

Phase II, Open-Label Study of Brivanib as Second-Line Therapy in Patients with Advanced Hepatocellular Carcinoma

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Abstract

Purpose: Brivanib, a selective dual inhibitor of fibroblast growth factor and VEGF signaling, has recently been shown to have activity as first-line treatment for patients with advanced hepatocellular carcinoma (HCC). This phase II open-label study assessed brivanib as second-line therapy in patients with advanced HCC who had failed prior antiangiogenic treatment.

Experimental Design: Brivanib was administered orally at a dose of 800 mg once daily. The primary objectives were tumor response rate, time to response, duration of response, progression-free survival, overall survival (OS), disease control rate, time to progression (TTP), and safety and tolerability.

Results: Forty-six patients were treated. Best responses to treatment with brivanib ($N = 46$ patients) using modified World Health Organization criteria were partial responses for two patients (4.3%), stable disease for 19 patients (41.3%), and progressive disease for 19 patients (41.3%). The tumor response rate was 4.3%; the disease control rate was 45.7%. Median OS was 9.79 months. Median TTP as assessed by study investigators following second-line treatment with brivanib was 2.7 months. The most common adverse events were fatigue, decreased appetite, nausea, diarrhea, and hypertension.

Conclusion: Brivanib had a manageable safety profile and is one of the first agents to show promising antitumor activity in advanced HCC patients treated with prior sorafenib. *Clin Cancer Res*; 18(7); 2090–8. ©2012 AACR.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide (1) and the third leading cause of cancer-related death (2). Angiogenesis plays a key role in growth and metastasis of many tumors, including HCC (3),

and is generally mediated by several growth factors, including the fibroblast growth factor (FGF) and VEGF families (4). Agents that target the VEGF axis provide a survival benefit in patients with advanced-stage HCC (5, 6). Nevertheless, current VEGF-targeted agents fail to produce enduring clinical responses in most patients as a result of *de novo* or acquired resistance (7, 8). With regard to HCC, the only systemic agent that has been shown to improve survival is sorafenib, an oral multikinase inhibitor (5, 6). Beyond sorafenib, several studies are evaluating novel combinations (9), and although benefits have been observed with sorafenib, other single agents (e.g., sunitinib) have not shown efficacy in HCC (10).

To overcome these challenges, the FGF pathway is being pursued as a therapeutic target in HCC. FGF belongs to a family of heparin binding, multifunctional proteins that bind to one of 4 isoforms of FGF receptors (FGFR 1 to 4; ref. 11). FGF signaling regulates fundamental cellular developmental processes (12), and aberrant FGF signaling is associated with tumorigenesis (8, 11–13). In addition, FGF-2 has potent effects on vascular endothelial cell proliferation (14), and levels are elevated in tumors and/or serum in patients with a variety of cancers, including HCC (15–18). Recent clinical data suggest that upregulation of alternate proangiogenic signaling pathways, such as the FGF

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Translational Relevance

The only systemic agent that has been shown to improve survival in patients with advanced hepatocellular carcinoma (HCC) is sorafenib, an oral multikinase inhibitor that targets VEGF signaling. However, many patients do not receive benefit with sorafenib, and those who do eventually progress. Recent clinical data suggest that upregulation of alternate proangiogenic signaling pathways, such as the fibroblast growth factor (FGF) signaling pathway, may play a role in the development of resistance with anti-VEGF therapies. These findings provide the rationale for the current phase II study evaluating brivanib, an oral selective dual inhibitor of FGF and VEGF signaling. This study shows the antitumor activity and tolerability of brivanib in patients with advanced HCC who had progressive disease while taking 1 prior antiangiogenic therapy (primarily sorafenib), and supports the ongoing phase III program in HCC. This article also incorporates an analysis using the newly proposed mRECIST.

signaling pathway, may play a role in the development of resistance with anti-VEGF therapies (19–22).

Brivanib, an oral, selective dual inhibitor of FGFR and VEGF receptor (VEGFR) tyrosine kinases, has shown anti-tumor activity in preclinical models of various cancers, including HCC (23–27). Brivanib has a half-life of 12 hours and is administered once daily at a dose of 800 mg. In addition, no differences in pharmacokinetics between Asian versus non-Asian subjects have been reported (28). A recent phase II study of brivanib as first-line treatment in 55 patients with advanced HCC reported a response rate of 7.3% and a disease control rate (DCR) of 51% (29). Median progression-free survival (PFS) and overall survival (OS) were 2.7 and 10 months, respectively. Brivanib was generally well tolerated; the most common adverse events (AE) included fatigue, hypertension, and diarrhea.

Here we present the results from an assessment of brivanib as second-line therapy in patients with advanced HCC. Importantly, this is the first completed study of a targeted agent in patients with advanced HCC who had progressive disease while taking 1 prior antiangiogenic therapy (primarily sorafenib).

Materials and Methods

Study design

This was a multicenter, open-label, phase II, single-agent study of once daily brivanib alaninate 800 mg in patients with unresectable, locally advanced, and/or metastatic HCC who had received 1 prior antiangiogenic therapy regimen. It was initiated following approval of sorafenib for the treatment of HCC and was carried out in accordance with the Declaration of Helsinki and International Conference on

Harmonization-Good Clinical Practice. The study protocol and any amendments were approved by the independent ethics committee of each center and by the authorities in each relevant country. Informed consent was obtained from each patient.

Sample size determination

The sample size was derived from an amended protocol at the time of sorafenib approval without another formal power calculation and was not determined by a statistical hypothesis. After approval of sorafenib, this study became a signal-finding phase II study for this newly defined population. This was originally a randomized study of brivanib versus doxorubicin in newly diagnosed HCC patients. At the time the protocol was initiated, no agent was proven to extend survival in HCC, and doxorubicin was used as a comparator arm. On the basis of positive phase III results with sorafenib (5), the study protocol was amended to discontinue the doxorubicin arm and to include patients who had progressed following a maximum of 1 prior treatment (the cohort included in this study). The study protocol was amended again later to include a cohort with second-line brivanib 400 mg twice daily. The master protocol included 3 patient cohorts: first-line brivanib 800 mg once daily, second-line brivanib 800 mg once daily, and second-line brivanib 400 mg twice daily. Results with the first-line brivanib cohort in this study are reported elsewhere (29).

Inclusion and exclusion criteria

To be eligible, patients had to meet the following inclusion criteria: (i) measurable, unresectable, locally advanced, and/or metastatic HCC that was either biopsy proven or had clinical evidence of HCC [fulfilling standard imaging criteria for HCC and having an α -fetoprotein (AFP) level 400 mg/L or more] with positive serology for hepatitis B or C virus; (ii) had progressed on one prior antiangiogenic therapy or discontinued treatment due to treatment-related toxicity and subsequently progressed prior to study entry; (iii) had a Cancer of the Liver Italian Program (CLIP) score 3 or less; (iv) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; and (v) had adequate hepatic function (total bilirubin 2.5 mg/dL or less, aspartate aminotransferase/alanine aminotransferase 5 or less times the upper limit of normal, serum albumin more than 2.8 g/dL, prothrombin time/international normalized ratio 1.8 or less, unless on therapeutic anticoagulation) and renal function.

Key exclusion criteria included the following: (i) CLIP score greater than 3; (ii) active bacterial infections, HIV/AIDS, or other diseases that would preclude study participation; (iii) gastrointestinal tract disease or prior surgery; (iv) pregnant or breast-feeding women; (v) primary malignancy in past 5 years; (vi) mental incapacitation or psychiatric illness; and (vii) uncontrolled or significant cardiovascular disease.

History of portal hypertension was not collected in the case report form; however, study entry restrictions included the following: clinically significant ascites refractory to

Table 1. Baseline demographic and clinical characteristics of patients treated

Characteristic	N = 46
Median age, y (range)	55 (21–81)
Gender, male/female, %	72/28
Race, Asian/non-Asian, %	67/33
Positive status for HBV/HCV, %	65/17
ECOG performance status 0/1/2, %	26/72/2
Extrahepatic spread ^a , %	78
Vascular invasion, %	15
Child-Pugh status A/B, %	91/9
BCLC stage B/C, %	4/96
CLIP score 0/1/2/3, %	9/30/39/22
AFP > ULN, %	83
Prior local therapy (TACE, RFA, etc) ^b , %	83
Prior systemic therapy	
Sorafenib/thalidomide, %	94/6
Median duration, mo (range)	3.14 (0.3–11.5)

Abbreviations: BCLC, Barcelona Clinic Liver Cancer staging system; HBV, hepatitis B virus; HCV, hepatitis C virus; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; ULN, upper limit of normal.

^aIndirectly calculated from IRRC tumor reports.

^bNo patients had prior surgical resection, radiotherapy, and transplant.

diuretic therapy; presence of portal systemic encephalopathy (evidenced by confusion, asterixis, significant sleep disturbance, or hypothermia less than 36°C); evidence of portal hypertension with bleeding esophageal or gastric varices within the past 2 months; and prior variceal bleed permitted if the patient had undergone banding and there had been no evidence of bleeding for 2 months.

Study endpoints

The primary endpoints of this trial were tumor response rate, time to response, duration of response, PFS, OS, DCR, time to progression (TTP), and safety and tolerability. The tumor response rate was the proportion of patients with a complete response (CR) or partial response (PR), and time to response was the time from the day of first dose until the first day criteria were met for CR or PR, whichever occurred first. The duration of response was the time from the first day all criteria were met for CR or PR, whichever occurred first, to the date progressive disease was first documented, or date of death. OS was the time from the day of first dose to the date of death. DCR was the proportion of treated subjects whose best response was PR, CR, or stable disease (SD) lasting 42 days or more.

Treatment

Patients were required to have progressive disease while taking 1 prior antiangiogenic therapy. In the assessment of progression on prior antiangiogenic therapy, the case record

Table 2. Summary of outcomes for second-line brivanib treatment in patients with HCC

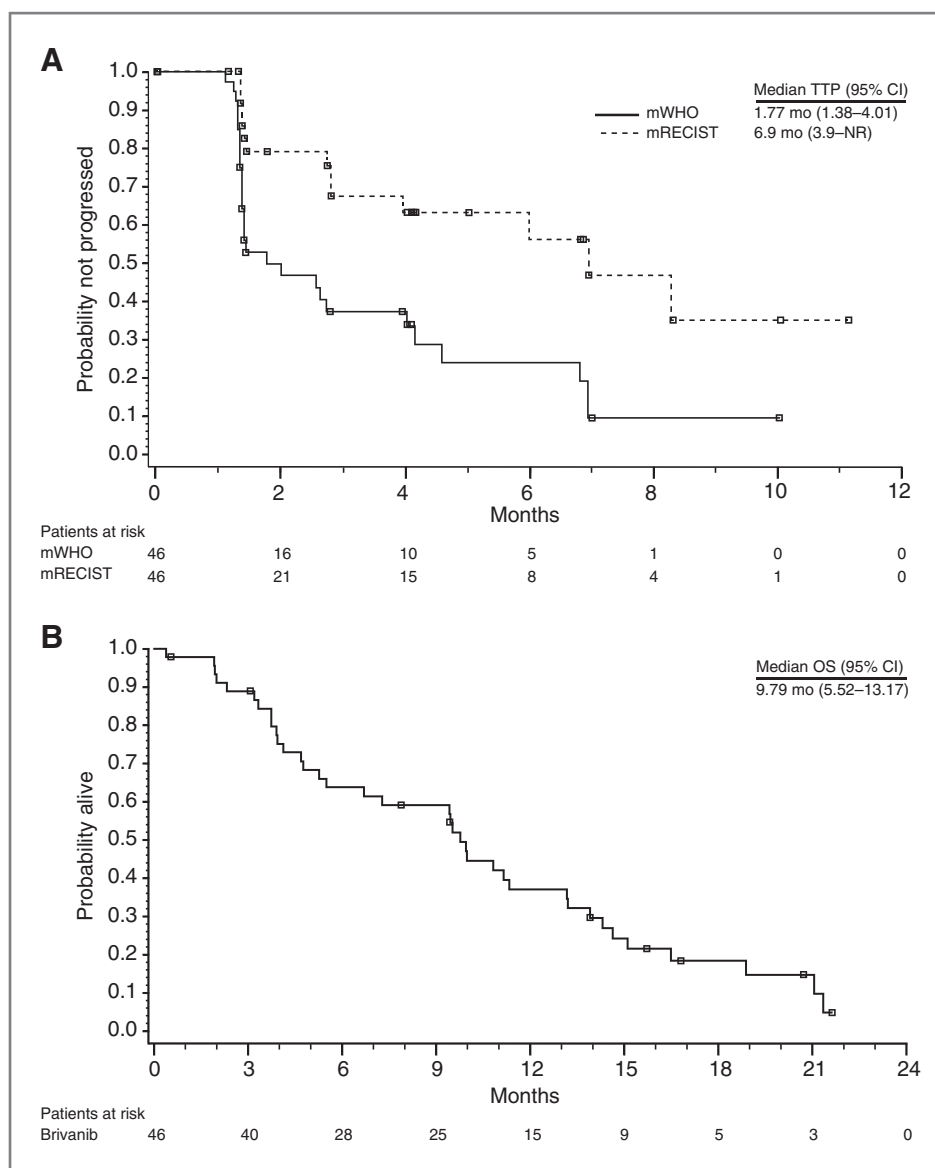
Measure	Results
Best response using mWHO criteria, per IRRC	<ul style="list-style-type: none"> • PR: 2 (4.3%) • SD: 19 (41.3%) • Progressive disease: 19 (41.3%) • Unable to determine: 6 (13.0%) • Tumor response rate: 2 (4.3%) • DCR: 21 (45.7%)
Best response using mWHO criteria, per investigator	<ul style="list-style-type: none"> • PR: 2 (4.3%) • SD: 20 (43.5%) • Progressive disease: 15 (32.6%) • Unable to determine: 9 (19.6%) • Tumor response rate: 2 (4.3%) • DCR: 22 (47.8%)
Best response using HCC mRECIST criteria, per independent radiologist	<ul style="list-style-type: none"> • PR: 5 (10.9%) • SD: 28 (60.9%) • Progressive disease: 7 (15.2%) • Unable to determine: 6 (13.0%) • Tumor response rate: 5 (10.9%) • DCR: 33 (71.7%)
Median OS, mo	9.79 (95% CI: 5.52–13.17)
Median PFS, mo	
Per IRRC	2.00 (95% CI: 1.41–3.91)
Per investigator	2.73 (95% CI: 1.45–4.04)
AFP response	<ul style="list-style-type: none"> • >50%: 23 (50.0%) • ≤50%: 21 (45.7%) • Not reported: 2 (4.3%)

form collected progression data as retrospectively assessed by the investigator based on medical practice and did not define or seek to confirm that these were indeed progressions. A 4-week washout period prior to receiving brivanib was required. Brivanib was administered orally on a continuous once daily schedule of 800 mg until disease progression or unacceptable toxicity. Doses were reduced or delayed according to protocol-specified criteria or, for lower grade toxicities, if the investigator deemed dose reduction or delay was required in the interest of safety of the patient.

Efficacy assessment

Tumor response was assessed every 6 weeks using the modified World Health Organization (mWHO) tumor response criteria via computed tomography/MRI. Tumor

Figure 1. A, Kaplan–Meier curves for TTP according to mWHO criteria (IRRC assessment) and mRECIST; B, Kaplan–Meier curve for OS. NR, not reached.



assessment was done by study investigators and by an Independent Response Review Committee (IRRC).

Post hoc exploratory analysis of efficacy with modified RECIST

This study was designed in April 2006 prior to the recent American Association for the Study of Liver Diseases–Journal of the National Cancer Institute (AASLD–JNCI) guidelines for HCC, which recommend alternative assessment of tumor responses, taking into account the viability of hepatic tumors using the new modified Response Evaluation Criteria in Solid Tumors (mRECIST) for HCC (30, 31). Using mRECIST for HCC, scans were retrospectively reassessed by an independent radiologist who was blinded to previous imaging and outcome results and was not involved in the initial reads. All

atypical intrahepatic and all extrahepatic lesions were assessed using conventional RECIST.

Biomarker assessment

In this study, serum AFP levels were collected at the same time points as disease assessments.

Collagen IV is a component of vascular basement membranes that appears to be elevated in the serum of HCC patients compared with those with chronic hepatitis or cirrhosis and has previously been identified as a potential pharmacodynamic biomarker of brivanib treatment (32). Whole blood samples for the measurement of plasma levels of collagen IV were drawn predose on the day of the first brivanib dose (day 1), at week 3 (day 22), week 6 (day 43), and end of treatment. Plasma collagen IV was measured using an ELISA kit (Biotrin International, Ltd).

Table 3. AEs (all grades occurring in more than 10% of patients)

Adverse event	Grade 1/2	Grade 3/4	N = 46%
Fatigue	25 (54.4)	2 (4.3)	27 (58.7)
Decreased appetite	25 (54.3)	0	25 (54.3)
Nausea	18 (39.2)	2 (4.3)	20 (43.5)
Diarrhea	16 (34.7)	3 (6.5)	19 (41.3)
Hypertension	15 (32.6)	4 (8.7)	19 (41.3)
Vomiting	14 (30.4)	2 (4.3)	16 (34.8)
Headache	9 (19.5)	2 (4.3)	11 (23.9)
Stomatitis	11 (23.9)	0	11 (23.9)
Constipation	10 (21.7)	0	10 (21.7)
Hypothyroidism	7 (15.2)	1 (2.2)	8 (17.4)
Musculoskeletal pain	7 (15.2)	0	7 (15.2)
Cough	7 (15.2)	0	7 (15.2)
Dysphonia	7 (15.2)	0	7 (15.2)
Abdominal pain	4 (8.7)	2 (4.3)	6 (13.0)
Abdominal pain upper	5 (10.8)	1 (2.2)	6 (13.0)
Dyspepsia	6 (13.0)	0	6 (13.0)
Back pain	6 (13.0)	0	6 (13.0)
Dizziness	6 (13.0)	0	6 (13.0)
Palmar-plantar erythrodysesthesia syndrome	6 (13.0)	0	6 (13.0)
Rash	6 (13.0)	0	6 (13.0)
Hyponatremia	1 (2.2)	4 (8.7)	5 (10.9)
Platelet count decreased	2 (4.3)	3 (6.5)	5 (10.9)
Weight decreased	5 (10.8)	0	5 (10.9)

Safety assessment

Safety was assessed via AEs, vital signs, physical examinations, and clinical laboratory tests, and graded according to National Cancer Institute Common Terminology Criteria, Version 3.0. Physical examinations were done weekly during the first month and every 3 weeks thereafter, or more frequently as clinically indicated. Physical examinations included assessment of mental status and neurologic changes.

Results

Patients

Forty-six patients received second-line systemic therapy with brivanib 800 mg once daily (Supplementary Fig. S1). Baseline characteristics are presented in Table 1. Of these patients, 72% were male, 67% were Asian, and 33% were non-Asian; 43 (93.5%) had progressed on sorafenib and 3 (6.5%) had progressed on thalidomide. Vascular invasion (portal vein invasion and/or portal vein thrombosis) was present at baseline in 7 patients (15.2%). Best responses to prior antiangiogenic therapy were 1 PR (2.2%), 15 SD (32.6%), 29 progressive disease (63.0%), and 1 unable to determine (2.2%). Median duration of prior antiangiogenic

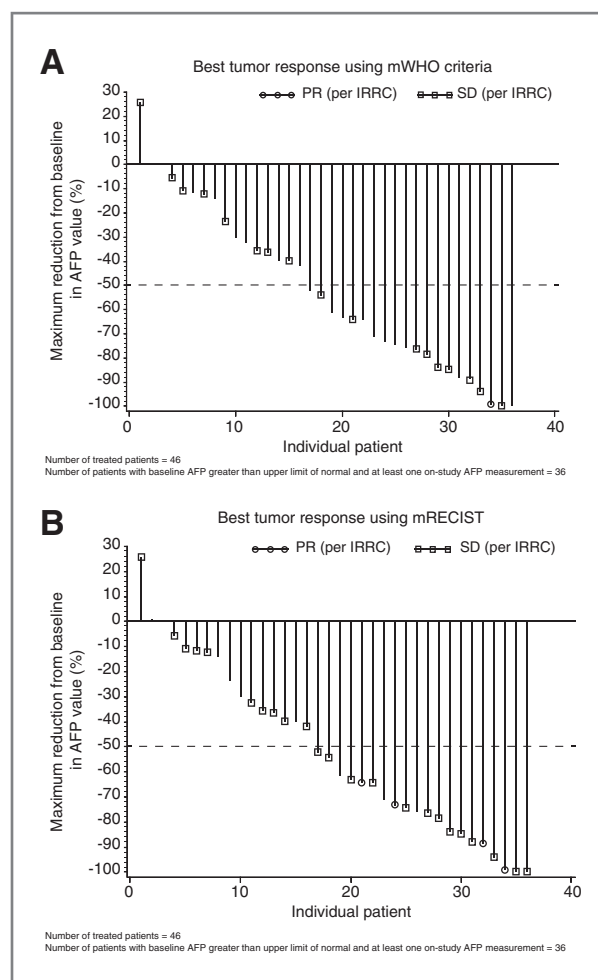


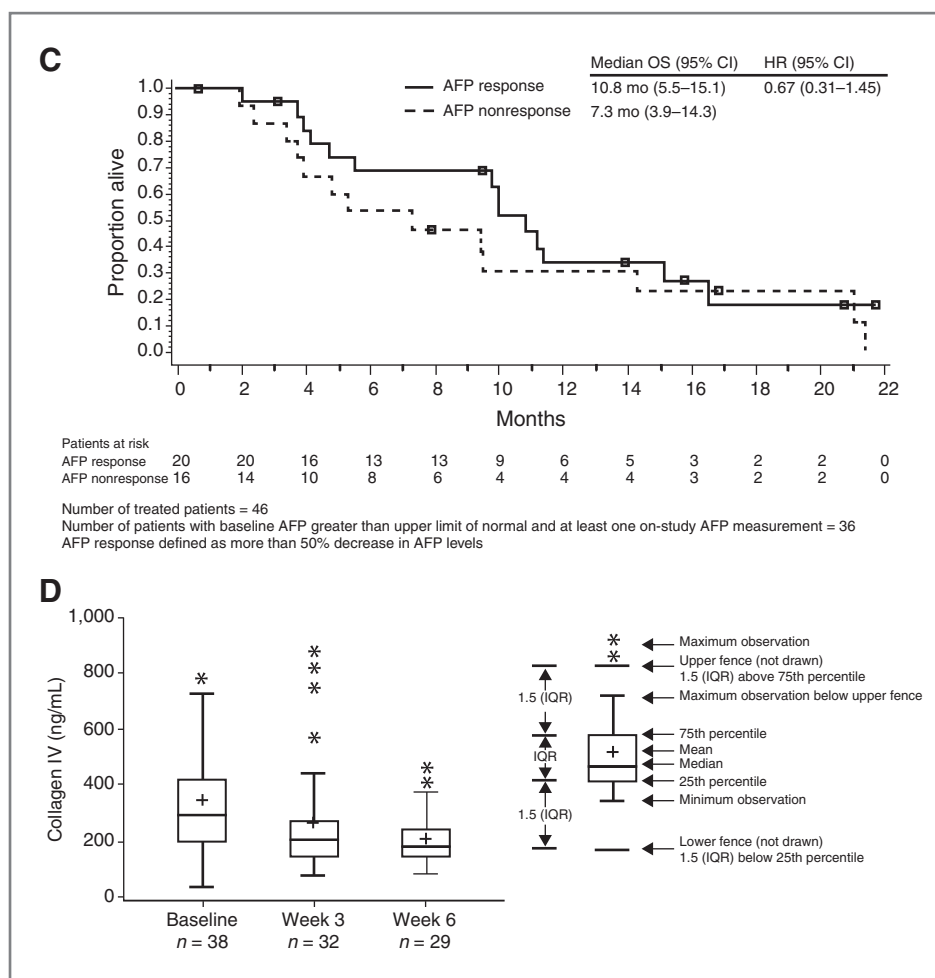
Figure 2. A, waterfall plot of best tumor response using mWHO criteria and best on-study decrease from baseline in AFP in patients with elevated baseline AFP (greater than the upper limit of normal). B, waterfall plot of best tumor response using mRECIST for hepatocellular carcinoma and best on-study decrease from baseline in AFP in patients with elevated baseline AFP (greater than the upper limit of normal).

therapy was 3.14 months (range: 0.26–11.47). Reasons for stopping prior antiangiogenic therapy were disease progression in 43 patients (93.5%) and toxicity in 3 (6.5%). These 3 patients did ultimately progress prior to study entry. Median TTP for 44 patients who had radiographic progression under prior antiangiogenic therapy was 2.97 months based on 44 events.

Efficacy results

Response to treatment with brivanib is summarized in Table 2. Best responses to treatment with brivanib using mWHO criteria per IRRC were PR for 2 patients (4.3%), SD for 19 patients (41.3%), progressive disease for 19 patients (41.3%), and unable to determine due to availability of only baseline scans in 6 patients (13.0%); the tumor response rate was 4.3% and the DCR was 45.7%. Best responses using mWHO criteria, per investigator, were PR

Figure 2. (Continued) C, OS by AFP response (>50% decrease from baseline in AFP) in patients with elevated baseline AFP (greater than upper limit of normal). D, circulating collagen IV levels at baseline and on study. IQR, interquartile range.



in 2 patients (4.3%), SD in 20 patients (43.5%), progressive disease in 15 patients (32.6%), and unable to determine in 9 patients (19.6%) due to discontinuation prior to disease assessment; the tumor response rate was 4.3% and the DCR was 47.8%. Median TTP per mWHO criteria assessed by IRRC was 1.77 months (95% CI: 1.38–4.01; Fig. 1A). Median OS was 9.79 months (95% CI: 5.52–13.17; Fig. 1B). Median PFS was 2.00 months (95% CI: 1.41–3.91) assessed by IRRC and 2.73 months (95% CI: 1.45–4.04) assessed by study investigators.

Results of post hoc exploratory analysis of efficacy using mRECIST

Best responses using HCC mRECIST per retrospective review by an independent radiologist were PR in 5 patients (10.9%), SD in 28 patients (60.9%), progressive disease in 7 patients (15.2%), and unable to determine in 6 patients (13.0%), due to the fact that only baseline images were available for review using mRECIST; the tumor response rate was 10.9% and the DCR was 71.7%. Median TTP per mRECIST was 6.9 months (95% CI: 3.9–not reached; Fig. 1A). Responses to brivanib were higher with mRECIST versus mWHO criteria.

Biomarker results

AFP responses (best on-study decrease from baseline) of more than 50% and 50% or less were reported in 23 patients (50.0%) and 21 patients (45.7%), respectively (Table 2). AFP responses were not reported for 2 patients (4.3%; Table 2). For patients with evaluable response as well as AFP changes (i.e., baseline AFP greater than the upper limit of normal and at least one on-study AFP measure), percent AFP change from baseline and radiographic response by mWHO criteria and mRECIST are presented in Figs. 2A and B, respectively. All patients who had a PR, regardless of assessment tool, had more than 50% decrease from their baseline AFP value. In addition, a number of patients with SD had more than 50% decrease from their baseline AFP value. Figure 2C shows survival for the same population of patients, comparing those who had more than 50% decrease from baseline in AFP value with those who did not. Median OS was 10.8 months for patients with more than 50% decrease from baseline in AFP versus 7.3 months for those without such an AFP response, with a HR of 0.67 (95% CI: 0.31–1.45).

Collagen IV levels were reduced at week 3 of brivanib treatment (day 21) and levels were maintained until week 6 regardless of response to brivanib (Fig. 2D). At baseline,

median (quartile [q1, q3] collagen IV levels were 293.80 ng/mL (195.0–459.8; $n = 39$). At week 3, the median (q1, q3) change from baseline in collagen IV levels was -69.10 ng/mL (-143.4 to 32.8 ng/mL; $n = 32$). At week 6, the median (q1, q3) change from baseline in collagen IV levels was -71.60 ng/mL (-150.0 to 31.1 ng/mL; $n = 29$).

Safety

On-study AEs were reported for all patients; 4 patients (8.7%) had grade 1 AEs, 18 (39.1%) had grade 2 AEs, 20 (43.5%) had grade 3 AEs, 2 (4.3%) had grade 4 AEs, and 2 (4.3%) had grade 5 AEs. The most common AEs are summarized in Table 3. The most frequently reported grade 3/4 AEs were hypertension (8.7%), hyponatremia (8.7%), decreased platelet count (6.5%), and diarrhea (6.5%). The 2 patients with grade 5 AEs had renal failure, cholecystitis, and disease progression. Hand-foot syndrome was rare, with only 6 of 46 patients (13%) experiencing this AE (all grade 1/2). Weight loss was reported in 5 patients (10.9%) and was generally mild (grade 1 in 3 patients and grade 2 in 2 patients). Encephalopathy was reported in 4 patients (8.7%) and was grade 2 in 2 patients and grade 3 in 2 patients. No grade 3/4 dermatologic AEs were observed. On-study drug-related AEs were reported for 43 (93.5%) patients: grade 1 in 10.9%, grade 2 in 41.3%, and grade 3 in 41.3%. Serious AEs were reported for 17 patients (37.0%). Thirteen patients (28.3%) had grade 3/4 serious AEs, and 2 patients (4.3%) had grade 5 serious AEs, both of which were considered unrelated to brivanib. Twelve patients (26.1%) discontinued the study due to AEs [7 (15.2%) were considered related to brivanib]. AEs leading to discontinuation in at least 2 patients were vomiting (2 patients; grade 3) and hypertension (3 patients; grade 2/3). Bleeding events were uncommon and included rectal hemorrhage (1 patient, grade 1), bloody discharge (1 patient, grade 1), epistaxis (3 patients, grade 1), and tumor hemorrhage (1 patient, grade 2). Three patients died within 30 days of the last dose of brivanib; the cause of death was underlying disease progression in 2 patients and a combination of acute renal failure and cholecystitis in the third. In addition, 28 (66.7%) patients had elevated thyroid stimulating hormone levels. Grade 4 laboratory abnormalities included 1 report in each of the following: thrombocytopenia, neutropenia, and renal dysfunction with hyponatremia and elevated creatinine.

Discussion

The approval of sorafenib was a significant step forward in the treatment of advanced HCC. However, still many patients do not receive benefit with sorafenib, and those who do eventually progress. This study is one of the first to report on a novel therapeutic agent for advanced HCC in the post-sorafenib era.

In this single-arm, phase II study, brivanib treatment seemed to provide additional clinical benefit to patients

with advanced HCC who had progressive disease while taking 1 prior antiangiogenic therapy (primarily sorafenib). This patient population currently has no proven therapeutic options. Although encouraging, these data will require prospective confirmation.

This study is also one of the first to report an exploratory analysis using mRECIST, the newly proposed response criteria by the AASLD-JNCI (30, 31). It has been proposed that changes in the unique imaging characteristics of HCC must be considered when assessing response of novel therapeutics in HCC clinical trials. Specifically, the hypervascular nature of HCC and its characteristic enhancement on contrast imaging must be taken into consideration when assessing the "longest tumor diameter" as is commonly done with RECIST (33). It is proposed that changes in the hypervascular component are considered. Results from a recent retrospective analysis of patients treated for advanced HCC suggest that the use of mRECIST may be a better way of assessing treatment efficacy with sorafenib (34). In this study, the responses to brivanib were higher based on mRECIST compared with mWHO criteria. Median TTP was 6.9 months per mRECIST versus 1.77 months per mWHO criteria assessed by IRRC. Further validation of these new assessment criteria is ongoing in the phase III randomized brivanib trials and will better define whether mRECIST is a better predictor for OS and benefit than conventional assessment criteria (RECIST).

As expected, the activity of brivanib in a pretreated population is less than that in a treatment-naive population (29). For comparison using mWHO criteria, in the first-line brivanib study, 1 patient achieved a CR, 3 patients achieved a PR, and 24 had SD, whereas in this study only 2 patients had a PR and 19 achieved SD. Median PFS (assessed by IRRC) and OS were 2.7 and 10 months, respectively, in the first-line setting (29) and 2.00 and 9.79 months in this study. Similarly, median TTP (assessed by IRRC) was 2.8 months in the first-line setting (29) and 1.77 months in this study. The apparent disconnection between OS and TTP may be a reflection of the initial interpretation of response based on mWHO; in this study, DCR based on mRECIST was greater than that based on mWHO.

We carried out exploratory biomarker analyses as part of this phase II study. Although the utility of AFP values and the optimal method to interpret AFP changes in the treatment of patients with advanced HCC remain controversial, we determined that all patients with a radiographic response by either mWHO criteria or mRECIST had more than 50% decrease from baseline in AFP, as did a number of patients with SD. In addition, there was a trend toward better survival in patients with more than 50% decrease from baseline in AFP versus those without such an AFP response. In addition, data from this study recapitulate the preclinical observation that brivanib modulates serum collagen IV levels. However, it is unclear as to whether this effect is FGF mediated. The utility of both AFP and collagen IV as predictive markers of response will require further study.

Safety results from this analysis of brivanib as second-line treatment and those from the analysis of brivanib as first-line treatment in patients with HCC (29) indicate that this agent has a manageable safety profile, with the most common AEs being fatigue, decreased appetite, nausea, diarrhea, and hypertension. Although the current results are from an open-label, single-arm study, they compare favorably with sorafenib outcomes in 2 large randomized, placebo-controlled phase III trials (5, 6). Specifically, brivanib has a very low incidence of hand-foot skin reaction, which is often a limiting toxicity with sorafenib. Clinically significant hypertension is more common with brivanib than with sorafenib (5, 6), and this may be a reflection of a more potent antiangiogenic effect. There were 3 deaths recorded within 30 days of completing study therapy, but none of those deaths were felt to be drug related in this study with advanced, treatment refractory HCC.

In conclusion, this single-arm study shows the activity and safety of brivanib in patients with advanced HCC after progression with sorafenib. These phase II results, together with the scientific rationale that dual FGFR and VEGFR inhibition may overcome VEGF therapy resistance, supports the ongoing phase III study of brivanib versus placebo in patients intolerant of, or progressing on, sorafenib

(NCT00825955). This will further inform the tolerability and efficacy of brivanib in this population with unmet need and will provide prospective, randomized data to fully assess the utility of mRECIST in HCC trials.

Disclosure of Potential Conflicts of Interest

R.S. Finn has served as a compensated consultant/advisor for Bristol-Myers Squibb and has conducted research funded by Bristol-Myers Squibb, Pfizer, and Novartis. I. Walters is employed by and owns stock in Bristol-Myers Squibb. C. Baudelet and D. Manekas are employed by Bristol-Myers Squibb. J-W. Park has served as a compensated consultant/advisor for Bristol-Myers Squibb. Y-K. Kang, M. Mulcahy, B.N. Polite, and H.Y. Lim declare no conflicts of interest.

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