A Randomized Phase II Open-Label Multi-Institution Study of the Combination of Bevacizumab and Erlotinib Compared to Sorafenib in the First-Line Treatment of Patients with Advanced Hepatocellular Carcinoma

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Abstract

Objectives: To investigate the clinical efficacy and tolerability of the combination of bevacizumab (B) and erlotinib (E) compared to sorafenib (S) as first-line treatment for patients with advanced hepatocellular carcinoma (HCC).

Methods: A total of 90 patients with advanced HCC, Child-Pugh class A– B7 cirrhosis, and no prior systemic therapy were randomly assigned (1: 1) to receive either 10 mg/kg B intravenously every 14 days and 150 mg E orally daily ($n = 47$) (B+E) or 400 mg S orally twice daily ($n = 43$). The primary endpoint was overall survival (OS). Secondary endpoints included event-free survival (EFS), objective response rate based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1), time to progression, and safety and tolerability.

Results: The median OS was 8.55 months (95% CI: 7.00–13.9) for patients treated with B+E and 8.55 months (95% CI: 5.69–12.2) for patients receiving S. The hazard ratio (HR) for OS was 0.92 (95% CI: 0.57–1.47). The median EFS was 4.37 months (95% CI: 2.99–7.36) for patients receiving B+E and 2.76 months (95% CI: 1.84–4.80) for patients receiving S. The HR for EFS was 0.67 (95% CI: 0.42–1.07; $p = 0.09$), favoring B+E over S. When OS was assessed among patients who were Child-Pugh class A, the median OS was 11.4 months (95% CI: 7.5–15.7) for patients treated with B+E ($n = 39$) and 10.26 months (95% CI: 5.9–13.0) for patients treated with S ($n = 38$) (HR = 0.88; 95% CI: 0.53–1.46).

Conclusions: There was no difference in efficacy between the B+E and S arms, although the safety and tolerability profile tended to favor B+E over S based on competing risk analysis.

Clinical trial No. NCT00881751.

Keywords

Hepatocellular carcinoma; Hepatoma; Clinical trial; Sorafenib; Bevacizumab; Erlotinib; Vascular endothelial growth factor; Epidermal growth factor; Targeted therapies

Introduction

Hepatocellular carcinoma (HCC) is a common tumor worldwide, and among the few malignancies for which both the incidence and the death rate continue to rise [1–4]. The multitargeted tyrosine kinase inhibitor (TKI) sorafenib (S) was the first systemic therapy to prolong the survival of advanced HCC patients [5] and is approved in the first-line setting, while regorafenib, a similar oral TKI, is approved for second-line treatment of advanced HCC [6]. Since chronic hepatic inflammation, cirrhosis, liver regeneration, and vascular invasion are common in HCC [7], substantial clinical research has focused on targeting oncogenic signaling pathways related to inflammatory cytokine expression, growth factor upregulation, and angiogenesis [8–14].

Increased growth factor expression, including hepatocyte, epidermal (EGF), vascular endothelial (VEGF), insulin-like, platelet-derived, and transforming growth factors [15], have been implicated in hepatocarcinogenesis [15–19]. HCC is a highly vascular tumor that commonly invades adjacent blood vessels [20]. Overexpression of VEGF has been observed in HCC cell lines and tumors, as well as in the serum of patients with HCC [21–23]. Elevated expression of VEGF in the serum and tumors of patients with HCC has been linked with HCC tumor grade, vascular invasion, disease recurrence, and poor disease-free and overall survival (OS) [9, 20, 24, 25]. The EGF receptor (EGFR) signaling pathway is commonly activated in liver disease and HCC [26–31] and EGFR plays a key role in hepatic regeneration triggered by acute liver injury [32, 33]. EGFR overexpression has been identified in 40–70% of HCCs and has been linked to tumorigenesis, but its precise role in malignant progression is poorly understood [30, 32, 34, 35]. However, EGFR activating mutations in exons 18–21 are rare in HCC [28, 36].

S is a multitargeted TKI with activity against Raf kinases via the Raf/MAPK (mitogen-activated protein kinase)/ERK (extracellular signal-regulated kinase) pathway, VEGF, platelet-derived growth factor, and c-Kit [37, 38]. The anticancer activity of S results from a

dual inhibitory effect on angiogenesis and tumor cell proliferation [38, 39]. S is currently the only first-line systemic therapy approved for the treatment of patients with advanced HCC based on results from the pivotal SHARP trial [5]; thus, additional effective and tolerable treatment options are needed for these patients.

Bevacizumab (B) is a monoclonal antibody that binds the circulating ligand of the transmembrane VEGF receptor [40–42]. Erlotinib (E) is a TKI that inhibits EGFR signal transduction [43]. There is a strong scientific rationale for evaluating the combination of B +E in advanced HCC, because the two agents target different pathways that are both important in hepatocarcinogenesis [11, 44, 45]. Preclinical studies in xenograft models of HCC and other tumor types have demonstrated that the combination of B+E results in greater efficacy than either agent alone [46–49]. Published data from several single-arm clinical trials (Table 1) suggest a clinical benefit from B+E in HCC, which provided the justification for this randomized phase II study comparing B+E to S.

Subjects and Methods

Study Population

Eligible patients had advanced HCC defined as: not amenable to transplantation, resection, or liver-directed therapy, or progressed after prior surgery or liver-directed therapy, with Child-Pugh class A–B7 liver function [50, 51], no prior systemic therapy, a Cancer Liver Italian Program (CLIP) [52–54] score 5, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2, platelets 75,000/mm^3, total bilirubin 2.0× ULN, and transaminases 5× ULN. Patients with fibrolamellar HCC and prior liver transplantation were excluded. Prior surgery, local ablation, transarterial hepatic artery embolization, and trans-arterial chemoembolization or radioembolization were allowed; any prior therapy had to have been completed 28 days prior to study entry.

Eligibility criteria also included no uncontrolled or significant cardiovascular disease, including: a history of stroke or transient ischemic attack within 6 months; a history of arterial thrombotic events of any type within the previous 6 months; and significant or symptomatic vascular disease (e.g., aortic aneurysm, aortic dissection, or peripheral vascular disease) within 6 months. As determined by the treating investigator, patients must have had well-controlled blood pressure, defined as systolic blood pressure < 150 mm Hg and/or diastolic blood pressure < 100 mm Hg, for the majority of measurements.

Patients with a history of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 bleeding esophageal or gastric varices within the previous 2 months were excluded unless they had undergone banding or sclerotherapy and there had been no evidence of bleeding for 2 months. All patients at risk for varices were screened (using either esophagogastroduodenoscopy or capsule endoscopy) unless screening had been performed within the prior 2 years and the patients were receiving medical prophylaxis for variceal bleeding. If varices were identified at screening that required intervention (banding), patients were not eligible until the varices were adequately treated [55]. Patients with gastric varices were not eligible.

Patients with a history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to registration were ineligible. Patients were also ineligible if they had a serious, non-healing wound, active ulcer, or untreated bone fracture; had a history of allergy to B, E, S, or related compounds; or had undergone a major surgical procedure or open biopsy, or had had a significant traumatic injury within 28 days prior to registration, or anticipated a need for a major surgical procedure during the course of the study.

Trial Design and Treatment

This was an investigator-initiated, industry-sponsored, open-label, randomized phase II first-line systemic therapy trial conducted at six sites throughout the USA. The primary objective of this study was to estimate clinical efficacy outcomes of patients treated with B+E and patients treated with S. OS was the primary objective; however, the trial was not designed to perform a hypothesis test for OS comparing the two groups, due to insufficient power. The goal was to estimate the degree of difference between the two arms to inform the design of a potential phase III trial. Most patients with HCC have underlying liver disease, which can complicate treatment of their cancer. In order to assess whether patients withdrew from the study due to drug-related toxicity and/or other clinical events related to liver disease and not necessarily to tumor progression, it was decided to incorporate a competing risk approach into the data analysis.

Based on the results seen in previous single-arm trials of B+E (Table 1), it was expected and of interest that there was a difference in OS between the B+E and the S arm, favoring the B+E arm with a hazard ratio (HR) of approximately 0.67 based on median OS times in the B+E and S arms of 15 and 10 months, respectively, in these trials. Forty-five patients in each arm were deemed sufficient to achieve precision in the estimation of median OS in each arm and for the estimated HR. If the true HR was 0.67, then the expected width of the 95% confidence interval (CI) would be 1.57, and 38% of the 95% CIs would exclude 1. Given that this was not a randomized phase III trial, we would not require a sample size that allowed 80% or more 95% CIs to exclude 1 if the true HR were 0.67. The primary objective was to estimate the HR for OS with B+E versus S with its 95% CI for a sample size of 90 evaluable patients. Secondary endpoints included event-free survival (EFS), safety and toxicity, and response rate (RR). All randomized patients who received at least one dose of the study drug(s) were considered evaluable.

The patients were randomized 1: 1 to receive 400 mg S orally twice daily, continuously, or 10 mg/kg B IV every 14 days and 150 mg E orally daily, continuously. Clinic visits for patients in both study arms were conducted weekly during the first cycle, and biweekly thereafter. The treatment cycles lasted 28 days. Treatment crossover was not allowed.

Outcomes and Assessments

The patients in each investigational arm underwent restaging evaluations every 8 weeks (2 cycles). All abdominal imaging was performed using a four-phase "liver protocol" image capture technique defined as using multislice spiral CT to obtain images during the precontrast, hepatic arterial, portal-venous, and delayed phases of intravenous contrast enhancement. The patients continued therapy until documentation of progressive disease due

to RECIST version 1.1 [56] intolerable toxicity, withdrawal of patient consent, or other events. Progressive disease necessitating patient withdrawal was determined by the investigator and confirmed by the diagnostic imaging collaborator at each site as well as by central radiologic review. The patients were followed up for survival every 3 months for 1 year following treatment discontinuation. In the subsequent years, those patients who were enrolled or reconsented to be followed up for survival were contacted every 6 months.

OS was defined as the number of months from the date of randomization to the date of the patient's death from any cause. Secondary endpoints included EFS, time to progression, RR, and toxicity and tolerability. EFS was defined as the time from randomization to any of the following four types of event: (1) progression, (2) withdrawal due to excessive toxicity, (3) another clinical event requiring withdrawal from the study, or (4) death from another cause (i.e., not progression of HCC). EFS was analyzed using the same approaches as described above for OS. Time to progression is defined as the time from initiation of therapy until documented disease progression, with deaths from other causes censored at the time of death.

Statistical Analysis

Kaplan-Meier curves were used to display OS and EFS distributions in the two treatment groups, and to examine the impact of several factors important to HCC, including ECOG PS, Barcelona Clinic Liver Cancer (BCLC) stage [57–59], and Child-Pugh class. Survival curves were compared with log-rank tests. The precision of median OS was calculated using Greenwood's formula. HRs and their 95% CIs for OS were estimated using the Cox proportional hazards model. The proportional hazards assumption was tested using graphical approaches, and it appeared to be met.

Comparisons of continuous variables across treatment groups were made with two-sample t tests; comparisons of categorical variables were made with Fisher's exact test. RRs and toxicity rates were estimated with exact 95% CIs. A competing risks approach was used to analyze time to progression, where deaths from non-HCC causes and discontinuation due to adverse events (AEs) were considered competing risks. Specifically, patients were (a) censored if they neither had died nor had disease progression by the end of the study; (b) treated as having progression if they had disease progression prior to death or the end of the study, or if death was due to disease; (c) treated as having died from other cause if they had died from a cause unrelated to the disease and prior to another event; and (d) treated as having discontinued treatment due to an AE if they were removed from the study due to a study-related AE. Cumulative incidence [60] was calculated for each class of event and graphically displayed. Cumulative risk regression [61] was used to calculate HRs comparing risk rates and their 95% CIs. Wald tests were used for testing the significance of the HRs.

Results

Patients

A total of 95 patients were registered and randomized, 5 patients withdrew, and 90 patients received at least 1 dose of the study drug and were evaluable (Fig. 1). The patient characteristics are summarized in Table 2.

Efficacy

The efficacy results are summarized in Table 3 and Figure 2. Investigator assessment, confirmed by the diagnostic imaging collaborator at each institution and by centralized blinded radiology review, was used in determining tumor response and progression. The median OS of the patients treated with B+E and those treated with S were essentially the same. The 12-month survival was 37% (95% CI: 25–55) among patients treated with B+E, and 35% (95% CI: 22–55) among patients treated with S. The HR for OS was 0.92 (95% CI: 0.57–1.47). The objective RR for B+E was 15% (95% CI: 6.2–28) and that for S was 9% (95% CI: 2.6–22). OS did not differ between the B+E and the S arm based on ECOG PS or BCLC stage A or B versus BCLC stage C.

Since most other randomized HCC trials included only patients with Child-Pugh class A liver function [5, 62–65], OS was also assessed for the subgroup of patients in this study who were Child-Pugh class A versus B7 (Fig. 2d). The median OS of the patients treated with B+E ($n = 39$) was 11.4 months (95% CI: 7.5–15.7) and that of the patients treated with S ($n = 38$) was 10.26 months (95% CI: 5.9–13.0) (median OS in the SHARP trial: 10.7 months). The 12-month survival among the Child-Pugh class A patients was 45% (95% CI: 31–65) with B+E and 40% (95% CI: 26–61) with S (HR = 0.88; 95% CI: 0.53–1.46) (1-year survival in the SHARP trial: 44%), thus the trial was negative for any difference in OS based on overlapping CIs for the HR.

Median EFS (Fig. 2e, f) was 4.37 months (95% CI: 2.99–7.36) among all patients treated with B+E and 2.76 months (95% CI: 1.84–4.80) among the patients treated with S. The HR for EFS was 0.67 (95% CI: 0.42–1.07; $p = 0.09$). These data suggest that the patients in the B+E arm were able to stay on therapy longer than those in the S arm, even if the difference was not statistically significant.

Safety and Tolerability

The causes and grades of the 25 most common AEs in each arm are summarized in Table 4. Table 5 summarizes the safety and tolerability data by treatment arm. The overall number of grade 1–4 AEs (serious AEs [SAEs]) in the B+E arm was higher than the number in the S arm; however, the AE rate (where the rate is SAE or AE number/number of cycles of treatment administered) was slightly higher in the S arm than in the B+E arm. All SAEs including investigator-assessed causality are described for B+E and S in online supplementary Tables 1 and 2 (see www.karger.com/doi/10.1159/000485384 for all online suppl. material). Of note, the incidence of grade 3 or 4 hemorrhage was higher in the B+E arm ($n = 9$) than in the S arm ($n = 2$), which can likely be attributed to B.

The results of the competing risk analysis are summarized in Figure 3. A competing risk is an event that either hinders the observation of the event of interest, which in this study was survival, or modifies the chance that this event occurs. The cumulative incidence of progression based on the competing risk analysis was slightly higher in the B+E arm (HR = 1.32; $p = 0.35$) (Fig. 3a). The cumulative incidence rates of death from other causes and of other clinical events were comparable in the two groups (results not shown).

Figure 3b shows that the S arm had a statistically significantly higher rate of treatment discontinuation due to toxicity than the B+E arm, with an HR of 0.40 ($p = 0.03$) favoring B+E. Figure 3c shows the number of cycles administered and the time to treatment discontinuation in the two study arms. The patients in the B+E arm stayed on treatment longer than those in the S arm: 87% of the patients in the B+E arm received more than one cycle of treatment, compared with 65% of the patients in the S arm (Fig. 3c; $p = 0.02$). Taken together, the competing risk analysis showed that the B+E regimen was generally better tolerated by the patients in this study than the S regimen, and the patients in the two arms had similar rates of progression.

Discussion

Although this was a negative study that did not meet its primary endpoint of demonstrating significant improvement in median OS for patients treated with B+E despite the dual targeting of important pathways in HCC, the results are nonetheless informative. The outcomes are confounded in part by the inclusion of Child-Pugh class B patients in this study, who are well known to have shorter OS than Child-Pugh class A patients [66–68]. This is confirmed by the finding that the median OS for the S arm of 8.6 months (95% CI: 5.7–12.2) is lower than that reported in several other randomized trials where only Child-Pugh class A patients were included [5, 62–65, 69]. The median OS of the Child-Pugh class A patients treated with S in this trial (10.26 months) is essentially the same as the median OS of 10.7 months reported in the pivotal SHARP trial [5]. Although the current study had a randomized, open-label, phase II design and its results cannot be compared directly to the results of other trials, the outcomes for the S arm are generally consistent with those seen in other studies.

This study suggests that the combination of B+E has some efficacy compared to S in patients with advanced HCC based on the RR of 15 versus 9%, EFS of 4.37 versus 2.76 months, and median OS of 11.4 versus 10.26 months when the data for Child-Pugh class A patients only are analyzed, although there was no statistically significant difference in any endpoint. It is acknowledged that the magnitude of the difference in OS based on the analysis of Child-Pugh class A patients only is not significant. However, the B+E regimen was better tolerated by the patients than was the S regimen, as evidenced by slightly lower AE and SAE rates as well as a statistically significant difference in the number of treatment cycles the patients were able to receive and the longer time on treatment. The competing risk analysis showed that the patients in the S arm were more likely to discontinue treatment due to toxicity than were the patients in the B+E arm (HR = 0.40).

Given strong preclinical rationale supporting the use of growth factor-targeting agents in HCC, the clinical efficacy of B+E should have been more impressive. Unfortunately, as yet, translating promising preclinical data into significant clinical benefits for HCC patients has been disappointing across multiple drugs, drug combinations, and trial designs [62–64, 70, 71]. It is certainly possible that in this trial, OS was confounded by postprogression therapy, although these data were not captured. The trial design and its potential for success were likely hampered by an ambitious primary endpoint based on singlearm, single-institution trials, which commonly overestimate clinical benefits [72–74].

The long history of negative clinical trials of "targeted" agents in HCC underscores the urgent need for better identification of the key driving carcinogenic mechanisms in HCC that are prognostic, predictive, and "actionable." An identification of such validated targets has been lacking in all trials of growth factor inhibitors in HCC [75, 76]. While targeting signaling pathways themselves has always held appeal in anticancer drug development, the underlying genetic alterations that lead to deregulation of signaling pathways may represent better biotargets than growth factor expression itself [77]. Given the complexity and heterogeneity of HCC, unraveling the pattern of genomic alterations that are intrinsic to the liver itself, versus those due to hepatocarcinogenesis and the surrounding inflammatory milieu, is pivotal to identifying systemic therapies that will further improve patient outcome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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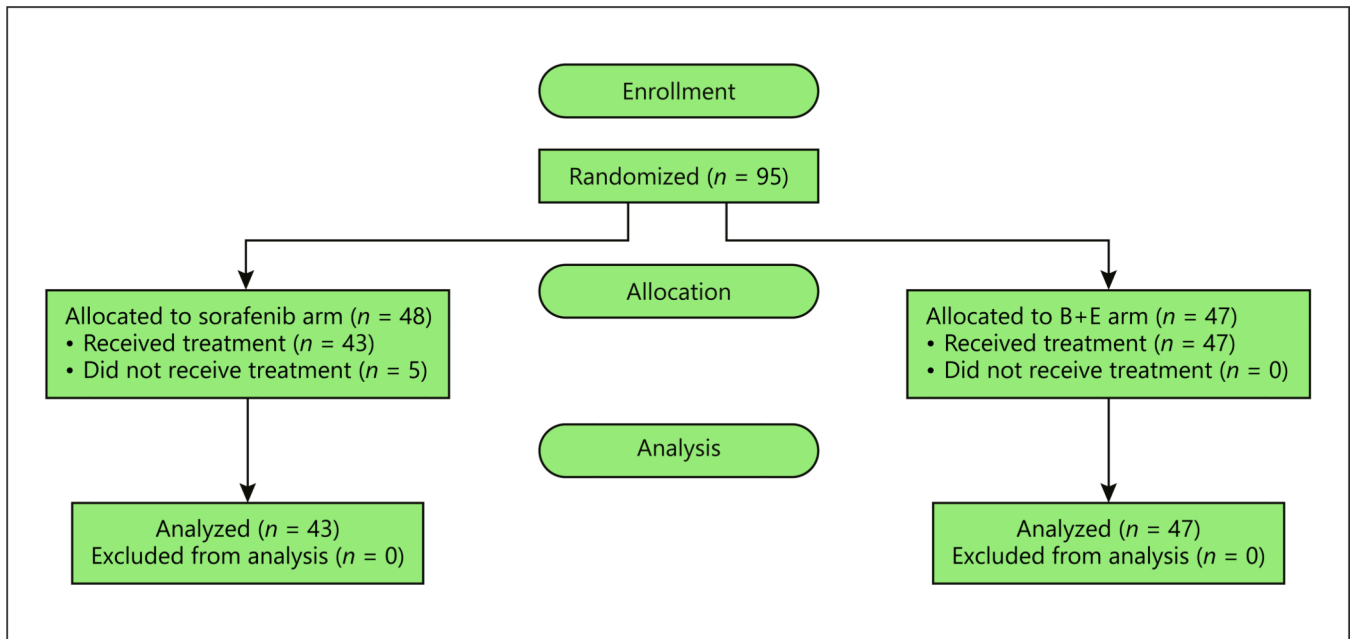
Fig. 1.
Enrollment summary.
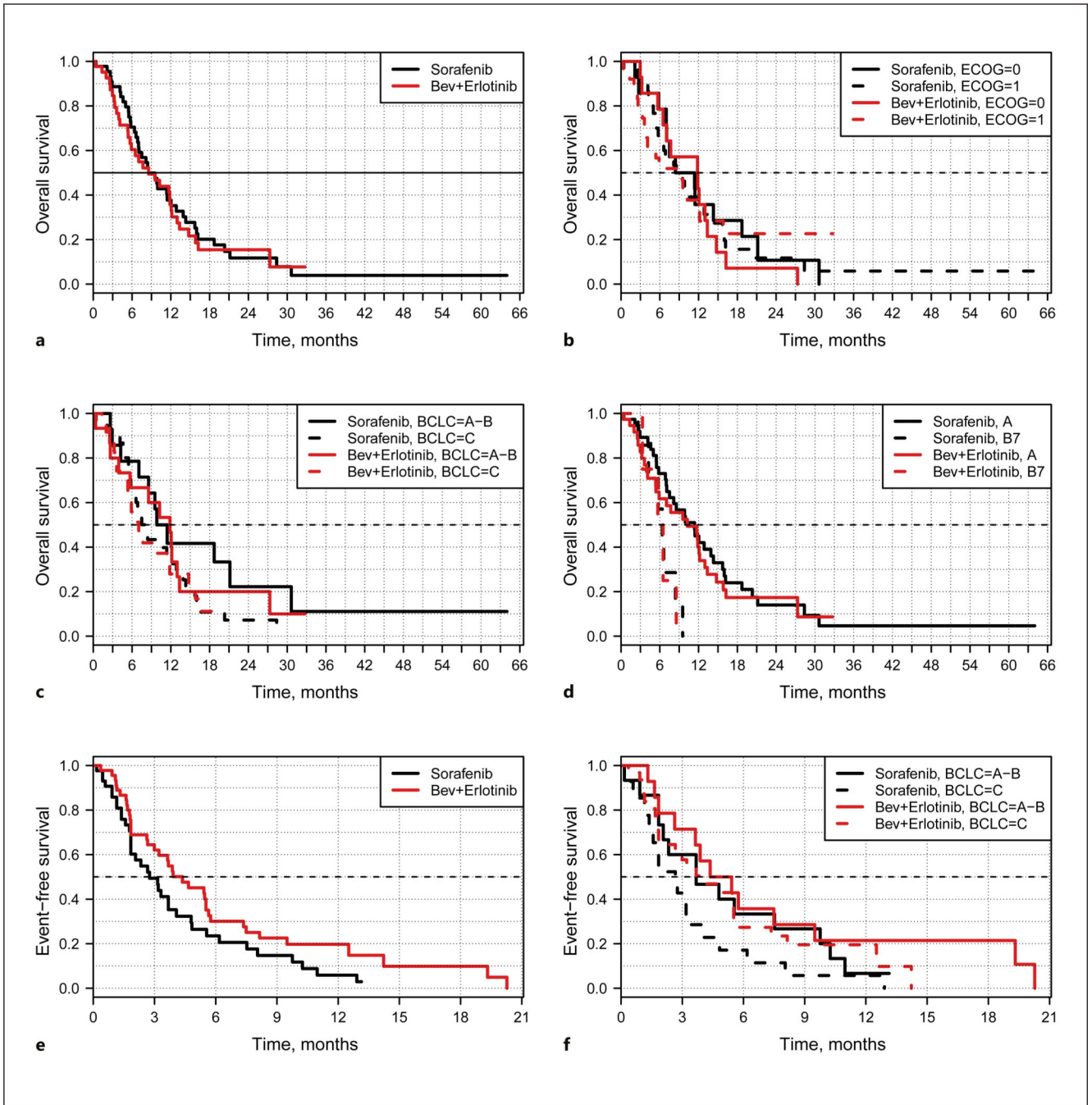
Fig. 2.
Survival summary. **a** Overall survival. **b** Overall survival by ECOG status. **c** Overall survival by BCLC stage. **d** Overall survival Child-Pugh class A versus B. **e** Event-free survival. **f** Event-free survival by BCLC stage. The *p* value for testing overall survival was 0.73 using the Cox proportional hazards model; however, a hypothesis test for overall survival comparing the two groups was not included in the study design due to insufficient power. Bev, bevacizumab.
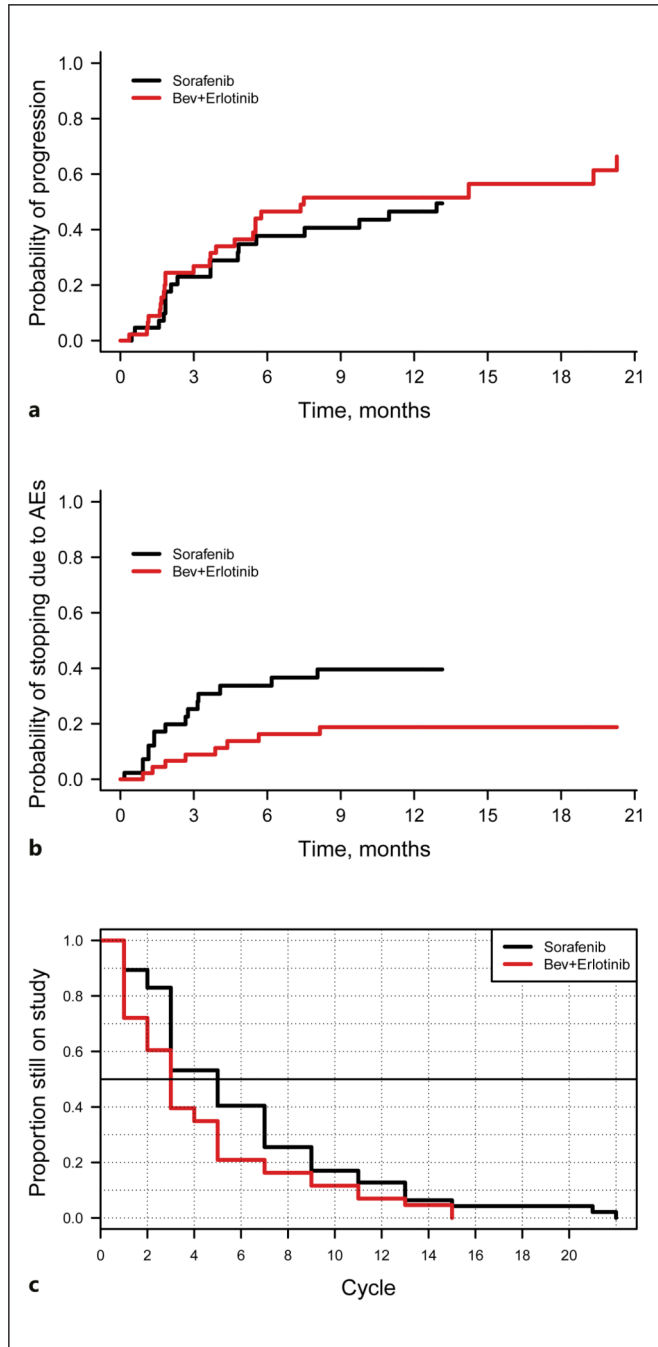
Fig. 3.

Competing risk analysis. **a** Progression as a reason for discontinuation. HR = 1.32 ($p =$ 0.35). **b** Toxicity as a reason for discontinuation. HR = 0.40 ($p =$ 0.03). **c** Time on treatment. This plot shows the number of cycles administered in each study arm. The data show that the sorafenib (S) patients discontinued treatment sooner than the bevacizumab plus erlotinib (B +E) patients. Of the 43 evaluable patients in the S arm, 15 (35%) received only one cycle of treatment. In the B+E arm, 6 of the 47 evaluable patients (13%) received only one cycle. The

difference in the curves is significant ($p = 0.02$) by a log-rank test. Bev, bevacizumab; AEs, adverse events.

Table 1.

Phase II trials of bevacizumab plus erlotinib in advanced HCC

Study	Patient population	Sample size, *n*	Outcome		
			mOS, months	mPFS, months	RR, %
First line for advanced HCC					
Govindarajan et al.	Child-Pugh A	21	8.3		
Philip et al.	Child-Pugh A 74%	27	9.5		
	Child-Pugh B 26%				
Hsu et al.	Child-Pugh A	51	10.7	2.9	
Second line for advanced HCC					
Thomas et al.	Child-Pugh A 87%	40	15.6	9.0	25
	Child-Pugh B 13%				
Yau et al.	Child-Pugh A	10	4.37		
Kaseb et al.	Child-Pugh A 86%	59	13.7	7.2	24
	Child-Pugh B 14%				
Kaseb et al.	Child-Pugh A 98%	44	9.9		
	Child-Pugh B 2%				

HCC, hepatocellular carcinoma; mOS, median overall survival; mPFS, median progression-free survival; RR, response rate.

Table 2.

Distribution of clinical and demographic characteristics of the patients ($N = 90$)

Characteristic	S ($n = 43$)	B+E ($n = 47$)	p value[1]
Age, years			0.72
Median	61	61	
Range	44–81	43–82	
ECOG performance status			0.44
0	17 (40)	15 (32)	
1	25 (58)	32 (68)	
2	1 (2)	0	
Child-Pugh class [8, 9]			0.56
A	38 (88)	39 (83)	
B7	5 (12)	8 (17)	
CLIP score [10, 11]			0.81
0	4 (9)	7 (15)	
1	10 (23)	10 (21)	
2	17 (40)	16 (34)	
3	9 (21)	8 (17)	
4–5	3 (7)	6 (13)	
Race			0.27
White	31 (72)	28 (60)	
Other	12 (28)	19 (40)	
BCLC stage [12, 13]			0.40
A	4 (9)	1 (2)	
B	11 (26)	14 (30)	
C	28 (65)	32 (68)	
Prior treatment			
Resection	5 (11)	7 (15)	0.76
Ablation	5 (11)	1 (2)	0.10
Transarterial intrahepatic therapy	15 (35)	13 (27)	0.50
Tumor characteristics			
Extrahepatic spread	11 (25)	19 (40)	0.18
Gross vascular invasion	11 (25)	8 (17)	0.44

Values are presented as n (%) unless specified otherwise. S, sorafenib; B+E, bevacizumab plus erlotinib.

[1] p values based on two-sample t test for continuous variables; Fisher's exact test for categorical variables.

Table 3.

Efficacy summary

Study arm	Response rate, %	mOS (HR = 0.92; 95% CI: 0.57–1.47)		mEFS, months (HR = 0.67; 95% CI: 0.42–1.07)	mOS Child-Pugh class A patients (HR = 0.88; 95% CI: 0.53–1.46) (S, n = 38; B +E, n = 39)	
		median, months	12-month, %		median, months	12-month, %
S (n = 43)	9 (2.6–22)	8.6 (5.7–12.2)	35 (22–55)	2.76 (1.84–4.80)	10.26 (5.9–13.0)	40 (26–61)
B+E (n = 47)	15 (6.2–28)	8.6 (7.0–13.9)	37 (25–55)	4.37 (2.99–7.36)	11.4 (7.5–15.7)	45 (31–65)

Values in parentheses are 95% CI. mOS, median overall survival; mEFS, median event-free survival; S, sorafenib; B+E, bevacizumab plus erlotinib.

Table 4.

Safety and tolerability

AE type	S arm			B+E arm		
	grade		total	grade		total
	1–2	3–4		1–2	3–4	
Fatigue	25	8	33	30	3	33
Diarrhea	26	4	30	37	4	41
Nausea	16	2	18	24	0	24
Anorexia	16	1	17	26	2	28
Weight loss	17	0	17	25	0	25
Platelets decreased	15	2	17	16	1	17
Hand-foot skin reaction	12	4	16	0	0	0
Dry skin	16	0	16	24	0	24
Pruritus	0	0	0	22	1	23
Vomiting	14	1	15	0	0	0
Acne	0	0	0	18	9	27
Limb edema	13	1	14	0	0	0
Dysgeusia	9	0	9	21	0	21
Epistaxis	0	0	0	21	0	21
Hypertension	11	3	14	17	4	21
Weakness	12	2	14	0	0	0
AST increased	9	4	13	20	5	25
Bilirubin increased	9	3	12	16	3	19
Hemoglobin decreased	9	3	12	17	3	20
Hyponatremia	6	6	12	11	4	15
Dizziness	11	0	11	0	0	0
ALT increased	9	2	11	16	1	17
Rash	11	0	11	16	0	16
Back pain	9	1	10	0	0	0
Abdominal pain	8	2	10	17	7	24
Fever	0	0	0	14	1	15

AE type	S arm			B+E arm		
	grade		total	grade		total
	1–2	3–4		1–2	3–4	
Dry mouth	0	0	0	13	1	14
Chills	0	0	0	13	1	14
Proteinuria	0	0	0	13	1	14
Hypoalbuminemia	0	0	0	13	1	14
Constipation	10	0	10	0	0	0
Alopecia	7	0	7	0	0	0
Alkaline phosphatase increased	6	2	8	14	4	18
Total	306	51	357	460	56	516

The worst grade experienced per patient is included in the table. For example, if a patient had grade 3 diarrhea and then grade 4 diarrhea, the grade 4 diarrhea would be included in the table and the grade 3 diarrhea would not. This table includes the 25 most common AEs in each arm (complete AE information included in online suppl. Tables S1 and S2). AE, adverse event; S, sorafenib; B+E, bevacizumab plus erlotinib.

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Table 5.

Summary of the safety and tolerability data for the treatment arms

Event	S ($n = 43$)	AE rate[1]	B+E ($n = 47$)	AE rate[1]
Number of cycles[2] initiated per arm	184		287	
Median number of cycles initiated	3		5	
Total number of grade 1–2 AEs per arm	306	1.6	461	1.6
Total number of grade 3–4 AEs per arm	51	0.27	56	0.19
Total number of SAEs in treatment arm	30	0.163	40	0.139

AE, adverse event; SAE, severe AE; S, sorafenib; B+E, bevacizumab plus erlotinib.

[1] The AE rate is the total number of events/total number of cycles.

[2] One cycle = 28 days.