Phase I/II Randomized Trial of Sorafenib and Bevacizumab as First-Line Therapy in Patients with Locally Advanced or Metastatic Hepatocellular Carcinoma: North Central Cancer Treatment Group trial N0745 (Alliance)

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Abstract

Background—Angiogenesis has been a major target of novel drug development in hepatocellular carcinoma (HCC). It is hypothesized that the combination of two antiangiogenic agents, sorafenib and bevacizumab, will provide greater blockade of angiogenesis.

Objective—To determine the optimal dose, safety, and effectiveness of dual anti-angiogenic therapy with sorafenib and bevacizumab in patients with advanced HCC.

Patients and Methods—Patients with locally advanced or metastatic HCC not amenable for surgery or liver transplant were eligible. The phase I starting dose level was bevacizumab 1.25 mg/kg day 1 and 15 plus sorafenib 400 mg twice daily (BID) days 1–28. In the phase II portion, patients were randomized to receive bevacizumab and sorafenib at the maximum tolerated dose (MTD) or sorafenib 400 mg BID.

Results—17 patients were enrolled in the phase I component. Dose-limiting toxicities included grade 3 hand/foot skin reaction, fatigue, hypertension, alanine/aspartate aminotransferase increase, dehydration, hypophosphatemia, creatinine increase, hypoglycemia, nausea/vomiting, and grade 4 hyponatremia. 7 patients were enrolled onto the phase II component at the MTD: sorafenib 200 mg BID days 1–28 and bevacizumab 2.5 mg/kg every other week. 57% (4/7) had grade 3 AEs at least possibly related to treatment,. No responses were observed in the phase II portion. Estimated

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Compliance with Ethical Standards
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median time to progression and survival were 8.6 months (95% CI: 0.4–16.3) and 13.3 months (95% CI 4.4 – not estimable), respectively.

Conclusions—The MTD of the combination is sorafenib 200 mg twice daily on days 1–28 plus bevacizumab 2.5 mg/kg on days 1 and 15 of a 28-day cycle. In the phase II portion of the trial, concerns regarding excessive toxicity, low efficacy, and slow enrollment led to discontinuation of the trial. (Clinical Trials ID: NCT00867321.)

1. INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth leading cause of cancer and third leading cause of cancer-related deaths worldwide [1]. HCC accounts for approximately 30,000 new cancer diagnoses each year in the United States, a number that is steadily increasing due to virus-associated etiologies. Fewer than 20% of patients presenting with HCC are candidates for potentially curative treatment such as surgical resection, liver transplantation, or radiofrequency ablation [2]. Once HCC becomes advanced, there are few systemic therapy options for management.

HCC is a highly vascular malignancy, and the overexpression of vascular endothelial growth factor (VEGF) is felt to play a critical role in the development and progression of HCC [3, 4]. Sorafenib is an oral multi-kinase inhibitor, which targets the VEGF-receptor 2 (R2) intracellularly, as well as kinases downstream the VEGF signaling pathway including Raf [5]. A large randomized phase III trial demonstrated an overall survival (OS) of 10.7 months in the sorafenib arm compared to 7.9 months for placebo (p<0.001) [6], which led to regulatory approval for use in unresectable HCC at a dose of 400 mg twice daily.

Bevacizumab is a monoclonal antibody that targets VEGF by binding to the VEGF ligand thereby preventing its interaction with the VEGF-R2 and blocking VEGF-induced angiogenesis [7]. Results from a phase II trial of single agent bevacizumab for patients with unresectable HCC showed promising activity with median progression-free survival (PFS) time of 6.9 months (95% CI, 6.5 to 9.1 months) and a one-year OS rate of 53% [8].

The combination of bevacizumab and sorafenib could result in enhanced inhibition of VEGF-mediated angiogenesis by more broad inhibition of VEGF signaling and targeting downstream intracellular processes such as the RAF/RAS/MEK pathway. A previous phase I study in advanced solid tumors found the maximum-tolerated dose (MTD) of the combination was sorafenib 200 mg twice daily and bevacizumab 5 mg/kg every 2 weeks. Of the 37 assessable patients, seven had a partial response (PR), and PR or disease stabilization for   4 months was seen in 22 (59%) of 37 assessable patients [9].

A phase I/II clinical trial was conducted through the North Central Cancer Treatment Group (NCCTG) to evaluate the safety and efficacy of sorafenib and bevacizumab in HCC.

2. PATIENTS AND METHODS

2.1 Patient Selection

Patients ≥ 18 years of age with locally advanced or metastatic HCC not candidates for surgery or liver transplant were eligible for enrollment. Inclusion criteria for the trial included: no prior systemic chemotherapy or external beam radiation therapy for HCC, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, measurable disease, total bilirubin ≤ 1.5 × upper limit of normal (ULN), AST ≤ 5 × ULN, alkaline phosphatase ≤ 5 × ULN, and adequate bone marrow and renal function. Patients with Child Pugh A or B7 liver disease were allowed on the study. Patients must have had ≥ 3 months life expectancy to participate in the trial.

Patients who had chemoembolization, radioembolization, radiofrequency ablation (RFA), or other local ablative therapies < 6 weeks prior to registration were excluded. Patients who had treatment of known or clinically suspected esophageal varices ≤ 6 months prior to registration were not eligible. Patients with bleeding diathesis or on chronic anticoagulation were ineligible. Patients with brain metastases, uncontrolled hypertension (defined as systolic blood pressure > 150 mmHg or diastolic blood pressure > 100 mmHg), class III or IV congestive heart failure, ventricular arrhythmia or arterial thrombotic event in the previous 6 months, non-healing wound, major surgery or trauma within 4 weeks, and any other illness which the investigator felt would make the patient inappropriate for study entry were excluded.

This study was approved by the Mayo Clinic Institutional Review Board (IRB) and by the IRBs of the individual memberships of the North Central Cancer Treatment Group (NCCTG) that participated in the study. Each participant signed an IRB-approved, protocol-specific informed consent in accordance with federal and institutional guidelines. Clinical Trials ID: NCT00867321.

2.2 Treatment

The goal of the phase I component was to determine the MTD for treating this patient population with sorafenib plus bevacizumab. The phase I portion of this trial was a standard 3 + 3 dose escalation/de-escalation design with the doses listed in Table 1. Sorafenib was administered twice daily (continuously per dose schedule) and bevacizumab was administered every 2 weeks on a 28-day cycle. Once the MTD was established, patients were randomly assigned using a Dynamic Allocation Procedure [10] to receive either the MTD of the dual agent combination or sorafenib monotherapy at 400 mg BID, days 1–28. Overall, patients were treated until they refused treatment or experienced progressive disease (PD) or unacceptable adverse events.

2.3 Patient Evaluation

Patients were evaluated every cycle for treatment adherence and adverse events. In the phase I portion, dose limiting toxicity (DLT) was defined as an adverse event (AE) ≥ grade 3 attributed (definitely, probably or possibly) to the study treatment based on NCI CTCAE v3.0 criteria in the first 28-day cycle. The maximum tolerated dose (MTD) was defined as

the dose level below the lowest dose that induces DLT in at least one-third of patients. If dose level (−1) was not tolerable, but dose (−3) or (−2) was below or at MTD, testing of alternate dose levels (−2a, −3a, −3b) were to occur as outlined in the table. These alternate dose levels would only be tested if full-dose sorafenib could not be combined with any dose of bevacizumab and the combination would require a sorafenib dose reduction to 200 mg twice daily or lower (dose level −2 or −3).

The phase I portion of this study was monitored by the rules specified for identifying DLTs. In the phase II portion, the Mayo Clinic Cancer Center (MCCC) Data and Safety Monitoring Board (DSMB) reviewed accrual and safety data twice a year.

2.4 Disease Assessment

All eligible patients who signed the consent form and began treatment were evaluable for response. Radiologic studies were performed at baseline, after four weeks, and then every two cycles (8 weeks) of therapy to assess tumor response using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 [11]. After completion of study treatment, patients were followed every 3 months until first documentation of progression and every 6 months after progression until death or for 2 years.

2.5 Statistical Considerations

The primary endpoint of the phase I component is the determination of the MTD (defined earlier), using the standard '3+3' phase I study design. Patients were evaluable for MTD determination during the first cycle of treatment. Patients enrolled at the MTD were considered evaluable for the assessing efficacy in the phase II portion of the study. The primary goal of the phase II component of this study was to compare time to progression (TTP) in the experimental arm (bevacizumab/sorafenib) to the control arm (sorafenib alone), where the alternative hypothesis was that the estimated hazard ratio (control:experimental) was at least 1.8. We designed this study using a non-definitive (alpha=0.15, power=0.85), "screening" comparison of the dual-agent arm (bevacizumab/sorafenib) against monotherapy with sorafenib as described by Rubenstein et al [12]. After determining the appropriate dose levels in the phase I component, we intended to enroll up to 76 patients (70 with an additional 6 allowed to account for ineligible patients) using a 1:1 randomization scheme with patients stratified by gender, ECOG PS (0 vs 1), and Child-Pugh class (A vs B7). At the time all patients were followed for at least 6 months, the p-value associated with a 1-sided log-rank test between the two Kaplan-Meier curves [13] was calculated and compared to alpha=0.15. A p-value less than 0.15 was an indication that adding bevacizumab to sorafenib improved TTP.

Secondary endpoints across the components of the study included assessing adverse events, TTP, progression-free survival (PFS), and overall survival (OS). Summary statistics and categorical data methods were used to summarize the distributions of patient characteristics, treatment dosing, and adverse events. Adverse events were summarized as the maximum severity of each type of event, per patient. Kaplan-Meyer methodology was used to estimate the distributions of TTP, PFS, and OS. The data analysis for this paper was generated using SAS/STAT software, Version 9.3 of the SAS System for Linux. (© 2002–2008 SAS Institute

Inc, Cary, NC, USA). All analyses were based on the study database frozen on May 5, 2014. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center.

3. RESULTS

3.1 PHASE I COMPONENT

3.11 Patient Accrual—From April 2009 to September 2010, a total of 17 patients were enrolled. Patient characteristics are shown in Table 2. The median age was 66 years (range 18 – 79). Two patients (12%) had prior radiation for bone metastasis, 1 patient (6%) had prior chemoembolization, 3 patients (18%) had vascular invasion, and 12 patients (71%) had ascites. Eight patients (47.1%) entered with intrahepatic (vs. extrahepatic) disease. Only 41% of patients had cirrhosis, which may be due to the relatively low incidence of viral hepatitis at the centers that participated in the trial.

3.12 Determination of Phase II Starting Dose Level—At dose level 0, two patients experienced DLTs including hand/foot skin reaction, fatigue, and hypertension. At dose level −1, one of three patients experienced a DLT (grade 3 events of alanine and aspartate aminotransferase increase, dehydration, and hypophosphatemia, and grade 4 hyponatremia). Two of the 3 subsequent patients enrolled at dose level −1 experienced DLTs: one patient experienced grade 3 creatinine increase and hypoglycemia, as well as grade 4 acidosis and syncope, and subsequently died (grade 5 sudden death) less than a month into treatment; another patient experienced grade 3 nausea and vomiting. At dose level −2 one patient had a treatment violation and was replaced. There were no DLT's experienced by the 3 evaluable patients on dose level −2. The next cohort of patients was enrolled to dose level −2a, and there were no DLTs in this cohort. Because dose level −1 was already deemed too toxic, further dose escalation was halted, and the MTD and recommended phase II dose was determined to be sorafenib 200 mg twice daily and bevacizumab 2.5 mg/kg every other week.

Overall, 17 patients received a total of 76 cycles of sorafenib (median 3 cycles, range: 0–19) and a total of 66 cycles of bevacizumab (median 3 cycles, range: 1–19). All patients have discontinued study treatment for reasons including disease progression (12), adverse events (4), and refusal (1).

3.13 Adverse Event Summary, Across Cohorts—All 17 patients are evaluable for toxicity. The frequency and severity of frade 3 and above adverse events at least possibly related to treatment appear in Table 3. Overall, 14 patients (82.4%) patients experienced grade 3+ adverse events at least possibly related to treatment, and 3 patients (17.6%) patients experienced grade 4+ adverse events at least possibly related to treatment. There was one grade 5 sudden death possibly related to treatment. Five patients have experienced grade 4 adverse events: Thrombosis (not related), hyponatremia (possibly related), acidosis (possibly related), hyperkalemia (possibly related), muscle weakness (unlikely related), hyperglycemia (unlikely related), syncope (possibly related), and dehydration (unlikely related).

3.14 Outcome Measures—Sixteen patients had at least one post-baseline assessment of disease. During treatment, there were two (12.5%) confirmed partial responses, 9 (56.3%) patients had stable disease, and 5 (31.3%) patients experienced progressive disease (Table 4). A 58-year-old-male experienced a PR after one cycle of treatment (Dose Level −2), lasting 6.1 months prior to the appearance of extrahepatic lesions. A 73-year-old male experienced a PR after nine cycles of treatment (Dose Level −2a), lasting 10 months until disease progression. Fourteen of the 16 patients progressed (5 - intrahepatic, 3-extrahepatic, and 3 - both intrahepatic and extrahepatic). One patient is alive with 18.2 months of follow-up. The estimated median time to progression (Table 4, Figures 2a–b) and survival were 3 months (95% CI: 1.7–7.2) and 9.2 months (95% CI: 3.7–11.9), respectively.

3.2 PHASE II COMPONENT

3.21 Patient Accrual—From November 2010 to October 2011, a total of 7 (4 bevacizumab/sorafenib, 3 sorafenib) patients were accrued at a rate of less than 1 patient per month. The study was subsequently closed after a review of toxicity and lower than expected time to progression for patients on the combination arm. At study entry (Table 2), patients aged from 54 to 80 (median 58.5) in the bevacizumab/sorafenib arm and from 52 to 61 (median 55) in sorafenib arm. All patients were Caucasian; 5 were male. Four patients presented with intrahepatic (vs. extrahepatic) disease. Neither prior chemoembolization nor vascular invasion was reported in patients. Overall, 3 (28.6%) patients had single metastatic sites: liver metastasis (2, bevacizumab/sorafenib arm) and abdominal metastases (1, sorafenib arm).

3.22 Outcome Measures—Six of 7 patients (4 bevacizumab/sorafenib, 2 sorafenib alone) have had at least one post-baseline assessment of disease. One patient was unable to comply with the study and refused further treatment prior to obtaining a post-baseline assessment. No responses were observed (Table 4). Five of the 7 patients have had disease progression (2 - intrahepatic, 3 - extrahepatic). Two patients remain alive with a median of 23.5 months of follow-up (range 22–24.9). The estimated median time to progression and survival were 8.6 months (95% CI: 0.4 –16.3) and 13.3 months (95% CI 4.4 - NE) (Table 4, Figures 2c–d). At 1 year, survival was 71.4% (95% CI: 25.8– 92%). The small sample size precludes meaningful conclusions with respect to study endpoints for the phase II component.

3.23 Treatment Summary—Patients on the bevacizumab/sorafenib arm received 11 (median 2, range 1–6) cycles of treatment; patients receiving sorafenib monotherapy received 21 (median 8, range 1–12) cycles of treatment. Two cycles of treatment (1 bevacizumab/sorafenib, 1 sorafenib alone) were delayed for the following reasons: dermatitis/rash/skin condition, and for sorafenib shipping. Sorafenib dose reductions at the initiation of a cycle occurred 6 times in 3 patients (1 bevacizumab/sorafenib, 2 sorafenib alone); no reductions were reported for bevacizumab. Seven patients completed study treatment. Reasons for discontinuing treatment include: disease progression (4), adverse events (1), refusal (1), and for inability to comply with the treatment schedule (1).

3.24 Adverse Event Summary—Overall, 4 of 7 (57%) patients (2 bevacizumab/ sorafenib, 2 sorafenib alone) experienced grade 3+ adverse events at least possibly related to treatment, and 1 patient receiving bevacizumab/sorafenib reported a grade 4+ adverse events at least possibly related to treatment (elevated aspartate aminotransferase). The frequency and severity of grade 3 and above adverse events at least possibly related to treatment appear in Table 3.

4. DISCUSSION

The MTD of bevacizumab combined with sorafenib in this patient population was sorafenib 200 mg twice daily and bevacizumab 2.5 mg/kg every other week. The dose of bevacizumab was lower than a prior phase I trial of this combination among patients with solid tumors reported by Azad et al [9] where the MTD was found to be sorafenib 200 mg twice daily plus bevacizumab 5 mg/kg every 2 weeks. Other patient populations have been able to tolerate the latter doses. For instance, the clinical trial N054C, which evaluated the combination of bevacizumab and sorafenib in patients with refractory metastatic colorectal cancer (mCRC), used the MTD from the aforementioned trial reported by Azad [14]. In the N054C trial, 68% of patients had a grade 3 toxicity at least possibly related to treatment, compared to 82.4% of patients in the phase I portion of this study. The reasons for the difference in dosing in our study are unclear, but possibly due to the poorer tolerability of cancer treatments in the HCC patient population. Liver dysfunction that coexists in patients with HCC may lead to different pharmacokinetics and drug deposition potentially increasing toxicity compared to cancer patients with normal liver function [15], However, since less than half of patients on the study had underlying cirrhosis, the poor tolerability of the regimen is not entirely explained by liver dysfunction.

For unclear reasons, attempts to the broaden the targets affecting the antiangiogenic pathway have not led to improved outcomes for patients with HCC [16]. Multiple randomized phase III trials involving kinase inhibitors have failed to demonstrate a survival benefit beyond sorafenib alone. Sunitinib, which targets VEGFR and PDGFR, was compared to sorafenib in the first-line treatment setting of HCC. Compared to sorafenib, patients in the sunitinib arm had inferior overall survival along with more frequent and severe toxicity [17]. Brivanib (targeting fibroblastic growth factor receptor [FGFR] and VEGFR) was not superior to sorafenib as first-line therapy for HCC patients, and those on the brivanib arm had poorer tolerability leading to a higher discontinuation rate (33% vs 43%) [18]. Linifanib, targeting VEGFR and PDGFR, was also found to be less effective compared to sorafenib in first-line setting for treatment of HCC [19].

Trials examining antiangiogenesis agents in the second-line setting have yielded mixed results. The use of brivanib failed to improve overall survival when compared to placebo in the second-line setting for HCC patients [20]. Ramucirumab, a monoclonal antibody against VEGF-R2, led to a 9.2 month overall survival versus 7.6 months for placebo as second-line therapy, but this did not reach statistical significance (p = 0.14).[21] Upon further analysis, it did appear that HCC patients with an alpha-fetoprotein (AFP) level > 400 ng/mL and Child-Pugh class 5 or 6 did have a significant survival benefit with ramurcirumab (HR, 0.61; 95% CI, 0.43–0.87; P = .01 and HR, 0.64; 95% CI, 0.42–0.98; P = .04 respectively. Finally,

regorafenib, a multikinase inhibitor targeting VEGF-R2 and mechanisms of VEGF therapy resistance including TIE2, did show an overall survival benefit compared to placebo among patients with advanced HCC who were intolerant of or progressed on sorafenib. Patients in the regorafenib arm had on overall survival of 10.6 months compared to 7.8 months in the placebo arm (HR 0.62, 95% CI: 0.50–0.78; p<0.001).[22]

Investigators are now evaluating drugs with alternative targets involved in HCC development and progression. Tivantinib is a novel inhibitor of the MET receptor. In a randomized [23]phase II randomized trial in the second-line setting, tivantinib had an improved TTP compared to placebo, 1.6 versus 1.4 months (HR 0.64, p = 0.04) [24]. A subgroup of patients whose tumor tissue demonstrated high MET expression levels had a longer TTP (2.7 months), and based on that subgroup analysis, a randomized phase III trial of tivantinib versus placebo in second-line setting for MET overexpression tumors is underway (ClinicalTrials.gov identifier: NCT01755767). A phase I/II study in patients in unresectable HCC with or without prior therapy investigating the mTOR inhibitor everolimus led to a median PFS of 3.8 months and an OS of 8.4 months. Currently a phase III randomized trial of everolimus versus placebo second-line after failure of sorafenib is ongoing (ClinicalTrials.gov identifier: NCT01035229).

In conclusion, the combination of sorafenib plus bevacizumab was difficult to administer in patients with unresectable HCC, leading to an MTD using sub-standard doses of both sorafenib and bevacizumab. Concerns over excess toxicity and decreased efficacy as well as slow enrollment led to early discontinuation of the randomized phase II portion of the trial. Novel agents that broaden the spectrum of angiogenic targets have not led to improvements in survival above sorafenib alone leading to a new focus on systemic therapies targeting alternative pathways such as RET and MET. The development of well-tolerated, effective therapies in the setting of liver dysfunction remains a challenge in this patient population.

Acknowledgments

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KEY POINTS

- The maximum tolerable dose of the combination of sorafenib and bevacizumab in HCC patients (200 mg twice daily and 2.5 mg/kg every 2 weeks respectively) is lower than the standard doses of these medications.

- Due to toxicity concerns and poor accrual, the phase II portion of the trial was unable to be completed.

- Despite the highly vascular nature of HCC tumors, the combination of bevacizumab and sorafenib in HCC patients had disappointing results.
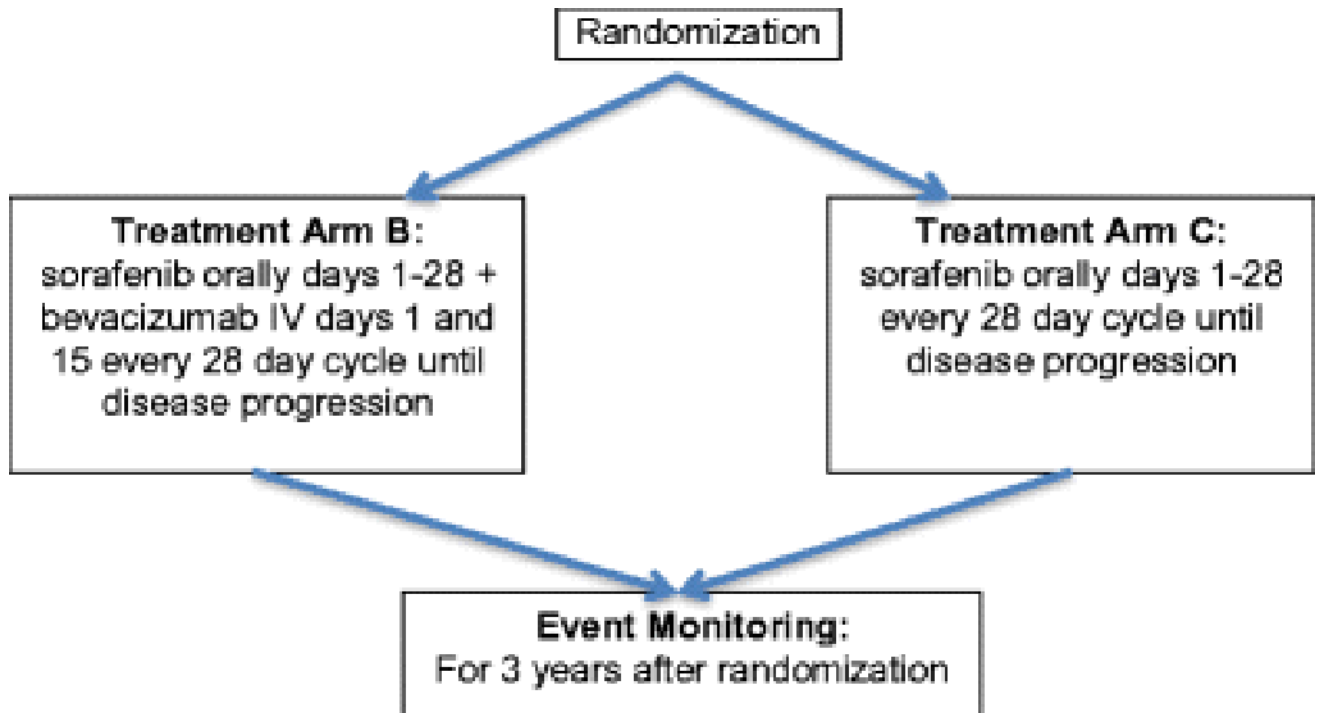
Figure 1.
Consort diagram for the Phase II portion
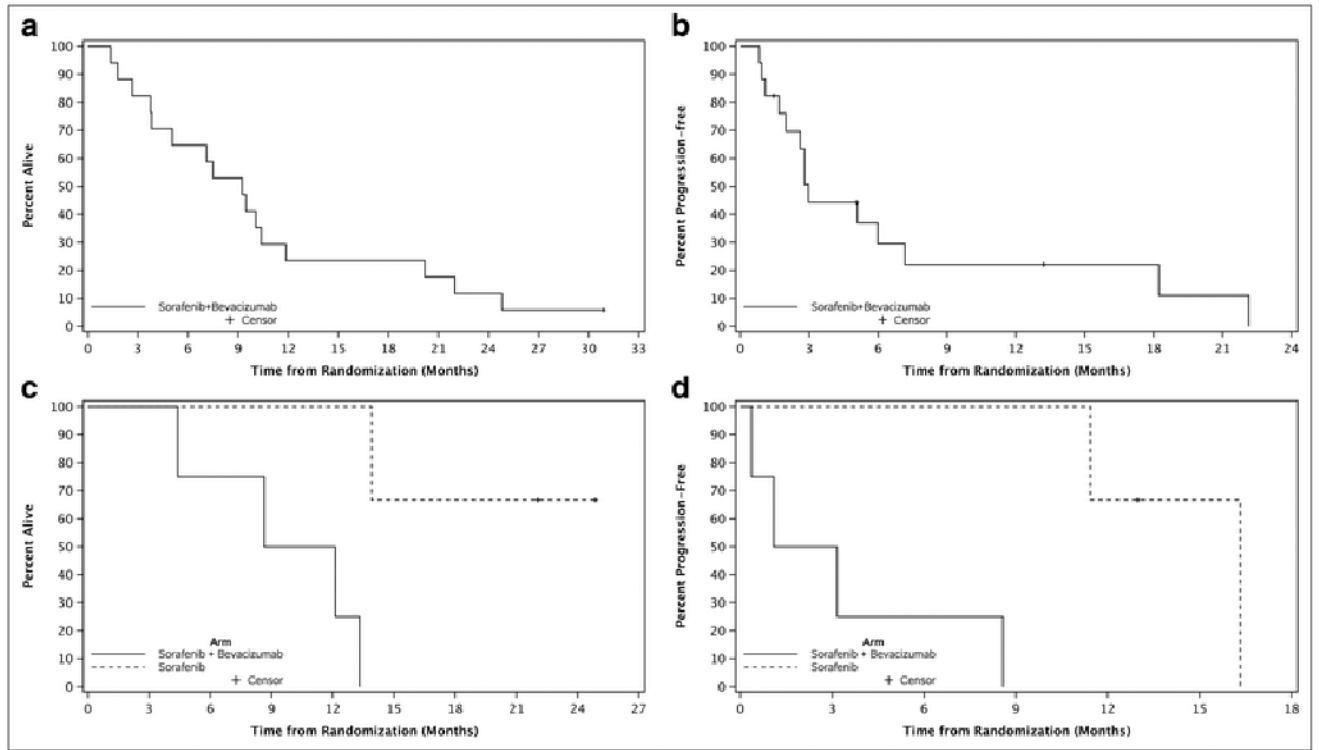
Figure 2.
a–d: Time to Progression & Survival, by Study Component

Table 1

Treatment Administration, by Study Component

Phase I Component		
Dose Level	**Sorafenib (twice daily)**	**Bevacizumab (every 2 weeks)**
+2	400 mg BID	5 mg/kg
+1	400 mg BID	2.5 mg/kg
0 *	400 mg BID	1.25 mg/kg
−1	400 mg BID, 5 consecutive days out of each 7 days	1.25 mg/kg
(−2a)	200 mg BID days 1–28	2.5 mg/kg
−2	200 mg BID days 1–28	1.25 mg/kg
(−3b)	200 mg BID, days 1–5 out of each 7 days	5 mg/kg
(−3a)	200 mg BID, days 1–5 out of each 7 days	2.5 mg/kg
−3	200 mg BID, days 1–5 out of each 7 days	1.25 mg/kg
Phase II Component		
Agent	**Dose Level**	**Route**	**Day**	**ReRx**
Arm A				
Bevacizumab	2.5 mg/kg	IV *	Day 1, 15(+/− 3 days)	Every 4 weeks
Sorafenib	200 mg BID	PO	Days 1–28	
Arm B				
Sorafenib	400 mg BID	PO	Days 1–28	Every 4 weeks

*
Starting dose level

Table 2

Patient Characteristics, by Study Component

	Phase I	Phase II		
	Sorafenib + Bevacizumab	Sorafenib + Bevacizumab	Sorafenib	Total
Age				
Median (Range in years)	66 (18–79)	59 (54–80)	55 (52–61)	57 (52–80)
Gender				
Female	3 (17.6%)	1 (25.0%)	1 (33.3%)	2 (28.6%)
Male	14 (82.4%)	3 (75.0%)	2 (66.7%)	5 (71.4%)
Race				
White	13 (76.5%)	4 (100.0%)	3 (100.0%)	7 (100.0%)
Black	2 (11.8%)			
Asian	2 (11.8%)			
ECOG Performance Score				
0		3 (75.0%)	2 (66.7%)	5 (71.4%)
1		1 (25.0%)	1 (33.3%)	2 (28.6%)
History of Cirrhosis				
Yes	7 (41.2%)	2 (50.0%)	2 (66.7%)	4 (57.1%)
No	10 (58.8%)	2 (50.0%)	1 (33.3%)	3 (42.9%)
Current Disease Status				
Intrahepatic	8 (47.1%)	2 (50.0%)	2 (66.7%)	4 (57.1%)
Extrahepatic	9 (52.9%)	2 (50.0%)	1 (33.3%)	3 (42.9%)
Vascular Invasion				
Yes	3 (20.0%)			
No	12 (80.0%)	4 (100.0%)	3 (100.0%)	7 (100.0%)
Missing	2			
Differentiation				
Well	2 (11.8%)			
Moderate	11 (64.7%)	3 (75.0%)	2 (66.7%)	5 (71.4%)
Poor	3 (17.6%)	1 (25.0%)	1 (33.3%)	2 (28.6%)
Undifferentiated, anaplastic	1 (5.9%)			
Tumor Status				
Recurrent		1 (25.0%)		1 (14.3%)
Unresected	17 (100.0%)	3 (75.0%)	3 (100.0%)	6 (85.7%)

Table 3

Maximum Adverse Event[1], by Study Component

Body System	Toxicity	Arm	Grade 3 N	Grade 3 %	Grade 4 N	Grade 4 %	Grade 5 N	Grade 5 %
		PHASE I COHORT						
Constitutional Symptoms	Fatigue	Sorafenib + Bevacizumab	4	23.5	0	0.0	0	0.0
	Weight loss	Sorafenib + Bevacizumab	1	5.9	0	0.0	0	0.0
Dermatology/Skin	Hand-and-foot syndrome/reaction	Sorafenib + Bevacizumab	3	17.6	0	0.0	0	0.0
Hematology	Platelet count decreased	Sorafenib + Bevacizumab	2	11.8	0	0.0	0	0.0
	Lymphocyte count decreased	Sorafenib + Bevacizumab	1	5.9	0	0.0	0	0.0
	Leukocyte count decreased	Sorafenib + Bevacizumab	1	5.9	0	0.0	0	0.0
Hepatic	Alanine aminotransferase increased	Sorafenib + Bevacizumab	1	5.9	0	0.0	0	0.0
	Aspartate aminotransferase increased	Sorafenib + Bevacizumab	1	5.9	0	0.0	0	0.0
	Bilirubin increased	Sorafenib + Bevacizumab	1	5.9	0	0.0	0	0.0
Metabolic/Laboratory	Acidosis	Sorafenib + Bevacizumab	0	0.0	1	5.9	0	0.0
	Serum glucose decreased	Sorafenib + Bevacizumab	1	5.9	0	0.0	0	0.0
	Serum phosphate decreased	Sorafenib + Bevacizumab	1	5.9	0	0.0	0	0.0
	Serum potassium increased	Sorafenib + Bevacizumab	0	0.0	1	5.9	0	0.0
	Serum sodium decreased	Sorafenib + Bevacizumab	0	0.0	1	5.9	0	0.0
Neurology	Syncope	Sorafenib + Bevacizumab	0	0.0	1	5.9	0	0.0
Renal /Genitourinary	Creatinine increased	Sorafenib + Bevacizumab	1	5.9	0	0.0	0	0.0
Death	Sudden death	Sorafenib + Bevacizumab	0	0.0	0	0.0	1	5.9
Cardiovascular	Arrhythmia	Sorafenib + Bevacizumab	1	5.9	0	0.0	0	0.0
	Hypertension	Sorafenib + Bevacizumab	1	5.9	0	0.0	0	0.0
	Electrocardiogram QTc interval prolonged	Sorafenib + Bevacizumab	1	5.9	0	0.0	0	0.0
Gastrointestinal	Anorexia	Sorafenib + Bevacizumab	1	5.9	0	0.0	0	0.0
	Dehydration	Sorafenib + Bevacizumab	1	5.9	0	0.0	0	0.0
	Esophageal ulcer	Sorafenib + Bevacizumab	1	5.9	0	0.0	0	0.0
	Nausea	Sorafenib + Bevacizumab	1	5.9	0	0.0	0	0.0

Body System	Toxicity	Arm	Grade 3 N	Grade 3 %	Grade 4 N	Grade 4 %	Grade 5 N	Grade 5 %
	Vomiting	Sorafenib + Bevacizumab	1	5.9	0	0.0	0	0.0
PHASE II COHORT								
Dermatology/Skin	Hand-and-foot syndrome/reaction	Sorafenib + Bevacizumab	1	25.0	0	0.0	0	0.0
	Rash desquamating	Sorafenib	1	33.3	0	0.0	0	0.0
Hematology	Lymphocyte count decreased	Sorafenib	1	33.3	0	0.0	0	0.0
Hepatic	Alanine aminotransferase increased	Sorafenib + Bevacizumab	1	25.0	0	0.0	0	0.0
	Aspartate aminotransferase increased	Sorafenib + Bevacizumab	0	0.0	1	25.0	0	0.0
	Bilirubin increased	Sorafenib	1	33.3	0	0.0	0	0.0
	Serum albumin decreased	Sorafenib	1	33.3	0	0.0	0	0.0
Metabolic/Laboratory	Serum phosphate decreased	Sorafenib + Bevacizumab	1	25.0	0	0.0	0	0.0
	Serum potassium decreased	Sorafenib + Bevacizumab	1	25.0	0	0.0	0	0.0
Gastrointestinal	Dehydration	Sorafenib + Bevacizumab	1	25.0	0	0.0	0	0.0
Infection/Febrile Neutropenia	Urinary tract infection(gr 0/1/2 ANC)	Sorafenib + Bevacizumab	1	25.0	0	0.0	0	0.0
Lymphatics	Localized edema	Sorafenib	1	33.3	0	0.0	0	0.0
Musculoskeletal	Muscle weakness	Sorafenib + Bevacizumab	1	25.0	0	0.0	0	0.0

[1] AEs at least possibly related to study treatment. Events are by patient across all cycles of treatment.

Table 4

Patient Outcome, by Study Component

Outcome	Estimate (% or 95% CI)			
	Phase I Cohort	**Phase II Cohort**		
	Sorafenib + Bevacizumab	Sorafenib + Bevacizumab	Sorafenib	All Patients
Best Objective Response				
Evaluable[a]	16	4	2	6
Not Evaluable	1	0	1	1
CR	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
PR	2 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SD	9 (56.3%)	2 (50.0%)	2 (100.0%)	4 (66.7%)
PD	5 (31.3%)	0 (0.0%)	0 (0.0%)	2 (33.3%)
Confirmed CR/PR	1 (6.3%)	2 (50.0%)	0 (0.0%)	0 (0.0%)
Time to Progression				
Events	14	4	2	6
Median[b] (95% CI)	3.0 (1.7–7.2)	2.1 (0.4–8.6)	16.3 (11.4–16.3)	8.6 (0.4–16.3)
% Progression-Free				
2 mos	69.7% (41.7–86.1)	50.0% (5.8–84.5)	100.0%	71.4% (25.8–92.0)
4 mos	44.3% (20.2–66.1)	25.0% (0.9–66.5)	100.0%	57.1% (17.2–83.7)
Survival				
Events	16	4	1	5
Median[b] (95% CI)	9.2 (3.7–11.9)	10.4 (4.4–13.3)	NE (13.9-NE)	13.3 (4.4-NE)
% Alive				
6 mos	64.7% (37.7–82.3)	75.0% (12.8–96.1)	100.0%	85.7% (33.4–97.9)
1 year	23.5% (7.3–44.9)	50.0% (5.8–84.5)	100.0%	71.4% (25.8–92.0)

[a] Number of patients having at least 1 post-baseline assessment

[b] Kaplan-Meier methodology