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Brivanib as Adjuvant Therapy to Transarterial Chemoembolization in Patients With Hepatocellular Carcinoma: A Randomized Phase III Trial

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Transarterial chemoembolization (TACE) is the current standard of treatment for unresectable intermediate-stage hepatocellular carcinoma (HCC). Brivanib, a selective dual inhibitor of vascular endothelial growth factor and fibroblast growth factor signaling, may improve the effectiveness of TACE when given as an adjuvant to TACE. In this multinational, randomized, double-blind, placebo-controlled, phase III study, 870 patients with TACE-eligible HCC were planned to be randomly assigned (1:1) after the first TACE to receive either brivanib 800 mg or placebo orally once-daily. The primary endpoint was overall survival (OS). Secondary endpoints included time to disease progression (TTDP; a composite endpoint based on development of extrahepatic spread or vascular invasion, deterioration of liver function or performance status, or death), time to extrahepatic spread or vascular invasion (TTES/VI), rate of TACE, and safety. Time to radiographic progression (TTP) and objective response rate were exploratory endpoints. The trial was terminated after randomization of 502 patients (brivanib, 249; placebo, 253) when two other phase III studies of brivanib in advanced HCC patients failed to meet OS objectives. At termination, median follow-up was approximately 16 months. Intention-to-treat analysis showed no improvement in OS with brivanib versus placebo (median, 26.4 [95% confidence interval {CI}: 19.1 to not reached] vs. 26.1 months [19.0-30.9]; hazard ratio [HR]: 0.90 [95% CI: 0.66-1.23]; log-rank $P = 0.5280$). Brivanib improved TTES/VI (HR, 0.64 [95% CI: 0.45-0.90]), TTP (0.61 [0.48-0.77]), and rate of TACE (0.72 [0.61-0.86]), but not TTDP (0.94 [0.72-1.22]) versus placebo. Most frequent grade 3-4 adverse events included hyponatremia (brivanib, 18% vs. placebo, 5%) and hypertension (13% vs. 3%). *Conclusions:* In this study, brivanib as adjuvant therapy to TACE did not improve OS. (HEPATOLOGY 2014;60:1697-1707)

Transarterial chemoembolization (TACE) is the most frequently used locoregional procedure for the management of unresectable hepatocellular carcinoma (HCC) confined to the liver.[1] This procedure blocks the principal arteries feeding the tumor while administering chemotherapy directly into the tumor for local disease control. TACE can prolong survival in selected patients.[2,3] However, the incidence of recurrence is high, and multiple TACE sessions are needed to eradicate residual tumors.[1]

Embolization induces hypoxia and the release of factors involved in tumorogenesis, angiogenesis, and fibrosis.[4,5] It is well documented that serum concentrations of vascular endothelial growth factor (VEGF)

Abbreviations: AE, adverse event; AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; GI, gastrointestinal; HCC, hepatocellular carcinoma; HR, hazard ratio; HTN, hypertension; ITT, intention to treat; IVRS, Interactive Voice Response System; mRECIST, Response Evaluation Criteria in Solid Tumors; OR, odds ratio; ORR, objective response rate; OS, overall survival; PES, postembolization syndrome; SAEs, serious adverse events; TACE, transarterial chemoembolization; TTDP, time to disease progression; TTES/VI, time to extrahepatic spread or vascular invasion; TTP, time to radiographic progression; TTUP, time to untreatable progression; VEGF, vascular endothelial growth factor.

and fibroblast growth factor (FGF), principal proangiogenic factors, increase after TACE.[6-10] These increases have been shown to be associated with increased risk of tumor growth, recurrence, metastasis, and poor survival.[6-10] Sorafenib, a multikinase inhibitor that targets multiple signaling pathways, including VEGF signaling, improves overall survival (OS) in advanced HCC patients.[11,12] These observations suggest that combining TACE with antiangiogenic agents has the potential to improve the effectiveness of TACE.

Brivanib (Bristol-Myers Squibb, Princeton, NJ), an oral selective dual inhibitor of VEGF and FGF receptor tyrosine kinases, exhibited both antiproliferative and -angiogenic activity in preclinical models and showed initial evidence of efficacy in a phase II trial of patients with advanced HCC.[13-18] Based on this activity profile of brivanib, we hypothesized that brivanib may potentially suppress the growth of microscopic lesions not treatable by TACE, shrink or stabilize tumors remaining after TACE, prevent tumors from spreading outside of the liver, and thereby improve OS. We tested this hypothesis in the present phase III trial that assessed the efficacy and safety of brivanib as adjuvant therapy to TACE in patients with unresectable HCC.

Patients and Methods

Patients. Men and women (age 18 or older) with unresectable HCC who were eligible for their first TACE therapy were enrolled. To be eligible for the first TACE, patients had to have specified histological, cytological, or radiological evidence of HCC. Patients with fewer than four lesions were to have at least one lesion measuring $\geq$5 cm in diameter and those with four or more lesions were to have at least one lesion measuring $\geq$2 cm in diameter. Other key inclusion criteria were Child-Pugh A or B liver function, an Eastern Cooperative Oncology Group performance status (ECOG-PS) score of 0 or 1, and adequate organ function. Key exclusion criteria included diffuse pattern of disease, presence of extrahepatic lesions, macroscopic vascular lesions, clinically significant ascites, previous TACE or transarterial embolization, and previous systemic treatment for HCC. A full list of inclusion and exclusion criteria for enrollment and randomization is provided in Supporting Table 1.

All patients provided written informed consent. The study was approved by the ethics committee/institutional review board at each center and was conducted according to good clinical practice guidelines and the Declaration of Helsinki. This study is registered with ClinicalTrials.gov (no.: NCT00908752).

Study Design. This was a randomized, double-blind, placebo-controlled, phase III study (acronym: BRISK-TA) in which 502 patients from 83 academic hospitals and community clinics across 12 countries were randomly assigned in a 1:1 ratio to receive either brivanib 800 mg or placebo once-daily orally. Randomization was performed after the first TACE

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procedure to ensure the patient's ability to safely receive study drug. The interval between TACE and study drug administration was no less than 48 hours, but no longer than 21 days. This interval was dependent on the individual patient's recovery of liver function (defined as alanine aminotransferase [ALT] and aspartate aminotransferase [AST] concentrations of $\leq 5\times$ the upper limit of normal and serum total bilirubin concentrations <3 mg/dL) and resolution of any postembolization syndrome (fever, nausea, vomiting, and abdominal pain) to grade ≤ 1. Response to TACE was not a criterion for randomization. Treatment assignment was performed centrally through an Interactive Voice Response System (IVRS) using a computer-generated sequence of random digits. Randomization was stratified by Child-Pugh Class (A vs. B), ECOG-PS score (0 vs. 1), maximum tumor size (<10 vs. ≥ 10 cm), and study site and was dynamically balanced for stratification factors using the method of Pocock and Simon.[19] All investigators, patients, and personnel involved in study conduct, data collection, and data analysis were blinded to treatment allocations. To maintain blinding, brivanib or matching placebo as film-coated tablets was supplied in identical boxes. An independent data monitoring committee met four times throughout the trial to assess safety data. All meetings resulted in a recommendation that the trial be continued.

TACE was repeated if there was incomplete necrosis, tumor regrowth, or appearance of new lesions. To ensure safety, study drug was stopped 2 days before TACE and restarted between days 3 and 21 after repeat TACE depending on individual patient's recovery of liver function and resolution of any PESs (as defined above in this section).

Only one of two TACE approaches was allowed during initial or repeat TACE: either (1) injection of an emulsion of a single anticancer agent with lipiodol, followed by embolization of the feeding artery with an embolization agent, or (2) injection of drug-eluting beads preloaded with a single chemotherapy agent. Each study site was required to maintain consistency in the TACE procedure and the use of chemoembolization agent throughout the study duration.

Patients continued on study treatments until disease progression, defined by any of the following events: development of extrahepatic metastasis; development of vascular invasion; deterioration of liver function to Child-Pugh Class C; deterioration of ECOG-PS by 2 points if related to liver disease or if not related to liver disease; deterioration of ECOG-PS by 2 points that lasted longer than 2 weeks; or death. Treatment was allowed beyond disease progression if the investigator determined that the patient was benefiting from the blinded treatment.

Assessments. Assessments for Child-Pugh class, ECOG-PS, and tumor were performed at screening, 4 weeks after the first TACE procedure, and every 8 weeks thereafter. Tumor was assessed using dynamic contrast-enhanced spiral computed tomography/magnetic resonance imaging. Scans were evaluated by investigators using the Response Evaluation Criteria in Solid Tumors modified for the assessment of HCC tumors (mRECIST for HCC).[20]

Safety was assessed continuously. Adverse events (AEs) and serious AEs (SAEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Guidelines for dose reductions and discontinuation from therapy resulting from AEs are described in Supporting Table 2. In general, patients who experienced any drug-related grade 3 nonhematologic or hematologic AEs had their treatment interrupted until AEs decreased to grade ≤ 1. Study treatments were reinitiated at a lower dose level. Only two dose reductions (600 mg, then 400 mg) were allowed. If the same grade 3 nonhematologic or hematologic toxicity recurred despite two dose reductions, patients were discontinued from therapy. Once reduced, treatment continued at the lower dose and the dose was not re-escalated. Patients who experienced drug-related grade 4 nonhematologic toxicities (with the exception of increased ALT, increased AST, hyperbilirubinemia, and hyponatremia, where dose reductions were allowed for grade 4 events; see Supporting Table 2) or grade 4 hematologic toxicities were discontinued from study therapy. Guidelines for the management of specific AEs, such as increased ALT, increased AST, hyperbilirubinemia, hyponatremia, hypertension (HTN), and hypothyroidism were provided.

Endpoints. The primary endpoint was OS, defined as the time from randomization to death from any cause. Secondary efficacy endpoints included time to disease progression (TTDP), a new composite endpoint defined as the time from the first TACE to the date of disease progression (as defined above under Study Design). Other secondary endpoints were time to extrahepatic spread or vascular invasion (TTES/VI; time from the date of the first TACE to the date when extrahepatic spread or vascular invasion was documented), and the total number of TACE procedures between randomization and the occurrence of any TTDP event or censoring for TTDP, and safety. Exploratory endpoints included objective response rate

(ORR; the percentage of randomized patients whose best response was a complete or partial response) and time to radiographic progression (TTP; the time from the first TACE procedure to first radiographic tumor progression). Tumor response and tumor progression were assessed by investigators using mRECIST for HCC.[20]

Statistical Considerations. Sample size was calculated assuming an exponential distribution of survival time. A total of 520 deaths were required to detect an OS difference between the arms with ≥90% power using a stratified log-rank test at $\alpha = 0.05$, assuming that the true hazard ratio (HR) of brivanib to placebo was 0.75. This HR corresponded to a 6.0-month increase in the median OS for brivanib over placebo, assuming that the median OS for the placebo arm was 18 months. The number of patients needed to be randomized was estimated at 870. The study was terminated 2 years earlier than planned when the phase III BRISK-FL and BRISK-PS trials evaluating brivanib as first- and second-line treatment of advanced HCC failed to achieve their primary OS objectives.[23,24] At termination, at total of 502 patients were randomized.

All efficacy endpoints were assessed in all randomly assigned patients (intention-to-treat [ITT] population). Analyses for safety and treatment exposure were based on data from randomly assigned patients who received at least one dose of any study treatment. The primary endpoint of OS was compared between the treatment groups using a stratified log-rank test at $\alpha=0.05$, as were TTDP, TTES/VI, and TTP. The HR of brivanib versus placebo for each of these endpoints and associated 95% confidence intervals (CIs) were computed using a stratified Cox's proportional hazards model. A multivariate Cox's regression model was used to adjust the treatment effect on OS for the following baseline factors: age, risk factors (hepatitis B or C infection or alcohol use), alpha-fetoprotein (AFP) levels, tumor morphology, and previous locoregional treatment and to determine the association of OS with these factors. A Cox's proportional hazards model was used to analyze OS for subgroups based on baseline factors listed above for OS adjustment as well as race, region, Child-Pugh class, tumor size, gender, and age of female patients. Medians for OS, TTDP, TTES/VI, and TTP were estimated using Kaplan-Meier's methodology; 95% CIs for medians were computed.[21] No formal between-group comparison for the number of TACE procedures was performed. Rate functions of TACE procedure between randomization and TTDP events were compared between groups using a stratified semiparametric Andersen-Gill's model (Wald test at $\alpha = 0.05$). The ORR was compared between groups using a stratified Cochran-Mantel-Haenszel's test at $\alpha = 0.05$; associated odds ratio (OR) and its 95% CI were estimated. The 95% CI of ORR was computed.[22] The log-rank test, proportional hazards models, Anderson-Gill's model, and Cochran-Mantel-Haenszel's test were all stratified by three randomization factors: ECOG-PS score (0 vs. 1); maximum tumor size (<10 vs. ≥10 cm); and Child-Pugh class (A vs. B). All 95% CIs were two-sided. Secondary endpoints were to be tested hierarchically in the following order: TTDP, TTES/VI, and rate of TACE. The *P* values presented are for descriptive purposes only. All data analyses were performed using SAS software (version 9.2; SAS Institute Inc., Cary, NC).

Results

Patients. Two hundred forty-nine patients were randomly assigned to receive brivanib and 253 to receive placebo from August 25, 2009 until trial termination and unblinding on August 28, 2012 and constituted the ITT population for the analysis of primary and secondary efficacy endpoints (Fig. 1). Two hundred forty-six of two hundred forty-nine patients in the brivanib group and all 253 in the placebo group received at least one dose of either brivanib or placebo, respectively, and were used for the analysis of treatment exposure and safety. At study termination, all patients were given the option to discontinue the study. At the database lock on November 27, 2012, 57 (23%) patients in the brivanib group and 3 (1%) in the placebo group were still on treatment (Fig. 1). The primary reasons for study discontinuation were administrative reasons related to study termination (n = 12 [5%] in the brivanib group vs. n = 92 [36%] in the placebo group), disease progression (n = 45 [18%] vs. n = 91 [36%]), and drug toxicity (n = 65 [26%] vs. n = 6 [2%]).

Demographics and disease characteristics were balanced between the groups (Table 1). The majority of the randomly assigned patients were from Asia (n = 434 [86%]) and had hepatitis B infection (n = 326 [65%]). Whereas the majority of the patients had intermediate-stage HCC (Barcelona Clinic Liver Cancer [BCLC] stage B, n = 279 [57%]), there were 122 (24%) with early-stage HCC (BCLC stage A, single lesions measuring longer than 5 cm in diameter) and 98 (20%) with advanced-stage HCC (BCLC stage C).

Efficacy. At this analysis, the Kaplan-Meier's estimate of median follow-up was 16.6 months (95% CI: 14.8-17.6) in the brivanib group and 15.6 months

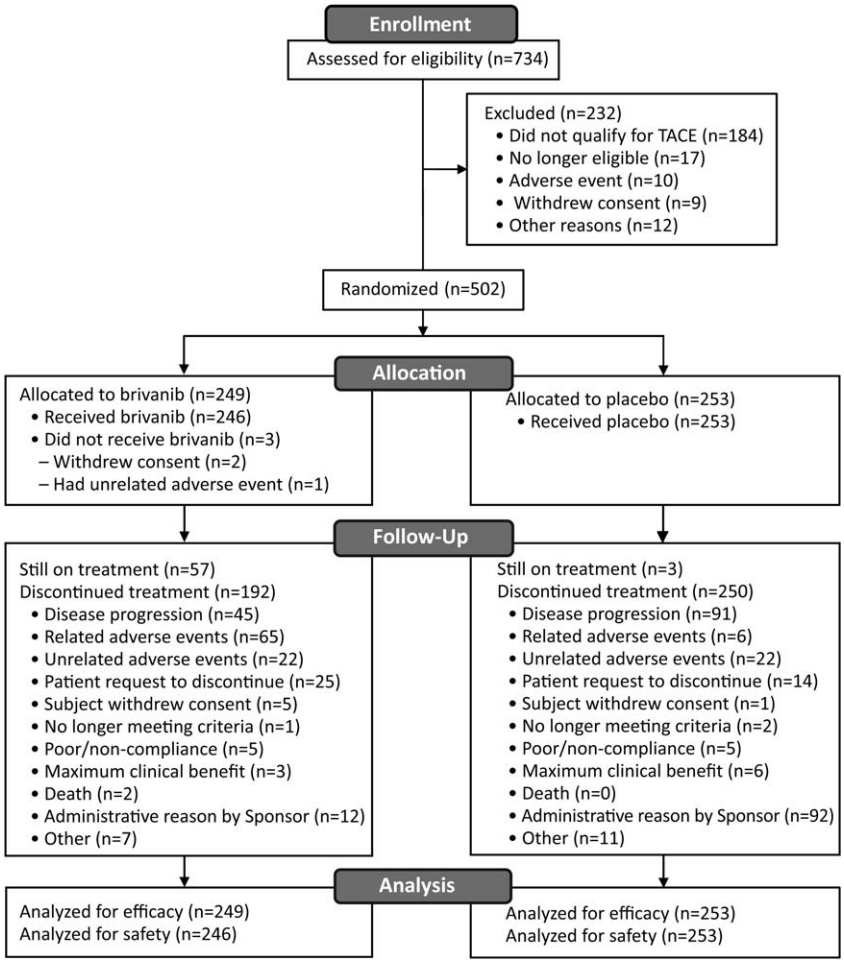

Fig. 1. Patient disposition. Ninety-one centers across 12 countries assessed 734 patients for eligibility. Eighty-three of these centers randomly assigned a total of 502 patients to treatment with either brivanib or placebo. The remaining eight centers assigned no patients to a study treatment. Countries (number of randomly assigned patients in parentheses) include: China (244), Japan (78), Korea (68), France (32), Taiwan (28), United States (18), Thailand (12), Spain (11), Hong Kong (4), Argentina (3), Canada (2), and Italy (2). A list of investigators who participated in the study is provided in Supporting Table 6.

(13.5-17.5) in the placebo group; 79 (32%) of 249 patients on brivanib and 85 (34%) of 253 on placebo had died, with the remaining being censored. The analysis showed no improvement in the primary endpoint of OS with brivanib versus placebo (HR, 0.90 [95% CI: 0.66-1.23]; $P = 0.5280$; Fig. 2). Median OS was 26.4 months (95% CI: 19.1 to not reached) in the brivanib group and 26.1 months (95% CI: 19.0-30.9) in the placebo group. Rates of OS in the brivanib group at 12 and 24 months were 74% (95% CI: 68-80) and 52% (43-61), respectively. Rates of OS in the placebo group at 12 and 24 months were 68% (61-75) and 54% (45-62), respectively. After adjusting for baseline factors, the effect of brivanib on OS versus placebo remained unchanged (HR, 0.92 [95% CI: 0.67-1.26]). Plasma AFP level at baseline (<100 vs. ≥ 100 ng/mL; $P < 0.0001$) was identified as a prognostic factor for OS in this study; other factors tested (age, risk factors, tumor morphologic feature, and previous locoregional therapy and/or surgery) were not prognostic. The OS results for selected subsets are presented in Fig. 3. Most HRs favored brivanib with a notable trend for a better OS in patients <65 years of age and in those with hepatitis B infection.

Thirty-six (14%) patients in the brivanib group and 53 (21%) in the placebo group received poststudy systemic therapies, with sorafenib being the most commonly used systemic therapy ($n = 31$ and $n = 44$, respectively). The number of patients who received poststudy nonsystemic therapies were 68 (27%) in the brivanib group and 54 (21%) in the placebo group, with TACE being the most commonly used nonsystemic therapy ($n = 53$ and $n = 33$, respectively).

There was no improvement in the composite endpoint of TTDP with brivanib versus placebo (median, 12.0 [95% CI: 9.5-15.3] vs. 10.9 [8.4-14.4] months; HR, 0.94 [0.72-1.22]; $p = 0.6209$; Fig. 4A), where death was the predominant event. TTES/IV was longer in the brivanib group than in the placebo group (median, not reached [95% CI: 17.6 to not reached] vs. 24.9 [13.8 to not reached] months; HR, 0.64 [0.45-0.90]; $P = 0.0096$; Fig. 4B). The median number of TACE procedures between randomization and disease progression and censoring was 0 (range, 0-13)

Table 1. Baseline Demographics and Disease Characteristics

Variable	Brivanib (N = 249)	Placebo (N = 253)
Age		
Median age (range), years	57 (21-85)	59 (25-85)
<65 years, n (%)	173 (70)	170 (67)
Male, n (%)	206 (83)	216 (85)
Region, n (%)		
Asia	216 (87)	218 (86)
Europe	22 (9)	23 (9)
Americas	11 (4)	12 (5)
ECOG-PS, n (%), per IVRS*		
0	201 (81)	203 (80)
1	48 (19)	50 (20)
ECOG-PS, n (%), per CRF†		
0	199 (80)	213 (84)
1	50 (20)	40 (16)
BCLC stage, n (%)		
A‡	65 (26)	57 (23)
B	129 (52)	150 (59)
C	54 (22)	44 (17)
D	1 (<1)	2 (1)
Child-Pugh Class, n (%)		
A	239 (96)	231 (91)
B	9 (4)	20 (8)
C	1 (<1)	2 (1)
Tumor morphology, n (%)		
Uninodular	91 (37)	83 (33)
Multinodular	158 (63)	170 (68)
Size of largest tumor nodule, n (%)		
≤10 cm	189 (76)	195 (77)
>10 cm	60 (24)	58 (23)
Risk factors, n (%)		
Any	222 (89)	228 (90)
Alcohol	40 (16)	38 (15)
Hepatitis B	158 (63)	168 (66)
Hepatitis C	49 (20)	42 (17)
Other	8 (3)	8 (3)
Serum AFP <100 ng/mL, n (%)	130 (52)	119 (47)
Previous nonsystemic treatment, n (%)		
Any	21 (8)	26 (10)
Liver resection	14 (6)	24 (9)
Radiofrequency ablation	10 (4)	4 (2)
Transcatheter arterial chemoembolization	3 (1)	2 (1)
Other	1 (<1)	2 (1)

*ECOG-PS was based on data from the IVRS and was used for stratification at randomization.

†ECOG-PS was based on Case Report Forms (CRFs) and was used for the calculation of the baseline BCLC stage.

‡Patients with single lesions measuring >5 cm in diameter.

in the brivanib group and 1 (range, 0-8) in the placebo group (Table 2). The rate of TACE was lower in the brivanib than in the placebo group (HR, 0.72 [95% CI: 0.61-0.86], $P = 0.0002$; Table 2). TTP was longer in the brivanib than in the placebo group (median, 8.4 [95% CI: 6.7-10.2] vs. 4.9 [4.7-6.5] months; HR, 0.61 [0.48-0.77]; $P < 0.0001$; Fig. 4C). The ORR was 48% in the brivanib group and 42% in the placebo group (Table 2). There were more complete responses (22% vs. 11%) and fewer documented disease progression events (9% vs. 18%) in the brivanib than in the placebo group. Disease control rate (the sum total of complete response, partial response, and stable disease) was 79% in both groups.

An exploratory posthoc subset analysis of OS and treatment duration by region was performed. The median OS values for brivanib versus placebo in Korea (n = 68), China (n = 244), Japan (n = 78), and the non-Asian region (North America, Europe, and Australia; n = 65) were 26.4 months versus not reached (HR, 0.55), 17.1 months versus not reached (HR, 0.80), not reached versus not reached (HR, 0.86), and 18.1 versus 17.5 months (HR, 1.41), respectively (Supporting Table 3). In the brivanib group, median treatment durations in Korea, China, and Japan were 10.1, 8.3, and 2.1 months, respectively (Supporting Table 4). In the placebo group, median treatment durations in Korea, China, and Japan were 10.6, 5.0, and 7.2 months, respectively. These results suggest regional variability in terms of OS and treatment duration.

Safety. At database lock, 79 (32%) patients in the brivanib group and 85 (34%) in the placebo group had died; disease was the primary cause (n = 61 and n = 75, respectively). Eighteen (7%) patients in the brivanib group and 12 (5%) in the placebo group had died within 30 days of the last dose; disease was the primary cause (n = 6 and n = 11, respectively). Four (2%) deaths in the brivanib group considered to be treatment related were the result of liver failure, bacterial peritonitis, intracranial bleeding, and pulmonary infection. One (<1%) death in the placebo group considered to be treatment related was the result of liver failure.

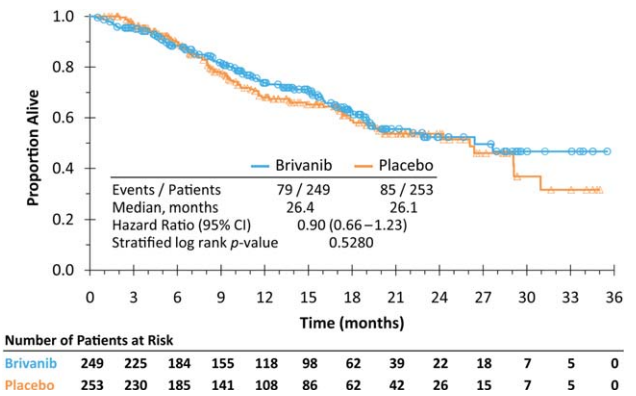

Fig. 2. Kaplan-Meier's curves for OS. OS was defined as the time from the date of randomization to the date of death from any cause. Patients who did not die were censored on the last dates known to have been alive or on the date the database was locked.

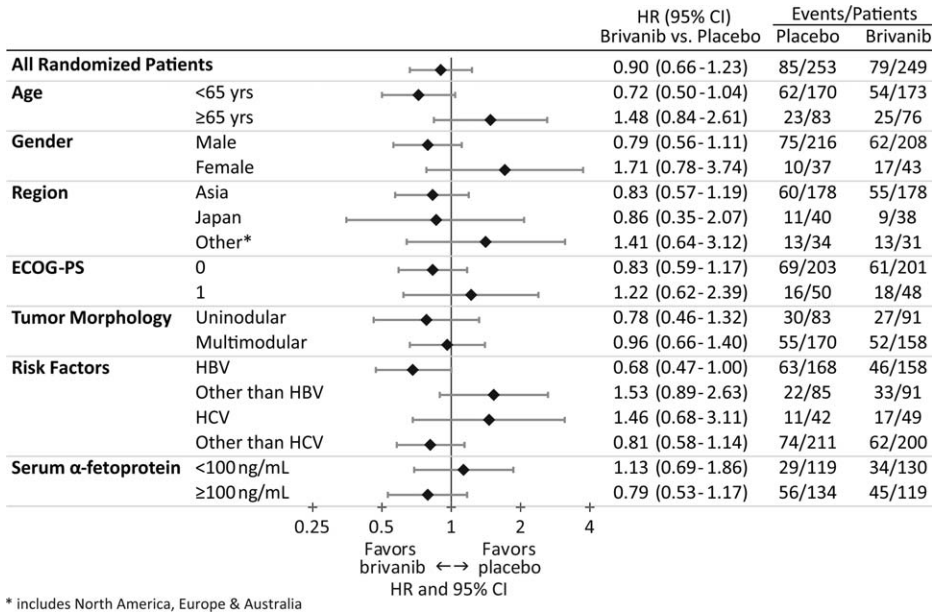

Fig. 3. OS in selected subsets.

One hundred eighteen (48%) patients in the brivanib group and 94 (37%) in the placebo group had one or more SAEs. The most frequent (≥2%) SAEs were malignant neoplasm progression (n = 15 in the brivanib group and n = 38 in the placebo group), ascites (n = 8 and n = 6), abdominal pain (n = 6 and n = 4), hepatic malignant neoplasm (n = 6 and n = 8), pyrexia (n = 6 and n = 5), decreased appetite (n = 5 and n = 2), hepatic encephalopathy (n = 5 and n = 2), and upper gastrointestinal (GI) hemorrhage (n = 5 and n = 2). SAEs reported in 2 or more patients are listed in Supporting Table 5.

The incidence of AEs was comparable between the brivanib and placebo groups (99% vs. 95%); however, incidence of grade 3-4 AEs was higher in the brivanib versus placebo group (69% vs. 43%; Table 3). The most frequently reported AEs (>20%, any grade) that occurred at a higher frequency (>10%) in the brivanib vs. the placebo group included HTN, decreased appetite, fatigue, diarrhea, hand-foot skin reaction, proteinuria, hyponatremia, and hypothyroidism (Table 3). Hepatic AEs of increased ALT, increased AST, and hyperbilirubinemia occurred at similar rates between the groups as did pyrexia, abdominal pain, and vomiting. Grade 3 AEs that occurred at a higher frequency in the brivanib (>5%) versus placebo group were hyponatremia, HTN, fatigue, diarrhea, and hand-foot skin reaction. Grade 4 AEs were infrequent.

One hundred twenty-one (49%) patients in the brivanib group and 16 (6%) in the placebo group had at least one dose reduction. Treatment-related AE was the primary cause of the first dose reduction (n = 68 [28%] in the brivanib group and n = 7 [3%] in the placebo group). Ninety-eight (40%) patients in the brivanib group and 46 (18%) in the placebo group discontinued treatment because of AEs. The most frequently reported AEs leading to discontinuation included malignant neoplasm (n = 13 in the brivanib group and n = 21 in the placebo group), HTN (n = 6 and n = 0), and proteinuria (n = 5 and n = 1). The Kaplan-Meier's estimate of median treatment duration was 6.0 months (95% CI: 4.7-7.7) in the brivanib group and 6.6 months (5.4-7.5) in the placebo group.

Discussion

This phase III randomized study showed no OS improvement with brivanib versus placebo (HR, 0.90; $P = 0.5280$) as adjuvant therapy to TACE in HCC patients. Adjusting the treatment effect for potential prognostic factors did not change the outcome (HR, 0.92). The median OS in the placebo group (26.1 months) of this study was longer than expected (18 months); this estimate is unreliable because of the early study termination and censoring. A potentially favorable OS outcome with brivanib in patients <65 years of age and in those with hepatitis B infection should be interpreted with caution because of the exploratory nature associated with subset analyses.

Although OS was similar between the brivanib and placebo groups, secondary and exploratory analyses of TTES/VI, TTP, and ORR suggested that brivanib in this setting may have slowed tumor growth and metastasis. Delayed TTES/VI is of particular interest, because

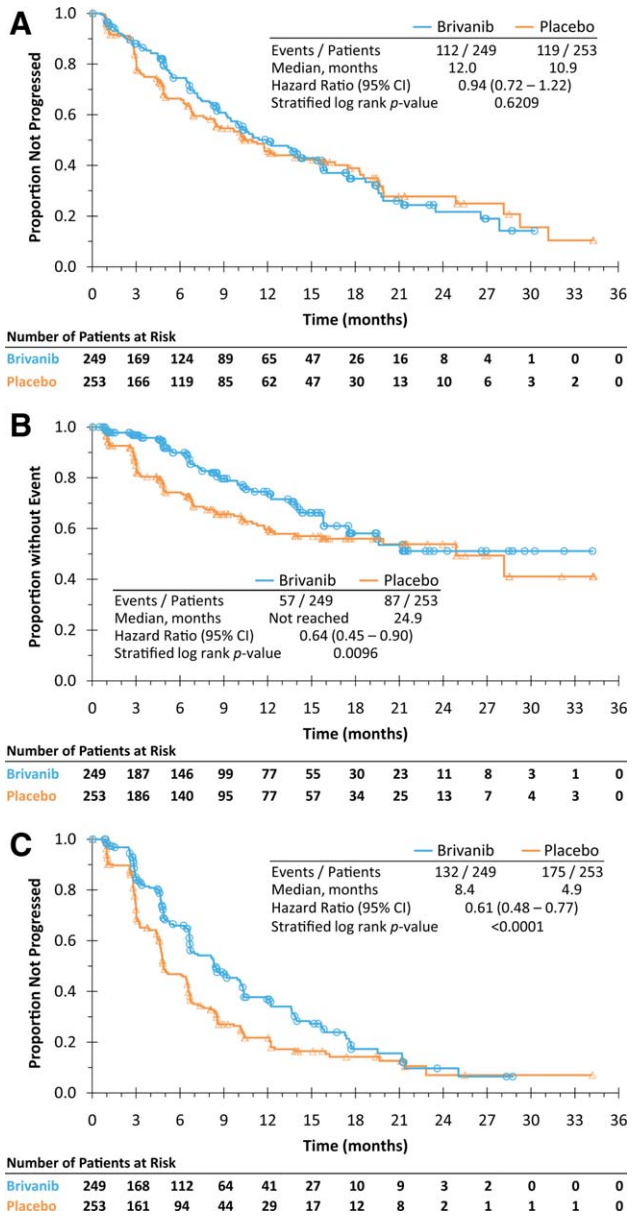

Fig. 4. Kaplan-Meier's curves for TTDP (A), TTES/VI (B), and TTP (C). (A) TTDP is a new composite endpoint defined as the time from the first TACE to the date of disease progression. Disease progression was defined as any of the following events: development of extrahepatic metastasis, development of vascular invasion, deterioration of liver function to Child-Pugh Class C, deterioration of ECOG-PS by 2 points if related to liver disease or if not related to liver disease, deterioration of ECOG-PS by 2 points that lasted for a period longer than 2 weeks, or death. Patients requiring alternative systemic therapy (e.g., sorafenib) before meeting the criteria for TTDP were censored at the time of their last assessment preceding alternative therapy where none of the events were observed. Patients without any of the events, and who did not receive alternative systemic therapy, were censored at their last assessment where none of the events were observed. (B) TTES/VI was defined as the time from the date of the first TACE to the date extrahepatic spread or vascular invasion was documented, whichever occurred first. Patients with no extrahepatic spread and no vascular invasion were censored at their last assessment where none of these events were observed. (C) TTP was defined as the time from the first TACE procedure to first radiographic tumor progression as assessed by investigators using mRECIST for HCC. Patients without radiographic tumor progression were censored at their last tumor assessment.

Table 2. Repeat TACE and Tumor Response

	Brivanib (N = 249)	Placebo (N = 253)
On-study repeat TACE		
Median number (range)	0.0 (0-13)	1.0 (0-8)
HR (95% CI)	0.72 (0.61-0.86)	
P value	0.0002	
ORR		
Events, n	120	106
ORR, % (95% CI)	48 (42-55)	42 (36-48)
OR (95% CI)	1.28 (0.90-1.83)	
Best response, n (%)		
Complete response	55 (22)	28 (11)
Partial response	65 (26)	78 (31)
Stable disease	76 (31)	93 (37)
Progressive disease	22 (9)	46 (18)
Unable to assess	31 (12)	6 (2)

The number of TACE was based on sessions between randomization and disease progression/censoring (i.e., excluding first TACE). The number of TACE and objective response rate were compared between arms using stratified Anderson-Gill's model and Cochran-Mantel-Haenszel's test, respectively. *P* values are for descriptive purposes only. Tumors were assessed by investigators using mRECIST for HCC.

this is an objective endpoint that may predict better prognosis when the disease is confined to the liver. Given the disease complexity characterized by the interplay between HCC and underlying liver disease, TTDP was introduced as another surrogate for OS. This composite endpoint was based on events (development of extrahepatic spread or vascular invasion, deterioration of liver function or ECOG-PS, or death) that would make patients ineligible for repeat TACE.[2,3] In the present study, TTDP was delayed only minimally with brivanib versus placebo (12.0 versus 10.9 months; HR, 0.94). This may be a result of death being the predominant TTDP event and non-tumor-related comorbidities being potential contributors to TTDP. The phase II SPACE trial comparing sorafenib/TACE combination with TACE alone in HCC patients used a different composite endpoint (time to untreatable progression; TTUP) based on ineligibility for further TACE and reported an HR for combination versus TACE alone of 1.586 for this endpoint.[25] Failure to achieve an objective response to treatment was the predominant event for TTUP. These results, including, in particular, the unexpected nature of factors that drove the composite endpoints, highlight the need for prospective studies to define relevant surrogate endpoints for OS.

In our study, there were fewer TACE sessions and a reduction in the risk of TACE in the brivanib group, compared to the placebo group. Fewer TACE sessions in the sorafenib group, compared to the placebo group, were also reported in the SPACE trial.[25] This lower rate of TACE could conceivably have been because the patient did not need further TACE as a

Table 3. Incidence of AEs

	Brivanib (N = 246)			Placebo (N = 253)		
AE, n (%)	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any	244 (99)	137 (56)	35 (14)	241 (95)	98 (39)	11 (4)
HTN	116 (47)	31 (13)	2 (1)	29 (11)	7 (3)	0
Pyrexia	93 (38)	2 (1)	0	115 (46)	1 (<1)	0
Decreased appetite	106 (43)	11 (4)	0	57 (23)	3 (1)	1 (<1)
Fatigue	101 (41)	22 (9)	0	59 (23)	6 (2)	0
Abdominal pain	90 (37)	10 (4)	0	101 (40)	10 (4)	2 (1)
AST increased	85 (35)	31 (13)	3 (1)	95 (38)	36 (14)	1 (<1)
ALT increased	88 (36)	22 (9)	2 (1)	84 (33)	26 (10)	0
Diarrhea	88 (36)	18 (7)	0	25 (10)	2 (1)	0
Hand-foot skin reaction	77 (31)	15 (6)	0	5 (2)	0	0
Proteinuria	71 (29)	12 (5)	0	24 (9)	2 (1)	0
Nausea	70 (28)	2 (1)	0	69 (27)	1 (<1)	0
Hyponatremia	68 (28)	42 (17)	2 (1)	27 (11)	11 (4)	2 (1)
Hypothyroidism	66 (27)	3 (1)	0	18 (7)	0	0
Vomiting	63 (26)	6 (2)	0	57 (23)	1 (<1)	0
Hyperbilirubinemia	60 (24)	14 (6)	5 (2)	57 (23)	5 (2)	2 (1)
Platelet count decreased	58 (24)	18 (7)	1 (<1)	42 (17)	10 (4)	0
Hypoalbuminemia	55 (22)	2 (1)	0	34 (13)	2 (1)	0
WBC count decreased	53 (22)	12 (5)	0	48 (19)	5 (2)	0
Dysphonia	45 (18)	3 (1)	0	5 (2)	0	0
Ascites	44 (18)	1 (<1)	0	18 (7)	6 (2)	1 (<1)
Upper abdominal pain	44 (18)	2 (1)	0	36 (14)	0	0
Peripheral edema	40 (16)	0	0	17 (7)	1 (<1)	0
Constipation	37 (15)	0	0	41 (16)	1 (<1)	0
Headache	39 (16)	1 (<1)	0	15 (6)	0	0
Abdominal distension	35 (14)	7 (3)	0	25 (10)	1 (<1)	0
Dizziness	34 (14)	3 (1)	0	8 (3)	0	0
Cough	31 (13)	0	0	19 (8)	0	0
GLT increased	32 (13)	5 (2)	0	34 (13)	8 (3)	2 (1)
PMN count increased	31 (13)	7 (3)	1 (<1)	29 (11)	8 (3)	0
Blood TSH increased	30 (12)	0	0	5 (2)	0	0
Insomnia	30 (12)	0	0	25 (10)	0	0
Blood ALP increased	23 (9)	1 (<1)	0	28 (11)	2 (1)	0
Rash	24 (10)	1 (<1)	0	13 (5)	0	0

Events listed are those (regardless of relationship to study treatment) occurring in at least 10% of the randomly assigned patients in either group who received at least one dose of any study treatment.

Abbreviations: WBC, white blood cell; GLT, λ-glutamyltransferase; PMN, peripheral blood neutrophil; TSH, thyroid-stimulating hormone; ALP, alkaline phosphatase.

result of either disease stabilization or drug toxicity. Though we cannot rule out the effect of drug toxicity (26% of patients came off for study drug toxicity in the brivanib arm vs. 2% in the placebo arm), the observed improvements in TTP and TTES/VI with brivanib suggest that disease stabilization by brivanib may have been a factor in reducing the number and risk of TACE with brivanib.

Optimal timing for drug administration, relative to TACE, has not been defined.[26] In our study, because of potential safety concerns, brivanib was stopped 2 days before a TACE session and restarted between days 3 and 21 after TACE. Because serum VEGF concentration peaks on day 1 after TACE,[9] brivanib may exert the greatest effects when administered immediately after or even before TACE. The ongoing ECOG E1208 phase III study (NCT01004978) will provide further insight on the time of the addition of sorafenib, relative to TACE, which may be useful for determining the timing of administration of other drugs in combination with TACE.

No unexpected safety findings for brivanib were identified in this study. Despite longer exposure to brivanib in this study (6.0 months), compared to BRISK-FL (3.2 months) and BRISK-PS (3.1 months) studies, AE profiles, rates of discontinuation (40%, 43%, and 42%, respectively) resulting from AEs, and rates of dose reduction (49%, 49%, and 54%, respectively) were comparable.[23,24] Rare treatment-related deaths were noted in all three studies, and the causes of these deaths were not unusual. As expected, AEs, including HTN, proteinuria, hyponatremia, and hypothyroidism, considered typical of brivanib, based on previous brivanib clinical studies,[23,24] were more frequent in the

brivanib group and were considered manageable. Hepatic AEs and certain GI AEs (e.g., abdominal pain and vomiting) occurred at higher rates in the placebo group, attesting to the seriousness of the underlying liver disease. Notably, these latter AEs appeared to be unaffected by brivanib administration. These data suggest that brivanib is reasonably well tolerated with an acceptable safety profile in patients with advanced or intermediate-stage HCC.

A major limitation of our study was its early closure. A sample size of 870 randomized patients with 520 death events for the primary OS analysis was planned. However, at final database lock, there were only 502 randomized patients and 164 death events (32% of the required events). Early closure thus compromised study power, warranting caution in interpreting the data. Furthermore, global studies aimed at evaluating TACE in combination with systemic agents are inherently challenging, given the heterogeneity in technique and interpretation of response.[1-3] In an attempt to manage these potential confounders, the study was designed not to assess the role of TACE in HCC, but the addition of brivanib by using a placebo control, requiring the use of standardized TACE procedures, standardizing response interpretation with mRECIST, using novel definition of disease progression, and stratifying by enrolling center (not just region or country), as well as using OS as the primary endpoint. Nevertheless, differences by region were still evident in a posthoc analysis of treatment duration and OS and may result, in part, from the regional differences in treatment practice. The present study underscores not only the need for rigorous definitions of trial design elements and assessments, but also the challenges such definitions may impose on trial execution.

In conclusion, brivanib as an adjuvant to TACE did not improve OS in this study. This study is the only phase III study using OS as the primary endpoint in the setting of combining TACE with an antiangiogenic agent. The only other published phase III trial evaluating the administration of sorafenib in patients who responded to TACE used TTP as the primary endpoint and OS as the secondary endpoint and showed improvement in neither TTP nor OS.[27] These results should be considered when planning future trials to evaluate the addition of antiangiogenic agents to TACE and point to the need for more rigorous preclinical and initial clinical investigations of combining antiangiogenic agents with TACE, innovative study design, and identification of predictive biomarkers for patient enrichment and relevant surrogate endpoints for survival. Better understanding of regional treatment practices and how they affect long-term outcomes are clearly needed.

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Supporting Information

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