	Baseline (sorafenib + DEB-TACE)	3 Weeks After DEB-TACE	Percent Change	P
	Tumor size (cm)	6.0 SD ±4.0	5.8 SD ±4.0	-4.6
Tumor enhancement, %	90 SD ±20	45 SD ±29	-50	< .001
Apparent diffusion coefficient	1.27 SD ±0.21	1.53 SD ±0.25	+23	< .001
	Response by RECIST/EASL Criteria (56 lesions)*			
	RECIST		EASL	
	No.	%	No.	%
Complete	—	—	2 of 56	4
Partial	5 of 56	9	30 of 56	54
Stable disease	48 of 56	86	24 of 56	43
Progressive disease	3 of 56	5	—	—

Abbreviations: DEB, doxorubicin-eluting beads; EASL, European Association for the Study of the Liver; RECIST, Response Evaluation Criteria in Solid Tumors Group; SD, standard deviation; TACE, transarterial chemoembolization.  
\*Evaluation per lesion.

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