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Sorafenib or Placebo with Either Gemcitabine or Capecitabine in Patients with HER-2–Negative Advanced Breast Cancer That Progressed during or after Bevacizumab

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Abstract

Purpose: We assessed adding the multikinase inhibitor sorafenib to gemcitabine or capecitabine in patients with advanced breast cancer whose disease progressed during/after bevacizumab.

Experimental Design: This double-blind, randomized, placebo-controlled phase IIb study (ClinicalTrials.gov NCT00493636) enrolled patients with locally advanced or metastatic human epidermal growth factor receptor 2 (HER2)–negative breast cancer and prior bevacizumab treatment. Patients were randomized to chemotherapy with sorafenib (400 mg, twice daily) or matching placebo. Initially, chemotherapy was gemcitabine (1,000 mg/m² i.v., days 1, 8/21), but later, capecitabine (1,000 mg/m² orally twice daily, days 1–14/21) was allowed as an alternative. The primary endpoint was progression-free survival (PFS).

Results: One hundred and sixty patients were randomized. More patients received gemcitabine (82.5%) than capecitabine (17.5%). Sorafenib plus gemcitabine/capecitabine was associated with a statistically significant prolongation in PFS versus placebo plus gemcitabine/capecitabine [3.4 vs. 2.7 months; HR = 0.65; 95% confidence interval (CI): 0.45–0.95; $P = 0.02$], time to progression was increased (median, 3.6 vs. 2.7 months; HR = 0.64; 95% CI: 0.44–0.93; $P = 0.02$), and overall response rate was 19.8% versus 12.7% ($P = 0.23$). Median survival was 13.4 versus 11.4 months for sorafenib versus placebo (HR = 1.01; 95% CI: 0.71–1.44; $P = 0.95$). Addition of sorafenib versus placebo increased grade 3/4 hand–foot skin reaction (39% vs. 5%), stomatitis (10% vs. 0%), fatigue (18% vs. 9%), and dose reductions that were more frequent (51.9% vs. 7.8%).

Conclusion: The addition of sorafenib to gemcitabine/capecitabine provided a clinically small but statistically significant PFS benefit in HER2-negative advanced breast cancer patients whose disease progressed during/after bevacizumab. Combination treatment was associated with manageable toxicities but frequently required dose reductions. *Clin Cancer Res*; 19(10); 2745–54. ©2013 AACR.

Introduction

Angiogenesis plays a critical role in the development and local progression of breast and other cancers and is associated with progression of metastatic disease (1). Therefore,

inhibition of angiogenesis with targeted therapies has become a key research strategy for drug development. The single-agent activity of antiangiogenics has been limited in metastatic breast cancer (MBC; refs. 2–4). However,

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Translational Relevance

Angiogenesis plays a critical role in the development and local progression of breast cancer. Bevacizumab, a monoclonal antibody targeting the proangiogenic vascular endothelial growth factor, has shown clinical activity in metastatic breast cancer (MBC) in the phase III setting when used in combination with chemotherapy. Sorafenib is an orally administered small-molecule inhibitor of multiple tyrosine kinases and has antiproliferative and antiangiogenic activities. Unlike bevacizumab, sorafenib affects angiogenesis at multiple steps and may target pathways involved in bevacizumab resistance. Sorafenib treatment has shown evidence of activity in patients with metastatic clear cell renal cell carcinoma refractory to sunitinib or bevacizumab. The randomized, placebo-controlled phase II study assessed the efficacy and safety of adding sorafenib to gemcitabine or capecitabine in patients with MBC whose disease progressed during or after treatment with bevacizumab. The addition of sorafenib was associated with a clinically small but statistically significant improvement in the primary endpoint of progression-free survival.

preclinical and clinical studies suggest that combinations of antiangiogenic therapy and chemotherapy are worthy of exploration (1, 5–8).

Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), is currently the only antiangiogenic to show clinical activity in MBC in the phase III setting when used in combination with chemotherapy (5–8). A phase III trial in patients with human epidermal growth factor receptor 2 (HER2)-negative MBC showed that adding bevacizumab to first-line paclitaxel improved progression-free survival [PFS; median, 11.8 vs. 5.9 months; hazard ratio (HR) = 0.60; 95% confidence interval (CI) 0.51–0.70; $P < 0.001$] with manageable toxicity (6). Additional phase III studies have also shown statistically significant but less marked improvements in PFS when bevacizumab is added to other standard chemotherapies for HER2-negative MBC, including docetaxel and capecitabine, among others (5–8). Nonetheless, the addition of bevacizumab to MBC chemotherapy has not been shown to improve overall survival (OS) to date.

There are a number of potential reasons for these observations with bevacizumab. The PFS benefit in the initial study of bevacizumab with frontline paclitaxel may have been an outlier (9). OS data can be confounded by the use of subsequent therapy at the time of progression (10). In late stages of tumor development, redundant and compensatory angiogenic mechanisms may overcome inhibition by bevacizumab, despite an initial response (11) and may lead to more aggressive disease at the time of progression (12, 13), or a rebound effect could occur after discontinuation of antiangiogenic therapy (6).

In November 2011, the U.S Food and Drug Administration revoked bevacizumab's indication for use in combination with paclitaxel. Despite this, the use of bevacizumab in MBC continues to be supported by the Centers for Medicare and Medicaid Services, the National Comprehensive Cancer Network, and the European Medicines Agency. Furthermore, ongoing studies in MBC are exploring bevacizumab in specific subsets of patients as part of adjuvant treatment regimens (14, 15). Thus, it is important to develop alternative treatment approaches targeting angiogenesis in general and to identify treatment strategies for patients whose disease progresses during or after bevacizumab therapy specifically. In this regard, clinical studies suggest that sequential use of antiangiogenic treatments may be beneficial in some solid tumors (16, 17).

Sorafenib is an orally administered small-molecule inhibitor of multiple tyrosine kinases indicated for unresectable hepatocellular carcinoma or advanced renal cell carcinoma. Sorafenib has antiproliferative and antiangiogenic activities, targeting RAF kinases, c-KIT, and Flt-3 and the proangiogenic VEGF receptor, and platelet-derived growth factor receptor tyrosine kinases (18). Because sorafenib affects angiogenesis at multiple steps, it may target pathways involved in bevacizumab resistance. Data from a phase II sorafenib trial showed evidence of activity in patients with metastatic clear cell renal cell carcinoma refractory to sunitinib or bevacizumab (16).

To rapidly assess sorafenib in combination with known effective palliative treatments for HER2-negative MBC, a series of 4 double-blind, randomized, placebo-controlled, phase IIb screening Trials to Investigate the Efficacy of Sorafenib (TIES) were developed. Three of these studies have been completed. SOLTI-0701 and NU07B1 assessed the treatment effect of sorafenib when added to capecitabine and paclitaxel, respectively, in patients not previously treated with VEGF inhibitors (19, 20). A separate TIES trial, investigating sorafenib in combination with docetaxel and/or letrozole in specific subpopulations without prior VEGF-targeted treatment, reported primary analysis of PFS and is ongoing (21).

Here, we report the final results of AC01B07, a TIES trial designed to assess whether sorafenib in combination with gemcitabine or capecitabine (GEM/CAP) could overcome clinical bevacizumab resistance in patients with MBC. Initially, gemcitabine was the only chemotherapy option based on the available safety data of sorafenib combinations and practice patterns at the time the study was launched. Gemcitabine is approved for MBC in combination with paclitaxel but is frequently used as a single agent within sequential monotherapy strategies as studies indicate that sequential use of chemotherapies is as effective as combination strategies and is better tolerated (22, 23). The rationale for combining sorafenib and gemcitabine was based on both preclinical and clinical studies that have shown the potential of sorafenib to enhance antitumor activity or disease stabilization when combined with chemotherapy agents including but not limited to gemcitabine, the distinct mechanisms of action with nonoverlapping

toxicities for sorafenib and gemcitabine, the good tolerability of the combination, and the lack of drug-to-drug interactions (24). Capecitabine is approved as a single agent for MBC. Once safety data for sorafenib with capecitabine became available, the protocol was amended to allow this second chemotherapy agent as an alternative at the treating physician's discretion (25).

Patients and Methods

Patients

Eligible patients were 18 years or older with histologically or cytologically confirmed HER2-negative adenocarcinoma of the breast with locally advanced (inoperable) or metastatic disease. Patients experienced disease progression during or after a bevacizumab regimen in the adjuvant or metastatic setting. Prior chemotherapy for advanced disease was limited to 1 regimen; prior hormone therapy and radiation therapy were allowed. Additional selection criteria included Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate bone marrow, liver, and renal function. Patients were not eligible if they had active brain metastases or were at significant risk of major cardiovascular, cerebrovascular, or bleeding events.

Study design

AC01B07 was a double-blind, randomized, placebo-controlled phase IIb screening trial conducted at 40 centers in the United States. Patients were stratified by site of metastatic disease (visceral vs. nonvisceral) and randomized in a double-blind fashion using 1:1 allocation to receive sorafenib or placebo in combination with gemcitabine/capecitabine. Randomization was conducted with a web-based Randomization and Product Inventory Control (RPIC) system. Patients initiated treatment within 3 working days of randomization. All efforts were made to maintain blinding throughout the duration of the study. Details of unblinding procedures are provided in the definitions portion of the Supplementary Appendix.

The primary endpoint was PFS and the secondary endpoints were time to progression (TTP), overall response rate (ORR), duration of response (DOR), OS, and safety. (See Supplementary Appendix for detailed descriptions of endpoints.) All patients provided written informed consent. The study protocol was approved by the internal review boards of participating institutions. The study is registered at ClinicalTrials.gov (NCT00493636).

Treatment

Sorafenib 400 mg or matching placebo was administered orally, twice daily. Gemcitabine was administered at a dose of 1,000 mg/m² i.v. on days 1 and 8 of a 21-day cycle. Capecitabine was administered orally at a dose of 1,000 mg/m² twice daily for the first 14 days of a 21-day cycle. The study protocol detailed dose modifications to resolve toxicity or to increase potency. A description of the dosing algorithm is available in the Supplementary Appendix.

Assessments

Clinical and radiologic assessments were conducted at baseline, every 6 weeks for the first 24 weeks, and every 9 weeks thereafter. Tumor response was assessed by the investigator, based on the modified Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0; ref. 26). Adverse events (AE) were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0). Correlative studies were not conducted.

Statistical analysis

Initially, the planned sample size was 220 patients, with a prespecified analysis of PFS after 120 events having 90% power to detect a HR of 0.65 at a 1-sided $\alpha = 0.14$. *A priori*, it was estimated that an observed HR of 0.82 or more would provide evidence that sorafenib treatment was more effective than placebo and an observed HR of or more 0.70 would be statistically significant at 1-sided $\alpha = 0.025$. A 1-sided rather than a 2-sided α was used on the basis of previous findings with bevacizumab, which indicated that the difference from the control would be unidirectional (6), and to limit the sample size as this was not a pivotal study but rather a screening trial designed to determine if a phase III study should be initiated (27). After a lower than expected accrual rate, it was determined that the sample size should be reduced to 160 while the number of events remained at 120 thus preserving the original power and alpha level. Because of the inconsistencies in bevacizumab studies noted earlier (5–8), the usage of bevacizumab and the regulatory environment changed during AC01B07, which likely impacted patient accrual.

Primary analyses of efficacy data were conducted using the intent-to-treat population (all patients randomized to study treatment). Secondary efficacy analyses were also conducted using the per-protocol population (all patients who received study treatment without major protocol violations). Analyses of safety data were based on patients who received any study treatment (safety population).

A stratified Cox regression was used for the primary analysis of time-to-event endpoints with treatment group and the stratification factor as covariates in the model. Median event-free times were estimated with the Kaplan–Meier method. Primary analysis of categorical endpoints used the Cochran–Mantel–Haenszel test adjusted for the stratification factor. Two-sided *P* values are reported unless noted otherwise. SAS version 9.1 (SAS Institute Inc.) was used for all statistical analyses.

Results

A total of 160 patients were randomized to treatment between June 2007 and August 2010 (Fig. 1); 156 received study treatment (safety population), and 150 received study treatment and were without major protocol violations (per-protocol population). Data cut-off was September 2010 for analysis of PFS, response, safety, and tolerability, and was February 2012 for OS.

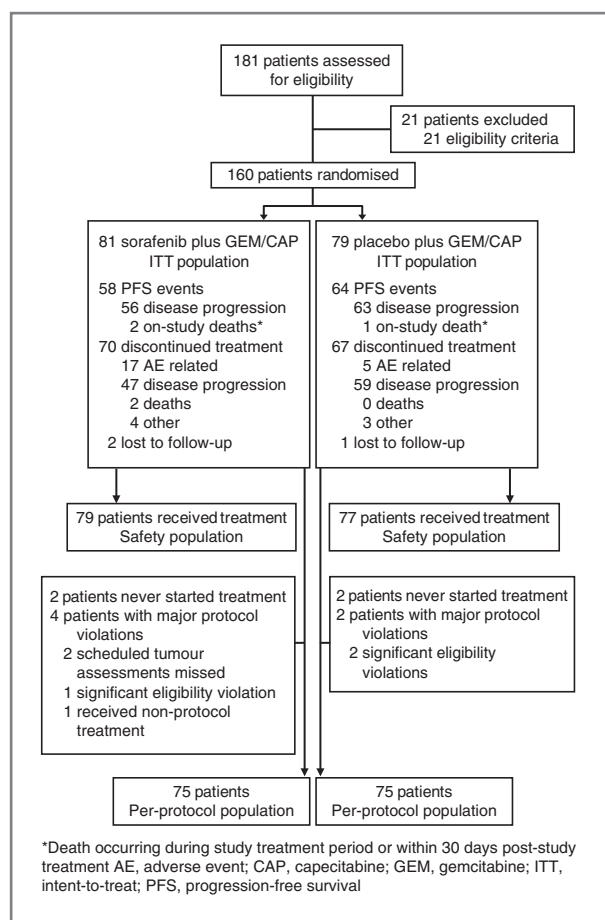


Figure 1. Patient disposition (data cut-off of September 2010).

Treatment arms were balanced for patient and disease characteristics, except for ECOG performance status (Table 1). All patients had received bevacizumab before enrolling in the study, most (97.5%) for metastatic (stage IIb/c or stage IV per American Joint Committee on Cancer staging) disease. The majority of patients (95.0%) had stage IV disease, and 84.4% had visceral metastases. As expected, more patients in the sorafenib and placebo treatment arms received gemcitabine (83% and 82%, respectively) than capecitabine (17% and 18%, respectively).

Efficacy

There were 122 PFS events. The combination of sorafenib plus gemcitabine/capecitabine provided a clinically small but statistically significant improvement in PFS compared with placebo plus gemcitabine/capecitabine [3.4 vs. 2.7 months; $P = 0.02$ (1-sided $P = 0.01$)], with a 35% reduction in the risk of disease progression or death (HR = 0.65; 95% CI: 0.45–0.95; Fig. 2). Analysis of the per-protocol population showed similar values (median PFS, 3.2 vs. 2.7 months; HR = 0.67; 95% CI: 0.46–0.98; $P = 0.04$), as did other sensitivity analyses (see Supplementary Appendix, Table SA1). Prespecified subgroup analyses of PFS were consistent with the overall results, with the exception of

chemotherapy type (Fig. 3). The addition of sorafenib improved outcome over placebo (HR = 0.54; 95% CI: 0.36–0.80) in the gemcitabine subgroup ($n = 132$), but this was not observed in the much smaller ($n = 28$) capecitabine subgroup (HR = 2.39; 95% CI: 0.79–7.23; $P = 0.11$).

At the time of the OS analysis cutoff, there were 64 deaths (59 due to disease progression) in the sorafenib arm and 60 deaths (54 due to disease progression) in the placebo arm. Median OS was 13.4 versus 11.4 months (HR = 1.01; 95% CI: 0.71–1.44; $P = 0.95$). Analysis of subgroups showed no notable differences between the treatment arms, with the exception of the chemotherapy type (Supplementary Appendix, Table SA2). As with the PFS subgroup data, sorafenib was favored compared with placebo in the gemcitabine subgroup (median 13.7 vs. 10.9 months; HR = 0.89; 95% CI: 0.60–1.30; $P = 0.53$) but not in the capecitabine subgroup (median 10.9 vs. 29.1 months; HR = 2.18; 95% CI: 0.85–5.56; $P = 0.10$).

Generally, the addition of sorafenib to gemcitabine/capecitabine was favorable for secondary efficacy endpoints (Table 2). TTP was significantly longer for sorafenib plus gemcitabine/capecitabine than for placebo plus gemcitabine/capecitabine (median, 3.6 vs. 2.7 months; HR = 0.64; 95% CI: 0.44–0.93; $P = 0.02$). There was no statistical difference in ORR (19.8% vs. 12.7%, respectively; $P = 0.235$). Median DOR (3.1 vs. 4.8 months, respectively) was longer for placebo.

Safety and tolerability

Treatment was associated with manageable toxicity (Table 3), but patients receiving combination therapy required more sorafenib dose reductions compared with the matching placebo (see Supplementary Appendix, Table A3). In the sorafenib arm of the gemcitabine subgroup, 52.5% of patients required dose reductions of sorafenib and 36.9% required reductions of gemcitabine, whereas in the placebo arm, 4.7% required reductions of placebo and 32.8% required reductions of gemcitabine.

There were no new or unexpected AEs. Grade 3 events occurred in 70% of patients in the sorafenib arm versus 47% in the placebo arm. Grade 4 events were infrequent, occurring in 14% versus 12% of patients, respectively. Grade 3 AEs that occurred more frequently in the sorafenib arm than in the placebo arm included stomatitis (10% vs. 0%), fatigue (18% vs. 9%), anemia (5% vs. 0%), and hand–foot skin reaction/syndrome (HFSR/HFS, 39% vs. 5%). The incidence of grade 3 HFSR was 37% (24/65 patients) versus 2% (1/64 patients), respectively, in the gemcitabine subgroup and 50% (7/14 patients) versus 23% (3/13 patients), respectively, in the capecitabine subgroup. Grade 3/4 thrombocytopenia occurred in 10% versus 1% of patients, respectively.

Overall, for patients receiving sorafenib plus gemcitabine/capecitabine, the average daily dose of sorafenib was 570 mg, corresponding to dose reductions in 51.9% of patients. For patients receiving placebo plus chemotherapy, the average daily dose of placebo was 751 mg,

Table 1. Baseline characteristics (intent-to-treat population)

	Sorafenib + GEM/CAP (n = 81)	Placebo + GEM/CAP (n = 79)
Age, mean (SD), y	53.5 (10.6)	54.2 (11.0)
Race/ethnicity, n (%)		
Caucasian	59 (72.8)	61 (77.2)
Hispanic	2 (2.5)	0 (0)
Black	16 (19.8)	13 (16.5)
Asian	2 (2.5)	5 (6.3)
ECOG status, n (%)		
0	32 (39.5)	42 (53.2)
1	47 (58.0)	37 (46.8)
AJCC stage, n (%)		
IIIb/IIIc	3 (3.7)	4 (5.1)
IV	77 (95.1)	75 (94.9)
Location of metastatic sites, n (%)		
Nonvisceral	12 (14.8)	13 (16.5)
Visceral	69 (85.2)	66 (83.5)
Measurable disease, n (%)		
Yes	72 (88.9)	72 (91.1)
No	8 (9.9)	7 (8.9)
Hormone receptor status, n (%)		
ER positive and/or PR positive ^a	54 (66.7)	52 (65.8)
ER negative and PR negative	23 (28.4)	27 (34.2)
Unknown	4 (4.9)	0 (0.0)
Prior chemotherapy for metastatic disease, n (%)		
Yes	76 (93.8)	76 (96.2)
No	4 (4.9)	3 (3.8)
Prior nonmetastatic treatment, n (%)		
Bevacizumab	2 (2.5)	2 (2.5)
Chemotherapy	66 (81.5)	53 (67.1)
Taxane	35 (43.2)	37 (46.8)
Anthracycline	41 (50.6)	39 (49.4)
Endocrine therapy	38 (46.9)	28 (35.4)
Radiotherapy	43 (53.1)	35 (44.3)
Prior metastatic treatment, n (%) ^b		
Bevacizumab	78 (96.3)	78 (98.7)
Chemotherapy	76 (93.8)	76 (96.2)
Taxane	52 (64.2)	48 (60.8)
Anthracycline	0 (0)	2 (2.5)
Endocrine therapy	39 (48.1)	35 (44.3)
Radiotherapy	22 (27.2)	14 (17.7)
Bevacizumab treatment (metastatic), n (%)		
Duration ≤6 months	40 (49.4)	43 (54.4)
Duration >6 months	38 (46.9)	35 (44.3)
Time since last treatment, median (range), months	1 (1–23)	1 (0–33)
Time since progression, n (%)		
≤1 month	66 (81.5)	63 (79.7)
>1 month	12 (14.8)	15 (19.0)

Abbreviations: AJCC, American Joint Committee on Cancer; CAP, capecitabine; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; GEM, gemcitabine; PR, progesterone receptor.

^aIncludes ER+/PR unknown or ER unknown/PR+.

^bIncludes patients with AJCC stage IIIb/IIIc breast cancer who received the treatments for advanced disease.

corresponding to dose reductions in 7.8% of patients. Discontinuation of study treatment due to AEs occurred in 21.0% of patients in the sorafenib arm and 6.3% in the placebo arm. The most common AEs leading to discontinuation were fatigue (6 patients in the sorafenib arm and 3 patients in the placebo arm) and HFSR/HFS (5 patients in the sorafenib arm).

There were 7 on-study deaths (during or up to 30 days post treatment). In the sorafenib arm, 3 on-study deaths were attributed to progressive disease (1), cardiac arrest related to treatment (1), and intracranial brain hemorrhage that was considered unrelated to combination therapy (1). In the placebo arm, 4 on-study deaths were attributed to progressive disease (3) and liver failure (1).

Discussion

This study met its primary endpoint, demonstrating a clinically small but statistically significant benefit for PFS with the addition of sorafenib to chemotherapy compared with chemotherapy alone in patients with HER2-negative advanced breast cancer who had previously received treatment with bevacizumab. In this poor prognosis cohort, the combination was associated with a 35% reduction in the risk of disease progression or death (median PFS, 3.4 vs. 2.7 months; HR = 0.65; 95% CI: 0.45–0.95; *P* = 0.02) and a 36% reduction in risk of disease progression (median TTP, 3.6 vs. 2.7 months; HR = 0.64; 95% CI: 0.44–0.93; *P* = 0.02), but this did not correspond to an improvement in OS (median 13.4 vs. 11.4 months; *P* = 0.95).

The toxicity associated with the combination of sorafenib to gemcitabine/capecitabine was manageable after dose interruptions and reductions, with the majority of patients maintaining treatment until disease progression. Most AEs associated with the addition of sorafenib were mild to moderate in severity, and the types of AEs were consistent with the known safety profiles of the individual agents. The most frequent AE associated with the addition of sorafenib was HFSR/HFS, which is nonlife threatening and reversible but can decrease quality of life and necessitate treatment modifications or discontinuation. As noted, dose modifications were more frequent in the sorafenib arm. Taken together, these data indicate that when using sorafenib in combination with chemotherapy, a lower dose of sorafenib may be appropriate with the opportunity to dose escalate as tolerated. Gemcitabine dose modifications were comparable between treatment arms.

In the blinded, controlled trial setting, there is concern that HFSR/HFS may effectively unblind treatment because of the difference in incidence between arms. We acknowledge that some investigators and patients may have overcome blinding by using toxicity experiences to guess treatment assignment. We have no evidence that such events were more frequent here compared with other trials of similar design but cannot exclude this as a potential study bias.

The AC01B07 study provides 2 kinds of clinically relevant evidence supporting further development of sorafenib in

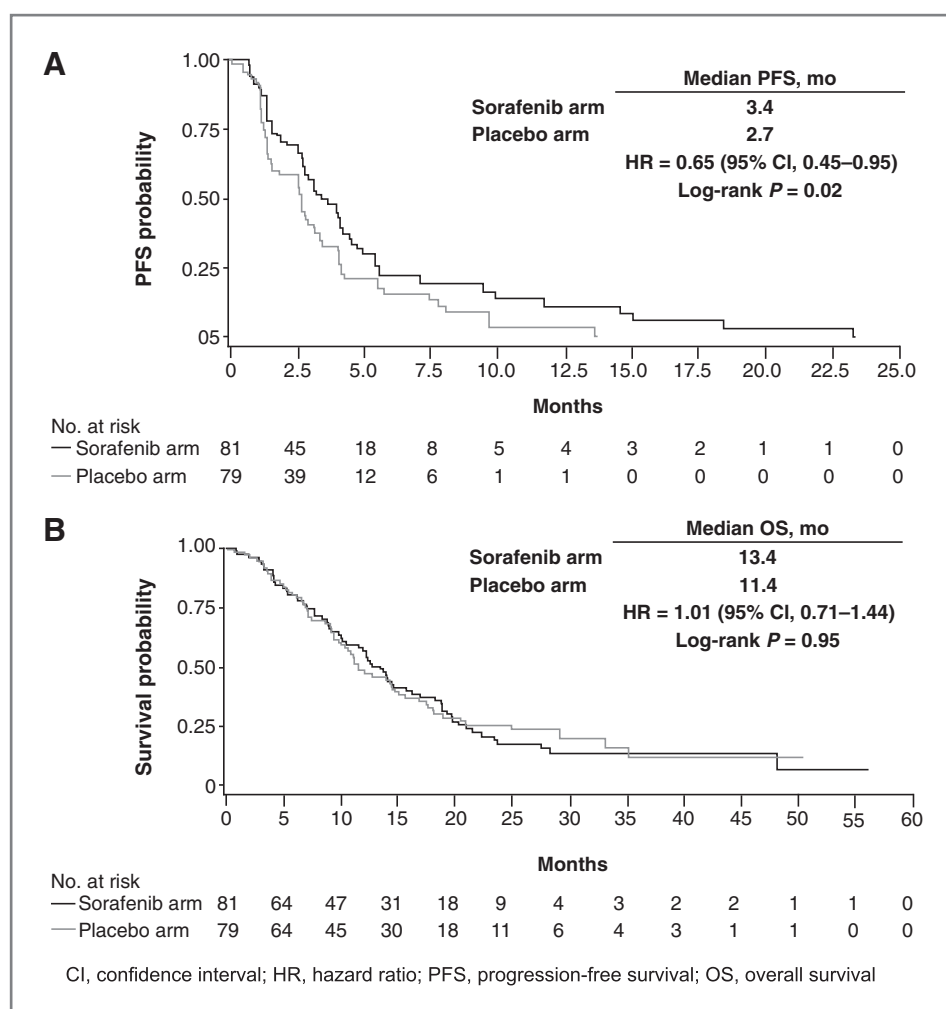


Figure 2. Kaplan–Meier analysis of (A) PFS (data cut-off of September 2010) and (B) overall survival (data cut-off of February 2012).

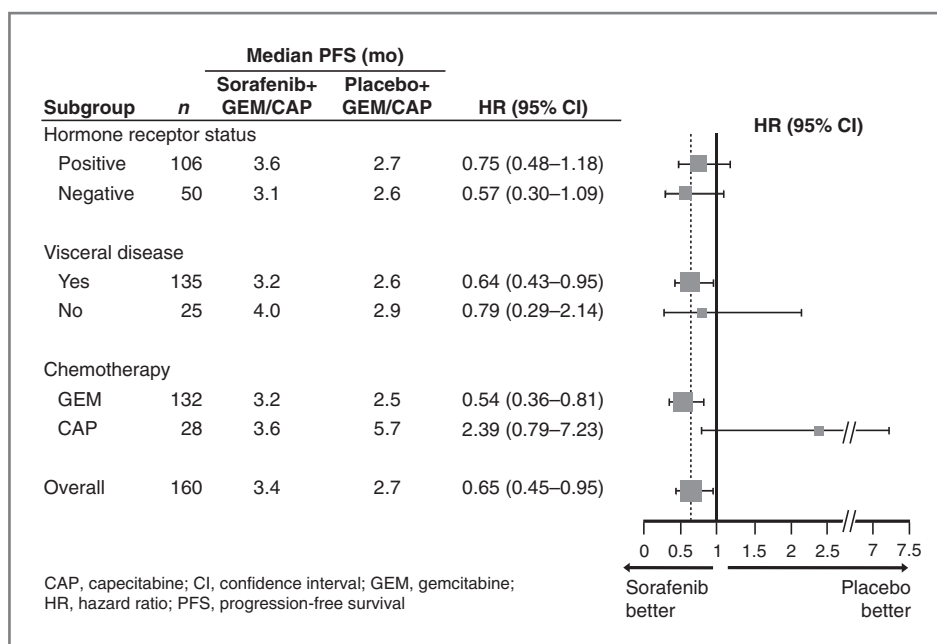
breast cancer. First, this study provides the only data to date that show a potential benefit for a second antiangiogenic agent in patients with MBC and progression after prior bevacizumab. Although bevacizumab is no longer indicated for MBC in the United States, it may remain part of the off-label treatment armamentarium and remains a treatment option in Europe. Second, the findings in this study are consistent with the SOLTI-0701 and NU07B1 TIES studies, which also showed activity when sorafenib was added to capecitabine and paclitaxel, respectively (19, 20). The other TIES study, FM-B01-07, did not demonstrate a clinical benefit when sorafenib was added to docetaxel/letrozole (21). Overall, the TIES program suggests activity for sorafenib when added to the selected chemotherapy agents in the various clinical scenarios. Of note, the lack of an association of benefit with any specific chemotherapy agent supports the hypothesis that, in the end, the activities of biologic agents are independent and not modulated by the companion chemotherapy regimen when used in combination (28).

We note that although PFS and TTP were significantly different between treatment arms in our study, the medi-

an durations of these endpoints were relatively brief. Most patients received gemcitabine during the current study, and the TTP results appeared comparable with small studies investigating single-agent gemcitabine in advanced breast cancer, with median TTP ranging from 1.9 to 6.3 months (29–32). However, it is difficult to compare results across studies in MBC because of differences in patient populations. In the current study, many patients had received previous treatment with anthracyclines and taxanes, and this is a unique population in that all patients had progressed during or after a bevacizumab regimen—97.5% in the metastatic setting. The lack of an OS benefit was not unexpected given the small improvement in PFS, and the size of the study population was too small to have adequate power to detect an OS benefit if present.

The disease course of MBC after discontinuation of bevacizumab has not been well characterized. Preclinical studies suggest that antiangiogenic therapy may induce more aggressive disease (12, 13), although a retrospective pooled analysis of randomized placebo-controlled trials in solid tumors (including breast) observed no significant

Figure 3. PFS in prespecified subgroups (data cutoff of September 2010).



difference in TTP or death after patients discontinued bevacizumab due to toxicity compared with those who discontinued placebo (33). Regardless, patients enrolled in this trial had relatively high-risk disease for early progression.

Unlike AC01B07, the other TIES studies excluded patients with prior bevacizumab treatment. In the SOLTI-0701 study, sorafenib plus capecitabine (first- or second-line) significantly improved median PFS compared with placebo plus capecitabine (6.4 vs. 4.1 months; HR = 0.58; 95% CI: 0.41–0.81; *P* = 0.001; ref. 19). The addition of sorafenib to capecitabine was associated with an increased incidence of grade 3 HFSR/HFS (44% vs. 14%). The SOLTI-0701 results have prompted the initiation of a confirmatory phase III

study with an adjusted dosing schema for sorafenib and more aggressive supportive care to improve tolerability (34). The starting dose of sorafenib has been lowered to 600 mg/day (200 mg in the morning and 400 mg in the evening), which can then be escalated to 800 mg/day as tolerated.

In view of the SOLTI-0701 data, and recognizing the very small number of patients (14 patients in each arm) in our trial randomized with capecitabine as the chemotherapy base, we do not believe that the point estimates for PFS and OS in this subset are interpretable. We also note that the choice of capecitabine may have been influenced by disease and patient factors that were not balanced

Table 2. Secondary efficacy endpoints for the intent-to-treat population

	Sorafenib + GEM/CAP (N = 81)	Placebo + GEM/CAP (N = 79)	HR (95% CI)	P
TTP, median, months	3.6	2.7	0.64 (0.44–0.93)	0.02 ^a
Overall response, % (95% CI)	19.8 (11.7–30.1)	12.7 (6.2–22.0)		0.235 ^b
Best response, n (%)				
Complete response	0 (0)	1 (1.3)		
Partial response	16 (19.8)	9 (11.4)		
Stable disease	35 (43.2)	34 (43.0)		
Progressive disease	19 (23.5)	30 (38.0)		
DOR, median, months ^c	3.1	4.8	0.88 (0.64–1.12) ^d	0.56 ^a

Abbreviations: CAP, capecitabine; CI, confidence interval; DOR, duration of response; GEM, gemcitabine; TTP, time to progression.

^a*P*-value from stratified log-rank test.

^b*P*-value calculated with Cochran–Mantel–Haenszel test.

^cSample size inadequate for statistical comparison.

^dIncluded nonresponse as an event with duration of 0.

Table 3. Adverse events reported in at least 10% of patients (safety population)

	Sorafenib + GEM/CAP (n = 79)			Placebo + GEM/CAP (n = 77)		
	Grade,%			Grade,%		
	Any	3	4	Any	3	4
Hand-foot skin reaction/syndrome ^a	57	39	–	18	5	–
Rash	28	4	0	16	0	0
Nausea	44	1	0	49	3	0
Diarrhea	35	6	0	22	1	0
Stomatitis	27	10	0	7	0	0
Constipation	23	1	0	27	0	0
Vomiting	27	1	0	23	0	0
Abdominal pain	14	3	0	13	5	0
Weight decreased	14	0	0	3	1	0
Fatigue	61	18	0	47	9	0
Pyrexia	19	3	0	18	1	0
Mucosal inflammation	14	1	0	7	0	0
Pain	14	1	0	10	0	0
Headache	24	1	0	18	0	0
Pain in extremities	19	1	0	8	0	0
Back pain	11	1	0	16	3	0
Arthralgia	10	1	0	17	3	0
Cough	23	1	–	20	0	–
Dyspnea	22	5	0	22	5	0
Epistaxis	17	0	0	12	0	0
Anorexia	19	1	0	7	0	0
Neutropenia	24	16	4	27	20	7
Anemia	14	5	0	8	0	0
Thrombocytopenia	11	4	6	9	1	0
Hypertension	20	4	0	9	1	0

Abbreviations: CAP, capecitabine; GEM, gemcitabine.

^aHand-foot skin reaction is associated with sorafenib, and hand-foot syndrome is associated with capecitabine.

between arms. The vast majority of patients received gemcitabine, and PFS data in this subgroup and for the study as a whole were consistent with those of the other TIES trials favoring the addition of sorafenib over placebo.

Validated biomarkers would help us better understand the variability in response to antiangiogenic therapies across patient populations. Unfortunately, biomarkers for antiangiogenics have not been validated, although studies have shown some correlations between treatment activity and VEGF plasma levels, *VEGF-2578* and *-5411 AA* genotypes, and treatment-emergent hypertension (35). Although correlative studies were not conducted for the current study, future studies investigating sequential use of antiangiogenic agents may consider correlating treatment response to plasma levels of various angiogenic activators, including the inhibitory target(s) and compensatory pathway molecules (e.g., VEGF, epidermal growth factor, and platelet-derived growth factor B).

In conclusion, AC01B07 data have shown that the combination of sorafenib plus gemcitabine/capecitabine provided a statistically significant benefit for PFS in patients with HER2-negative advanced breast cancer who had pre-

viously experienced disease progression during or after a regimen containing bevacizumab. Sorafenib may be a viable option for patients with MBC even after treatment with bevacizumab. However, these phase IIb trial results are not practice changing. Although the AC01B07 study met the predefined endpoint, a phase III study has not been planned as the duration of PFS was relatively short, the benefit was clinically small, and there was no corresponding improvement in OS. More clinical data are needed in patients with prior bevacizumab treatment to determine if there are definable subsets and whether any specific chemotherapy agents offer clinically meaningful benefits in combination with small-molecule antiangiogenics.

Disclosure of Potential Conflicts of Interest

K.W. Tauer has honoraria from speakers' bureau from Amgen and Lilly. R. C. Hermann has honoraria from speakers' bureau and is a consultant/advisory board member of Roche-Genentech. H. Rugo has a commercial research grant from Genentech and GSK to UCSF. M.R. Keaton is a consultant/advisory board member of Celgene. S.K. Ro is employed (other than primary affiliation; e.g., consulting) as Director, Biostatistics and has ownership interest (including patents) in Onyx Pharmaceuticals. N.A. Lokker is employed (other than primary affiliation; e.g., consulting) as Senior Director, Clinical Development and has ownership interest (including

patents) in Onyx Pharmaceuticals, Inc. C.A. Hudis has a commercial research grant from Onyx/Bayer. The other authors disclosed no potential conflicts of interest.

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