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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Brivanib Versus Sorafenib As First-Line Therapy in Patients With Unresectable, Advanced Hepatocellular Carcinoma: Results From the Randomized Phase III BRISK-FL Study

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ABSTRACT

Purpose
Brivanib is a dual inhibitor of vascular-endothelial growth factor and fibroblast growth factor receptors that are implicated in the pathogenesis of hepatocellular carcinoma (HCC). Our multinational, randomized, double-blind, phase III trial compared brivanib with sorafenib as first-line treatment for HCC.

Patients and Methods
Advanced HCC patients who had no prior systemic therapy were randomly assigned (ratio, 1:1) to receive sorafenib 400 mg twice daily orally (n = 578) or brivanib 800 mg once daily orally (n = 577). Primary end point was overall survival (OS). Secondary end points included time to progression (TTP), objective response rate (ORR), disease control rate (DCR) based on modified Response Evaluation Criteria in Solid Tumors (mRECIST), and safety.

Results
The primary end point of OS noninferiority for brivanib versus sorafenib in the per-protocol population (n = 1,150) was not met (hazard ratio [HR], 1.06; 95.8% CI, 0.93 to 1.22), based on the prespecified margin (upper CI limit for HR ≤ 1.08). Median OS was 9.9 months for sorafenib and 9.5 months for brivanib. TTP, ORR, and DCR were similar between the study arms. Most frequent grade 3/4 adverse events for sorafenib and brivanib were hyponatremia (9% and 23%, respectively), AST elevation (17% and 14%), fatigue (7% and 15%), hand-foot-skin reaction (15% and 2%), and hypertension (5% and 13%). Discontinuation as a result of adverse events was 33% for sorafenib and 43% for brivanib; rates for dose reduction were 50% and 49%, respectively.

Conclusion
Our study did not meet its primary end point of OS noninferiority for brivanib versus sorafenib. However, both agents had similar antitumor activity, based on secondary efficacy end points. Brivanib had an acceptable safety profile, but was less well-tolerated than sorafenib.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide.[1] Patients often present with unresectable, recurrent, or metastatic HCC, for which chemotherapy has been shown to be ineffective.[2,3] As HCC is a vascularized tumor, one approach to treatment is to target angiogenic factors, such as vascular endothelial growth factor (VEGF). Sorafenib, a multikinase inhibitor that targets multiple signaling pathways including VEGF signaling, is the only systemic agent to demonstrate overall survival (OS) benefit as first-line therapy in advanced HCC.[4,5] However, disease control with sorafenib is short-lived, some patients are intolerant of sorafenib, and the median survival rate is still less than 1 year. Thus, more effective first-line treatments for advanced HCC are needed.[3]

Like VEGF, fibroblast growth factor (FGF) is a key driver of angiogenesis in HCC.[6] FGF may have direct and indirect effects on tumors.[7-12] Upregulation of alternate angiogenic signals, such as FGF,

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may play a role in evasive resistance to VEGF-targeted therapy.[13-16] Notably, the combined administration of anti-FGF and anti-VEGF antibodies in a mouse HCC model has shown additive antitumor activity.[17] Thus, targeting both VEGF and FGF may offer therapeutic advantages over a blockade of VEGF alone.

Brivanib, a tyrosine kinase inhibitor, is an orally active, selective, dual inhibitor of FGF and VEGF signaling.[18] Brivanib had antiangiogenic and antiproliferative effects on tumor cells from multiple tumor types, including liver.[18-20] Brivanib demonstrated antitumor activity in xenograft HCC models expressing FGF receptors and in those resistant to sorafenib.[20-22] In a phase II study, brivanib showed evidence of antitumor activity in patients with previously untreated advanced HCC as well as in those who had experienced prior antiangiogenic therapy failure.[23,24] In the phase III BRISK-PS study of HCC patients who experienced sorafenib treatment failure, brivanib did not significantly improve OS as compared with placebo but did demonstrate improved time to progression (TTP), objective response rate (ORR), and disease control rate (DCR) according to modified Response Evaluation Criteria in Solid Tumors (mRECIST).[25] Herein, we present the results from a phase III study comparing brivanib with sorafenib as first-line therapy in patients with unresectable, advanced HCC.

PATIENTS AND METHODS

Ethics and Study Management

The study (No. NCT00858871) was approved by the institutional review board or ethics committee at each participating center and was conducted according to Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws. The study was monitored for safety and disease status by an independent Data Monitoring Committee, and an interim analysis for futility was performed.

Patients

Adults with advanced HCC who had no prior systemic therapy were eligible. Advanced disease was defined as disease not eligible for surgical and/or locoregional therapies, or progressive disease after surgical and/or locoregional therapies. Other key inclusion criteria included a Child-Pugh A liver function score, an Eastern Cooperative Oncology Group performance status (ECOG-PS) score of 0 or 1, and at least one untreated measurable lesion by computed tomography or magnetic resonance imaging. See Appendix Table A1 (online-only) for eligibility criteria.

Trial Design and Treatment

This was a multinational, randomized, double-blind, phase III trial. Eligible patients were randomly assigned centrally (assignment ratio, 1:1) by Interactive Voice Response System to receive brivanib 800 mg once daily orally plus sorafenib-matched placebo or sorafenib 400 mg twice daily orally plus brivanib-matched placebo. Randomization was stratified by ECOG-PS score (0 *v* 1), extrahepatic spread and/or vascular invasion (yes *v* no), and study site. Dose reductions for toxicity were permitted (Appendix Table A2). Treatment continued until unacceptable toxicity or disease progression. Treatment could continue beyond radiographic progression if the investigator determined that the patient was benefiting from the blinded treatment.

Assessments

The primary end point of the study was OS, defined as the time from randomization until the date of death from any cause. Secondary end points were TTP, ORR, DCR based on mRECIST, and safety. TTP was defined as the time from randomization to radiographic disease progression, ORR as the percentage of randomly assigned patients with complete response or partial response, DCR as the percentage of randomly assigned patients with complete response, partial response, or stable disease. Tumor measurements were performed at screening and every 6 weeks during treatment by contrast-enhanced, dual-phase spiral computed tomography or magnetic resonance imaging. A complete or partial response was confirmed by a second tumor measurement at least 4 weeks after the first assessment. Scans were assessed by the investigators using mRECIST for HCC.[3,26,27] The mRECIST for HCC takes into account the induction of intratumoral necrotic areas (using contrast-enhanced radiologic imaging) in estimating the decrease in viable tumor load rather than just a reduction in overall tumor size (modified WHO criteria or standard RECIST).

Safety was assessed in patients who received at least one dose of study therapy. Adverse events (AEs) were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). Quality of life was assessed by several instruments including the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30). Physical and role function scores of the EORTC QLQ-C30 questionnaire are presented, as these scores are representative of the patients' overall health status. The QLQ-C30 was self-administered by patients at baseline, at every 6-week clinic visit, and at the end-of-treatment visit.

Statistical Methods

The primary end point of OS was first tested for noninferiority for brivanib compared with sorafenib in the per-protocol population. Superiority was to be tested if noninferiority was concluded. A prespecified noninferiority margin of 1.08 (the upper limit of the 95% CI for hazard ratio [HR]) corresponding to a 2.8-week decrease in median OS on brivanib versus sorafenib was considered clinically acceptable. Assuming an exponential survival distribution and a median OS of 37.3 weeks (the average of the median OS in the SHARP [46.3 weeks][4] and the Asia-Pacific [28.3 weeks][5] trials), and taking into account one formal interim analysis for futility, it was estimated that 777 deaths were required in the per-protocol population (817 deaths in the intention-to-treat population, assuming a 5% protocol deviation) to have a 90% power to claim noninferiority, given a true HR of 0.85. A minimum observed HR of 0.94 was needed to claim noninferiority. Based on these assumptions, a maximum of 1,182 patients were to be randomly assigned.

The HR of brivanib to sorafenib for OS and its associated two-sided 95.8% CI (based on the interim analysis for futility) were computed using a Cox proportional hazards model stratified by ECOG PS (0 *v* 1), extrahepatic spread and/or vascular invasion (yes *v* no), and region (Asia *v* rest of the world). Median OS and associated 95% CI were estimated using the Kaplan-Meier method. OS was compared between arms using a stratified log-rank test at a two-sided alpha of .042. A Cox proportional-hazards model stratified by the above factors ($\alpha = .05$) was used to evaluate the association of prespecified baseline factors (age, risk factors [hepatitis B or C virus, alcohol], α-fetoprotein, tumor morphologic features, size of the largest tumor nodule, previous locoregional treatment and/or surgery, Child-Pugh score, and major portal vein invasion) with OS and to adjust the treatment effect for these factors. Analyses conducted to determine the *P* value, median, HR, and 95% CIs for TTP were as described for OS. Exact 95% CIs for ORR and DCR were calculated using the Clopper-Pearson method.[28] ORR and DCR in the two arms were compared using a Cochran-Mantel-Haenszel test with associated odds ratio estimates and 95% CIs stratified by the factors used for OS. Changes from baseline of symptom assessment score in physical and role functions at weeks 6 and 12 were compared between the two treatment groups using a Wilcoxon rank-sum test.

RESULTS

Patients

A total of 1,155 patients (intention-to-treat population) with advanced HCC were randomly assigned from May 2009 until August 2011 across Asia (62%), Europe (23%), the Americas (13%), Australia (0.8%), and Africa (0.6%); 1,150 patients were treated (Fig 1). At the time of the final analysis, 62 patients (11%) in the sorafenib arm and 35 patients (6%) in the brivanib arm remained on study. The most common reasons for study discontinuation were disease progression (sorafenib, 53%; brivanib, 46%) and study-drug toxicity (sorafenib,

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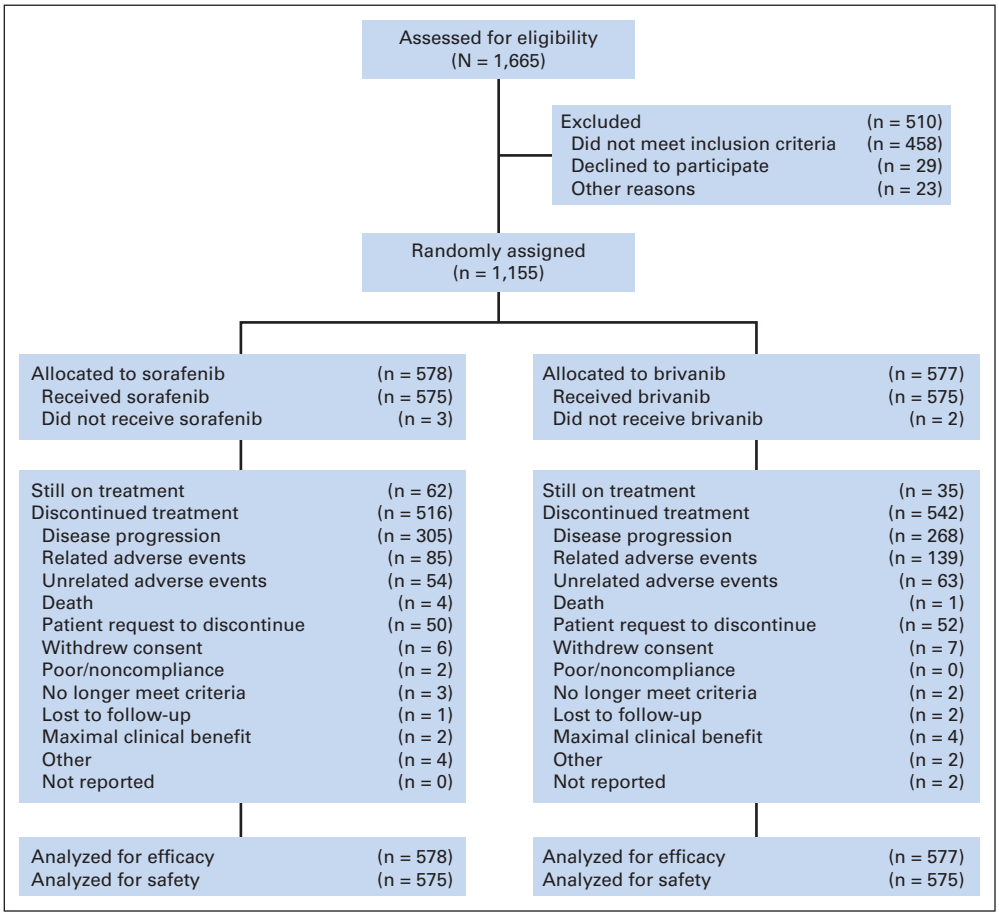

Fig 1. CONSORT diagram of patients with advanced hepatocellular carcinoma who had no prior systemic therapy in the BRISK-FL study, a multicenter, randomized, double-blind, placebo-controlled, phase III trial.

15%; brivanib, 24%). Baseline characteristics of the study population were balanced between the arms (Table 1). Patients had advanced HCC (Barcelona Clinical Liver Cancer stage C, 77%) with good liver function (Child-Pugh A, 92%) and good performance status (ECOG PS 0, 62%). The predominant risk factor was hepatitis B virus infection (44%), followed by hepatitis C virus infection (20%) and alcohol use (16%).

Treatment Exposure

The Kaplan-Meier estimate of the median treatment duration was 4.1 months (95% CI, 3.4 to 4.2) for sorafenib and 3.2 months (95% CI, 2.8 to 3.8) for brivanib. The median of the mean daily dose was 661 mg/d (range, 146 to 1,156 mg/d) for sorafenib and 716 mg/d (range, 204 to 1,070 mg/d) for brivanib. The median cumulative doses were 66,000 mg and 62,400 mg, respectively.

Efficacy

The study did not meet its primary objective of OS noninferiority for brivanib compared with sorafenib. In the per-protocol population (n = 1,150), the HR for brivanib to sorafenib was 1.06 with a 95.8% CI of 0.93 to 1.22 (Table 2). The upper limit of this CI exceeded the prespecified noninferiority boundary of 1.08. The median OS was 9.9 months in the sorafenib arm and 9.5 months in the brivanib arm. OS results were similar in the intention-to-treat population (HR, 1.07; 95.8% CI, 0.94 to 1.23; Fig 2A). A prespecified analysis showed that subset results were consistent with those for the overall study population (Fig 3). A multivariate Cox proportional-hazards model identified the following baseline factors as prognostic of OS: α-fetoprotein, tumor morphologic feature, size of the largest nodule, Child-Pugh score, and major portal vein invasion. After adjusting for the baseline factors, the effect of brivanib or sorafenib on OS remained unchanged (HR, 1.09; 95% CI, 0.95 to 1.25). Proportions of patients who received poststudy systemic treatments were similar between the sorafenib and brivanib arms (21% *v* 22%), as were proportions of poststudy nonsystemic treatments (17% *v* 19%).

TTP was similar between the sorafenib and brivanib arms (Table 2, Fig 2B) as were DCR and ORR (Table 2). In patients with baseline α-fetoprotein $\geq$ 200 ng/mL and at least one on-study α-fetoprotein assessment, α-fetoprotein reduction of $\geq$ 50% relative to baseline was observed in 31% of the sorafenib and 58% of the brivanib patients (Appendix Figure A1). Similar α-fetoprotein reductions were noted when baseline α-fetoprotein cutoff used was the upper limit of the normal or 400 ng/mL.

Safety

AEs (regardless of relationship) that occurred in at least 15% of the treated patients are listed in Table 3. Diarrhea, abdominal pain, constipation, hyperbilirubinemia, elevated AST, elevated ALT, and weight loss occurred at a similar rate in the two study arms. Hand-foot-skin reaction, alopecia, rash, and pyrexia were more frequent among sorafenib patients than with brivanib, whereas decreased appetite, fatigue, hypertension, nausea, vomiting, hyponatremia,

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Table 1. Baseline Demographics and Disease Characteristics

Variable	Sorafenib (n = 578) No. of Patients	%	Brivanib (n = 577) No. of Patients	%
Age, years				
Median	60		61	
Range	25-89		19-87	
Sex				
Male	484	84	483	84
Female	94	16	94	16
Region				
Asia	372	64	346	60
Europe	135	23	134	23
Americas	65	11	87	15
Others	6	1	10	2
ECOG PS				
0	352	61	361	64
1	226	39	216	36
Time from initial diagnosis of HCC to start of study therapy, days				
Median	149		138	
Range	4-9,368		2-6,134	
BCLC stage				
A	30	5	37	6
B	97	17	95	17
C	449	78	444	77
Child-Pugh class				
A	531	92	531	92
B	47	8	46	8
Macrovascular invasion				
Yes	158	27	155	27
No	420	73	422	73
Portal vein invasion and/or thrombosis				
Yes	111	19	112	19
No	47	8	43	7
Distant metastasis	291	50	283	49
Lymph node metastasis	161	28	156	27
Direct invasion of adjacent organs	45	8	60	10
Extrahepatic spread and/or macrovascular invasion				
Absent	217	38	216	37
Present	361	62	361	63
Risk factors				
Any	434	75	449	78
Alcohol	83	14	106	18
Hepatitis B	258	45	254	44
Hepatitis C	119	21	116	20
Other	37	6	39	7
Serum alpha-fetoprotein				
No. of patients	563		555	
Median, ng/mL	180		142	
Range, ng/mL	$0.6\text{-}9.3 \times 10^5$		$0.4\text{-}1.5 \times 10^6$	
> 200 ng/mL	278	49	261	47
Previous nonsystemic treatment	326	56	318	55
Liver resection	171	30	162	28
Transcatheter arterial embolization	37	6	32	6
Transcatheter arterial chemoembolization	208	36	204	35
Percutaneous ethanol injection	31	5	29	5
Radiofrequency ablation	98	17	74	13

Abbreviations: BCLC, Barcelona Clinic Liver Cancer Staging System; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma.

Table 2. Summary of Efficacy

Variable	Sorafenib (n = 578) No. of Patients	%	Brivanib (n = 577) No. of Patients	%
Overall survival, per protocol population*				
Median, months	9.9		9.5	
95.8% CI	8.5 to 11.5		8.4 to 10.7	
Hazard ratio	1.06			
95% CI	0.93 to 1.22			
P†	.3730			
Overall survival, intention-to-treat population				
Median, months	9.9		9.5	
95% CI	8.5 to 11.5		8.3 to 10.6	
Hazard ratio	1.07			
95.8% CI	0.94 to 1.23			
P†	.3116			
Time to progression, intention-to-treat population				
Median, months	4.1		4.2	
95% CI	3.1 to 4.2		4.1 to 4.3	
Hazard ratio	1.01			
95% CI	0.88 to 1.16			
P†	.8532			
Best response, intention-to-treat population‡				
Complete response	5	1	2	< 1
Partial response	46	8	67	12
Stable disease	323	56	309	54
Progressive disease	138	24	94	16
Unable to assess	66	11	105	18
Objective response rate				
%	9			12
95% CI	7 to 11		9 to 15	
Odds ratio	1.45			
95% CI	0.99 to 2.13			
P§	.0569			
Disease control rate	65			66
95% CI	61 to 69		61 to 69	
Odds ratio	1.02			
95% CI	0.80 to 1.30			
P§	.8739			

Abbreviation: HCC, hepatocellular carcinoma.
*575 patients in each study arm.
†Stratified log-rank test.
‡Based on investigator assessments using modified RECIST for HCC.
§Cochran-Mantel-Haenszel test.

headache, dysphonia, and dizziness were more frequent among brivanib patients. The most frequent grade 3 AEs were hand-foot-skin reactions in the sorafenib arm and hyponatremia, fatigue, and hypertension in the brivanib arm. Grade 4 events were infrequent.

The rate of treatment discontinuation as a result of AEs was 33% with sorafenib patients and 43% with brivanib. The most frequent AEs leading to treatment discontinuation were hyperbilirubinaemia (3%) and AST elevations (2%) in the sorafenib arm; fatigue (5%), hyponatremia (2%), decreased appetite (2%), hyperbilirubinemia (2%), and AST elevations (2%) in the brivanib arm.

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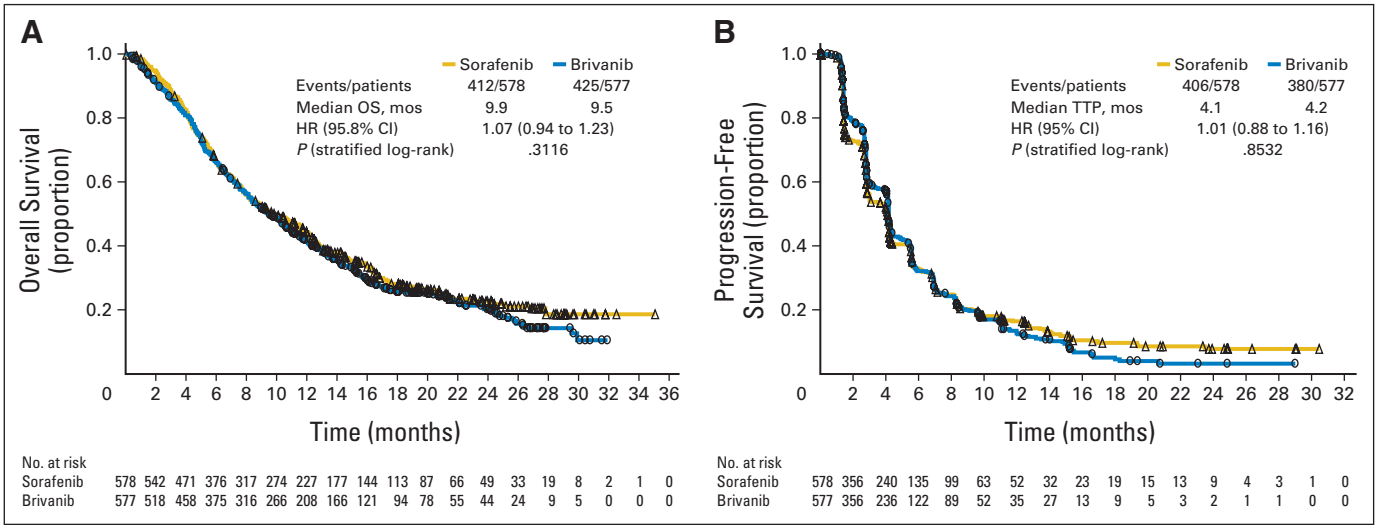

Fig 2. Kaplan-Meier estimates of overall survival (OS) and time to progression (TTP). (A) OS was computed based on the intention-to-treat (ITT) population. Patients who had not died or who were lost to follow-up were censored on the last date on which they were known to have been alive. (B) TTP was computed based on the ITT population. Patients whose disease had not progressed were censored on the date of last tumor assessment. Patients who had no on-study tumor assessments or who had no independent radiologic review were also censored on the date of random assignment. HR, hazard ratio.

The rate of dose reduction was similar between sorafenib and brivanib patients (50% *v* 49%). The rate of dose interruption was 58% in both treatment arms. In the sorafenib arm, dermatologic events were the dominant reason for both dose reduction (20% *v* 2% for brivanib) and dose interruption (21% *v* 3% for brivanib). No single AE caused dose reduction or interruption in more than 7% of brivanib-treated patients.

The overall incidence of serious AEs was 48% for sorafenib patients and 56% for brivanib patients. The most frequent serious AEs (grades 1 to 5) in the sorafenib arm were malignant neoplasm

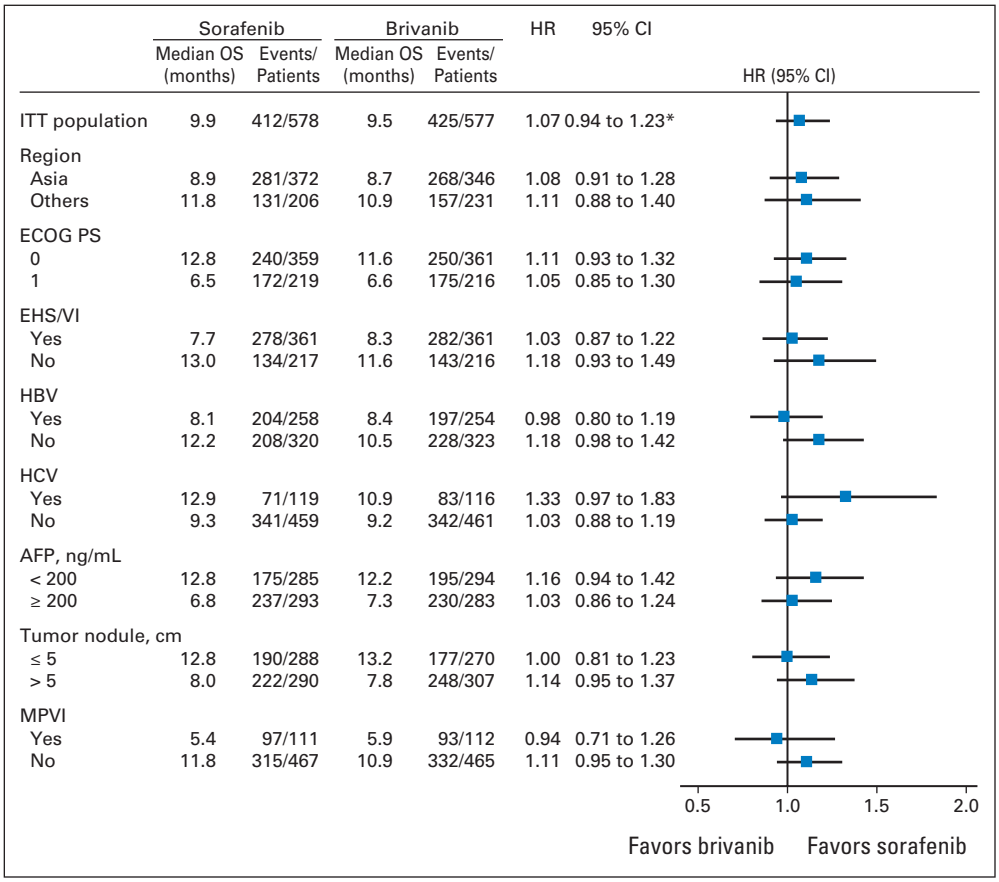

Fig 3. Overall survival (OS) in selected subsets. AFP, α-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS/VI, extrahepatic spread and/or vascular invasion; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; ITT, intention-to-treat; MPVI, major portal vein invasion. (*) 95.8% CI.

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Table 3. Incidence of Adverse Events by Percentage of Patients

Adverse Event	Sorafenib (n = 575)			Brivanib (n = 575)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Overall incidence	99	55	10	98	52	15
Decreased appetite	35	3	0	52	8	0.3
Fatigue	35	7	0	52	14	0.5
Hand-foot-skin reaction	52	15	0	18	2	0
Diarrhea	50	7	0	49	6	0.3
Hypertension	27	5	0.3	41	13	0.3
Nausea	19	0.3	0	38	2	0
Abdominal pain	32	5	0.3	32	6	1
Vomiting	16	0.5	0	27	3	0
AST increased	26	15	2	25	13	2
Hyponatremia	11	9	0.2	26	20	3
Alopecia	22	NA	NA	2	NA	NA
Pyrexia	21	0.3	0	15	0.5	0
Rash	21	2	0	10	1	0
Weight decreased	21	2	0	21	4	0
ALT increased	18	7	1	19	7	0.3
Headache	11	0.3	0	19	1	0
Hyperbilirubinemia	18	7	2	19	10	2
Constipation	16	0.2	0	18	0.3	0
Dysphonia	10	0	0	18	0	0
Dizziness	7	0.3	0	17	1	0

NOTE. Listed are adverse events (any grade, any cause) that occurred in at least 15% of the patients in either group.
Abbreviation: NA, not applicable.

Table 4. Quality of Life by EORTC QLQ-C30 Questionnaire

Variable	Sorafenib	Brivanib	*P**
Physical function			
Baseline point score			.3181
No. of patients	557	551	
Mean	83	83	
SD	17	17	
Median	87	87	
Range	0-100	0-100	
Change in point score at week 12 from baseline			.0002
No. of patients	423	396	
Mean	−18	−24	
SD	28	29	
Median	−7	−13	
Range	−100-87	−100-53	
Role function			
Baseline point score			.6061
No. of patients	557	551	
Mean	84	85	
SD	25	23	
Median	100	100	
Range	0-100	0-100	
Change in point score at week 12 from baseline			.0002
No. of patients	421	396	
Mean	−20	−28	
SD	33	34	
Median	−17	−33	
Range	−100-83	−100-67	

Abbreviations: EORTC QLC-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; SD, standard deviation.
*Based on comparison of brivanib to sorafenib using the Wilcoxon rank-sum test.

progression (14%), fatigue (2%), and hyponatremia (1%); the corresponding rates for brivanib patients were 13%, 5%, and 5%, respectively. Hepatic encephalopathy was reported as serious in 2% of sorafenib and 3% of brivanib patients. Serious AEs are listed in Appendix Table A3.

Overall patient deaths (sorafenib, 71%; brivanib, 74%), and deaths within 30 days of the last dose (sorafenib, 17%; brivanib, 16%) were similar between the two arms. The primary reason for death within 30 days of the last dose was disease progression (sorafenib, 13%; brivanib, 11%). Six patient deaths (sorafenib, one patient; brivanib, five patients) attributed by the investigators to study drug toxicity occurred within 30 days of the last dose. There were five additional treatment-related deaths (sorafenib, one patient; brivanib, four patients) that occurred after the 30 days after the last dose. Two treatment-related deaths in the sorafenib arm were as a result of esophageal variceal hemorrhage and myocardial ischemia. Nine treatment-related deaths in the brivanib arm were ascribed to hepatic failure, upper gastrointestinal hemorrhage, cardiorespiratory arrest/abdominal pain, depressed level of consciousness/cerebral infarction/cerebral hemorrhage, diarrhea/vomiting, cerebrovascular accident, asthenia/nausea, gastrointestinal hemorrhage, and hematemesis.

Quality of Life

At baseline, mean and median scores in physical function and role function, as assessed by the EORTC QLQ-C30 questionnaire, were similar in the two treatment arms (Table 4). After 12 weeks of treatment, mean and median scores in physical function and role function declined in both arms. The decline was more pronounced among brivanib patients than sorafenib patients.

DISCUSSION

Despite the success of sorafenib in the first-line treatment of advanced HCC, a need for safer and more effective treatments remains. This phase III study compared brivanib with sorafenib as first-line therapy in this patient population. The study did not meet its primary objective of OS noninferiority for brivanib versus sorafenib, because the upper limit of the CI for the HR exceeded the prespecified margin of 1.08. The difference in median OS for sorafenib and brivanib was 2.0 weeks in favor of sorafenib. The median OS for sorafenib (9.9 months) in this well-controlled study involving a large patient population is closer to that in the SHARP trial (10.7 months) than to that in the Asia-Pacific study (6.5 months), even though the majority of the patients in our study (64%) were from the Asia-Pacific region.[4,5] Although the underlying reason for the discrepancy in median OS is unclear, differences in baseline factors prognostic for OS between these studies, such as ECOG-PS, may have contributed to this.

The median OS of 9.5 months for brivanib is consistent with results from previously reported phase II and III trials of brivanib

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in advanced HCC.[23-25] The phase II study showed a median OS of 10 months in previously untreated patients and 9.8 months in patients who had prior antiangiogenic therapies, whereas a median OS of 9.4 months was reported in the phase III trial of patients who were intolerant to or experienced sorafenib failure.[23-25] Data for secondary efficacy end points showed that both brivanib and sorafenib had similar antitumor activity in our study. TTP, DCR, and ORR were all comparable between the drugs. The rate of α-fetoprotein reduction was higher with brivanib. These data are consistent with those in the phase III BRISK-PS study of post-sorafenib HCC patients, in which brivanib improved TTP, ORR, and DCR and reduced α-fetoprotein compared with placebo.[25] It should be noted that ORR in our study was higher than historical data for sorafenib.[4,5] This higher rate is likely a reflection of the use of mRECIST for HCC that is believed to better capture tumor response to targeted therapies in HCC patients by differentiating viable tumors from necrotic tissues.[3,26,27]

Overall, brivanib had an acceptable safety profile. There were no new or unexpected safety findings with either agent. Certain AEs typical of VEGF inhibition were more frequent with brivanib than with sorafenib, consistent with brivanib being a more potent VEGF inhibitor. Skin toxicities including hand-foot-skin reaction were more common with sorafenib than with brivanib, whereas hyponatremia was reported more frequently with brivanib, suggesting that these AEs are compound-specific. Similar results for skin toxicities and hyponatremia were reported in previous studies evaluating brivanib in various cancer types including HCC, sarcoma, ovarian, and colorectal cancers.[23-25,29-32] Causes for 11 patient deaths (sorafenib, two patients; brivanib, nine patients) considered by investigators to be treatment-related were not unusual for this patient population.

Brivanib appeared to be less well-tolerated than sorafenib, based on overall safety profile and treatment discontinuation. Although treatment discontinuation owing to AEs was more frequent with brivanib than with sorafenib, the rate of dose reduction/interruption was similar for both agents. Given the clinical relevance of skin toxicities for sorafenib therapy, it is noteworthy that skin toxicities caused dose reduction/interruption in 20% to 21% of the sorafenib-treated patients versus 2% to 3% of the brivanib-treated ones. In our study, declines in physical and role functions were more pronounced in the brivanib arm than in the sorafenib arm. The differences between arms were represented by six points for physical function and eight points for role function. However, though the decrease in both domains was statistically greater for brivanib compared with sorafenib, the clinical impact of these differences remains unclear.[33]

The present data underscore the difficulty in developing drugs for HCC, a disease with complex molecular abnormalities. A large phase III study evaluating sunitinib against sorafenib in the first-line treatment of advanced HCC was halted at the interim analysis, because of an unfavorable risk-benefit profile for sunitinib versus sorafenib.[34] Interestingly, in the sunitinib study, patients with prior Hepatitis C infection had a longer OS rate with sorafenib than with sunitinib. In our study, sorafenib seemed to have longer OS than brivanib in patients with prior Hepatitis C, but no conclusion can be drawn because of the exploratory nature associated with subset analyses. Though both sorafenib and sunitinib inhibit VEGF and platelet-derived growth factor signaling, sorafenib is also a potent inhibitor of raf kinase, raising the intriguing possibility that raf kinase inhibition may contribute to the therapeutic effects of sorafenib.[35] Further understanding of the disease at the molecular level should help select patient subtypes most likely to benefit from a specific treatment.

In conclusion, this study did not meet its primary OS objective in the first-line treatment of advanced HCC, based on a noninferiority statistical design, but it did show similar antitumor activity for brivanib and sorafenib, based on TTP, ORR, and DCR data. Brivanib had an acceptable safety profile; however, it was less well-tolerated than sorafenib.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(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 compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: David Liu, Bristol-Myers Squibb (C); Rana Ezzeddine, Bristol-Myers Squibb (C); Ian Walters, Bristol-Myers Squibb (C) **Consultant or Advisory Role:** Philip J. Johnson, Bristol-Myers Squibb (C); Joong-Won Park, Taiho Pharmaceutical (C); Ronnie T.P. Poon, Bristol-Myers Squibb (C); Jean-Luc Raoul, Bristol-Myers Squibb (C), Bayer Schering Pharma (C); Philip A. Philip, Bristol-Myers Squibb (C), Roche (C), Bayer (C); Ann-Lii Cheng, Eisai (C), Bayer HealthCare (C) **Stock Ownership:** David Liu, Bristol-Myers Squibb; Rana Ezzeddine, Bristol-Myers Squibb; Ian Walters, Bristol-Myers Squibb **Honoraria:** Philip J. Johnson, Bayer Healthcare; Joong-Won Park, Bayer Healthcare; Jean-Luc Raoul, Bayer Schering Pharma; Philip A. Philip, Bristol-Myers Squibb, Sanofi-Aventis, Bayer; Ann-Lii Cheng, Eisai, Bayer HealthCare **Research Funding:** Philip A. Philip, Bristol-Myers Squibb, Lilly, Bayer; Chih-Hung Hsu, Bristol-Myers Squibb; Seung-Woon Paik, Bristol-Myers Squibb, Bayer **Expert Testimony:** None **Patents:** None **Other Remuneration:** Philip J. Johnson, Bristol-Myers Squibb

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Appendix

Table A1. Patient Eligibility Criteria

Inclusion criteria
• Men and women ages 18 years or older
• Histologically or cytologically confirmed, advanced HCC
• Advanced disease was defined as disease not eligible for or progressive after surgical or locoregional therapy
• No prior systemic therapy for HCC
• Locoregional therapy must have been completed at least 3 weeks before the baseline scan
• At least one untreated measurable lesion by MRI or spiral CT
• Cirrhotic status of Child-Pugh Class A
• ECOG performance status 0 or 1
• Life expectancy of at least 12 weeks
• Adequate hematologic function with absolute neutrophil counts $\geq$ 1,500/μL, platelet count $\geq 60 \times 10^9$/L, and hemoglobin $\geq$ 8.5 g/dL
• Adequate hepatic function with serum total bilirubin $\leq$ 3 mg/dL, serum albumin $\geq$ 2.8 g/dL, and ALT and AST $\leq 5 \times$ the institutional ULN
• Amylase and lipase $< 1.5 \times$ ULN
• Adequate renal function with serum creatinine $\leq$ 2.0 mg/dL
• INR $\leq$ 2.3 or PT $\leq$ 6 seconds above control
Exclusion criteria
• Brain metastasis or evidence of leptomeningeal disease
• Known fibrolamellar HCC or mixed cholangiocarcinoma and HCC
• Any encephalopathy
• Any ascites
• Bleeding esophageal or gastric varices within 2 months before inclusion
• Previous or concurrent cancer except cervical carcinoma-in-situ, treated basal cell carcinoma, superficial bladder tumors (Ta, Ti, and T1). Any cancer curatively treated $>$ 5 years before entry is permitted
• History of active cardiac disease including uncontrolled hypertension congestive heart failure, active coronary artery disease, unstable or newly diagnosed angina or myocardial infarction less than 12 months before study, cardiac arrhythmias requiring antiarrhythmic therapy other than beta blockers or digoxin, and valvular heart disease $\geq$ CTCAE grade 2
• QTc (Fridericia) $>$ 450 msec on two consecutive ECGs
• Thrombotic or embolic events within the past 6 months and pulmonary embolism
• Any other hemorrhage/bleeding event $\geq$ CTCAE grade 3 within 8 weeks except for esophageal or gastric varices
• Infection
• History of HIV infection
• Active, untreated hepatitis B virus infection
• Active bacterial infection, fewer than 7 days after completing systemic antibiotic therapy
• History of nonhealing wounds or ulcers, or bone fractures within 3 months of fracture
• Pre-existing thyroid abnormality with thyroid function that cannot be maintained in the normal range with medication
• Hyponatremia with sodium $<$ 130 mmol/L
• Baseline serum potassium $<$ 3.5 mmol/L
• Prior use of any systemic anticancer chemotherapy, immunotherapy, or targeted agents for HCC except for sorafenib
• Radiotherapy within 4 weeks before start of study drug (palliative radiotherapy for symptomatic control was acceptable)

Abbreviations: CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; INR, international normalized ratio; MRI, magnetic resonance imaging; PT, prothrombin time; ULN, upper limits of normal.

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Table A2. Dose Modification Schedule for Toxicity

AE	Occurrence	Dose Modification
Baseline ALT/AST $< 2.5 \times$ ULN increase to $> 5 \times$ ULN or baseline ALT/AST 2.5-5 $\times$ ULN increase to $> 10 \times$ ULN	First	• Hold study drugs until ALT/AST $\leq 5 \times$ ULN. • When resuming study drugs, decrease by one dose level from the previous dose level.
	Second	• Hold study drugs until ALT/AST $\leq 5 \times$ ULN. • When resuming study drugs, decrease by one dose level from the previous dose level.
	Third	• Stop study drugs or discuss with medical monitor.
Total bilirubin $\geq 3 \times$ ULN	First	• Hold study drugs until bilirubin $< 3 \times$ ULN. • When resuming study drugs, decrease by one dose level from the previous dose level.
	Second	• Hold study drugs until bilirubin $< 3 \times$ ULN. • When resuming study drugs, decrease by one dose level from the previous dose level.
	Third	• Stop study drugs or discuss with medical monitor.
Grade 3 hyponatremia <130-120 mmol/L	First	• Continue study drugs and start medical intervention until sodium $\geq$ 130 mmol/L.
	Persistent for $\geq$ 7 days or second	• Hold study drugs and start medical intervention. • Resume study drugs when sodium $\geq$ 130 mmol/L; decrease by one dose level from the previous dose level.
	Third	• Hold study drugs and start medical intervention. • Resume study drugs when sodium $\geq$ 130 mmol/L; decrease by one dose level from the previous dose level.
	Fourth	• Stop study drugs or discuss with medical monitor.
Grade 4 hyponatremia $<$ 120 mmol/L	First	• Hold study drugs and start medical intervention. • Resume study drugs when sodium $\geq$ 130 mmol/L; decrease by one dose level from the previous dose level.
	Second	• Stop study drugs or discuss with medical monitor.
Grade 1 skin AEs	Any	• Continue study drugs and consider topical therapy for symptomatic relief.
Grade 2 skin AEs	First	• Continue study drugs and consider topical therapy for symptomatic relief. • If no improvement within 7 days, see next section.
	No improvement within 7 days or second or third occurrence	• Interrupt study drugs until toxicity resolves to grade 0-1. • When resuming treatment, decrease dose by one dose level.
	Fourth	• Stop study drugs.
Grade 3 skin AEs	First or second	• Interrupt study drugs until toxicity resolves to grade 0-1. • When resuming treatment, decrease dose by one dose level.
	Third	• Stop study drugs.
Any other drug-related grade 3 nonhematologic or hematologic toxicity	First	• Hold study drugs. • Resume study drugs when toxicity decreases to $\leq$ grade 1; decrease by one dose level from the previous dose level.
	Second	• Hold study drugs. • Resume study drugs when toxicity decreases to $\leq$ grade 1; decrease by one dose level from the previous dose level.
	Third	• Stop study drugs or discuss with medical monitor.
Any other drug-related grade 4 nonhematologic or hematologic toxicity	First	• Stop study drugs or discuss with medical monitor.

NOTE. Two dose reductions were allowed for brivanib with the first at 600 mg once daily and second at 400 mg every other day. Two dose reductions were allowed for sorafenib with the first at 400 mg once daily and second at 400 mg every other day.

Abbreviations: AE, adverse event; ULN, upper limit of normal.

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Table A3. Percentage of Patients Experiencing Serious Adverse Events Resulting From Any Cause (> 1% of patients)

Event	Sorafenib (n = 575)				Brivanib (n = 575)			
	Grade 1-5	Grade 3	Grade 4	Grade 5	Grade 1-5	Grade 3	Grade 4	Grade 5
Any	47.8	20.2	5.4	15.3	56.3	25.7	8.9	15.0
Neoplasm malignant*	14.3	2.8	0.5	8.7	12.5	2.8	0.7	7.7
Hyponatremia	1.0	1.0	0	0	5.2	4.3	0.9	0
Fatigue	2.3	1.9	0	0	4.9	3.5	0.2	0
Decreased appetite	1.0	0.9	0	0	3.5	2.8	0.2	0
Hepatic encephalopathy	1.7	0.9	0.7	0.2	3.5	2.4	0.5	0.3
Abdominal pain	2.8	1.4	0.3	0	3.3	2.3	0.3	0.2
Diarrhea	2.3	1.9	0	0	3.1	1.7	0.3	0
Ascites	2.8	1.9	0.2	0	2.4	1.9	0	0
Dehydration	0.5	0	0	0	2.4	1.9	0	0
Hypertension	0.7	0.2	0.3	0	2.4	1.2	0.2	0
Hepatic failure	2.1	0.3	0.2	1.2	2.3	0.5	0.9	0.7
Hyperbilirubinemia	2.1	1.2	0.9	0	2.3	1.9	0.3	0
Vomiting	0.3	0.2	0	0	2.1	1.4	0	0
Esophageal varices hemorrhage	1.6	0.9	0.5	0	1.7	1.0	0.2	0.2
Nausea	0.3	0	0	0	1.6	0.9	0	0.2
Hyperkalemia	0.2	0.2	0	0	1.6	0.9	0.2	0
Abdominal pain upper	1.0	0.7	0	0	1.4	0.9	0	0
Encephalopathy	0.5	0.3	0	0	1.4	0.9	0.3	0
Pyrexia	2.8	0	0	0	1.4	0.2	0	0
Upper GI hemorrhage	1.4	0.7	0.2	0.5	0.7	0.2	0	0.3
AST increased	0.7	0.5	0.2	0	1.2	0.9	0.3	0
Asthenia	1.0	0.7	0	0	1.2	1.0	0	0
Gastrointestinal hemorrhage	1.2	0.3	0.2	0	1.0	0.3	0.2	0.2
General physical health deterioration	0.5	0	0.2	0.2	1.2	1.0	0	0
Hepatic neoplasm malignant	1.2	0.2	0	1.0	1.2	0	0	1.0
Pneumonia	0.7	0.3	0	0	1.2	0.7	0	0.5
Urinary tract infection	0.2	0.2	0	0	1.2	0.9	0	0

*Grade was unknown for 32 patients (5.6%) in the sorafenib group and 20 patients (3.5%) in the brivanib group.

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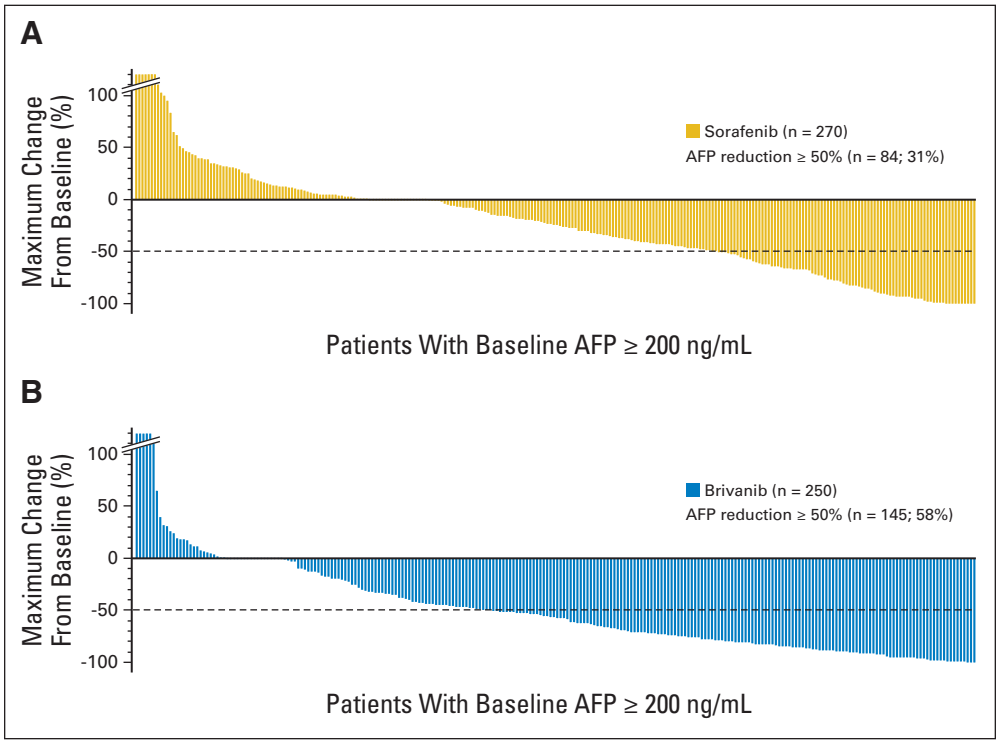

Fig A1. Waterfall plots for changes in serum α-fetoprotein (AFP) relative to baseline in patients with advanced hepatocellular carcinoma treated with (A) sorafenib or (B) brivanib. Plotted were the patients who had baseline assessments and at least one on study assessment.

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