Published in final edited form as:

*Clin Breast Cancer*. 2017 December ; 17(8): 585–594.e4. doi:10.1016/j.clbc.2017.05.006.

# RESILIENCE: Phase III Randomized, Double-Blind Trial Comparing Sorafenib With Capecitabine Versus Placebo With Capecitabine in Locally Advanced or Metastatic HER2-Negative Breast Cancer

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This trial is registered at Clinicaltrials.gov: NCT01234337.

**Disclosure**

Patricia Maeda, Liping Huang, and Gerold Meinhardt are employees of Bayer HealthCare Pharmaceuticals and Joshua Zhang is a former employee. The remaining authors have stated that they have no conflicts of interest.

**Supplemental Data**

Supplemental data accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clbc.2017.05.006.

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## Abstract

A previous randomized phase II trial suggested that sorafenib might enhance the efficacy of capecitabine in patients with metastatic breast cancer. However, in this randomized, placebo-controlled phase trial of 537 patients with advanced HER2-negative breast cancer we found that the combination of sorafenib with capecitabine did not improve progression-free survival, overall survival, or overall response rate, but increased treatment-related toxicities and discontinuations.

**Introduction—**Sorafenib is a multikinase inhibitor with antiangiogenic/antiproliferative activity. In this randomized, double-blind, placebo-controlled phase III trial we assessed first- or second-line capecitabine with sorafenib or placebo in patients with locally advanced/metastatic HER2-negative breast cancer resistant to a taxane and anthracycline and with known estrogen/progesterone receptor status.

**Patients and Methods—**A total of 537 patients were randomized to capecitabine 1000 mg/m$^2$ orally twice per day for days 1 to 14 every 21 days with oral sorafenib 600 mg/d or placebo. The primary end point was progression-free survival (PFS). Patients were stratified according to hormone receptor status, previous chemotherapies for metastatic breast cancer, and geographic region.

**Results—**Treatment with sorafenib with capecitabine, compared with capecitabine with placebo, did not prolong median PFS (5.5 vs. 5.4 months; hazard ratio [HR], 0.973; 95% confidence interval [CI], 0.779–1.217; $P = .811$) or overall survival (OS; 18.9 vs. 20.3 months; HR, 1.195; 95% CI, 0.943–1.513; $P = .140$); or enhance overall response rate (ORR; 13.5% vs. 15.5%; $P = .515$). Any grade toxicities (sorafenib vs. placebo) included palmar-plantar erythrodysesthesia syndrome (79.2% vs. 59.6%), diarrhea (47.3% vs. 37.8%), mucosal inflammation (15.4% vs. 6.7%), and hypertension (26.2% vs. 5.6%). Grade 3/4 toxicities included PPES (15.4% vs. 7.1%), diarrhea (4.2% vs. 6.4%), and vomiting (3.5% vs. 0.7%).

**Conclusion—**The combination of sorafenib with capecitabine did not improve PFS, OS, or ORR in patients with HER2-negative advanced breast cancer. Rates of Grade 3 toxicities were higher in the sorafenib arm.



### Keywords

Hormone-receptor status; Multikinase inhibitor; Overall survival; Progression-free survival; Raf kinases


## Introduction

Metastatic breast cancer is incurable. Despite therapeutic advances, the primary treatment goal remains palliative, with median survival usually 2 to 3 years. Regimens that combined diverse cytotoxic agents have shown clinical benefits but also increased toxicities compared with monotherapy.[1–4] Several agents that target HER2, including trastuzumab, pertuzumab, and trastuzumab emtansine, have shown survival benefits when combined with chemotherapy in patients with HER2-positive disease.[5,6] Moreover, palbociclib, an inhibitor of cyclin-dependent kinases 4 and 6, was recently approved by the US Food and Drug

Administration, in combination with letrozole or fulvestrant, to treat patients with HER2-negative metastatic breast cancer.[7,8]

Angiogenesis is critical in breast cancer development, progression, and metastasis.[9–11] Angiogenesis has been associated with metastatic disease, disease recurrence, and patient survival, with angiogenic growth factors expressed early in tumorigenesis.[12–15] Of several antiangiogenic compounds tested in patients with metastatic breast cancer, one, bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor (VEGF), was found to prolong progression-free survival (PFS) but not overall survival (OS) when combined with standard chemotherapy regimens (eg, capecitabine, paclitaxel, and docetaxel) as first- or second-line treatment.[16–20]

Sorafenib is an oral multikinase inhibitor targeting regulation of alphafetoprotein/mitogen-activated protein kinase kinase/extracellular signal-regulated kinase (Raf/MEK/ERK), VEGF receptors, and platelet-derived growth factor receptor signaling pathways, with antiproliferative and antiangiogenic effects.[21–23] On the basis of phase III clinical trials that showed PFS and/or OS benefit, sorafenib was approved for treatment of advanced renal cell, hepatocellular, and thyroid carcinoma, and has shown antitumor activity in other tumor types.[24–27] Although trials of sorafenib monotherapy showed little benefit in patients with metastatic breast cancer,[28,29] a randomized, double-blind, placebo-controlled phase IIB trial of sorafenib with capecitabine, an oral prodrug of 5-fluorouracil (5-FU), suggested that combination therapy might be more effective.[30] Capecitabine has been approved for monotherapy in the treatment of patients with metastatic breast cancer resistant to previous anthracycline and taxane-based chemotherapy[30] and for combination therapy with docetaxel in patients with metastatic breast cancer resistant to anthracycline-based treatment.[31–33]

One randomized phase II trial compared sorafenib (400 mg twice per day [b.i.d.]) with oral capecitabine (1000 mg/m$^2$ b.i.d. on days 1–14 of each 21-day cycle) with capecitabine and placebo, as first- as well as second-line treatment, in 229 patients with HER2-negative locally advanced or metastatic breast cancer.[30] Median PFS was significantly longer in the combination group (6.4 vs. 4.1 months; hazard ratio [HR], 0.58; $P = .001$). However, median OS (22.2 vs. 20.9 months; HR, 0.86; $P = .42$) and overall response rate (ORR; 38.3% vs. 30.7%; $P = .25$) did not differ significantly in the 2 groups.

A second randomized, double-blind, placebo-controlled phase IIB trial compared sorafenib (400 mg b.i.d.) with gemcitabine (1000 mg/m$^2$ intravenously on days 1 and 8 of each 21-day cycle) with gemcitabine alone, with a later-allowed alternative of oral capecitabine (1000 mg/m$^2$ b.i.d. on days 1–14 of each 21-day cycle), in 160 patients with HER2-negative locally advanced or metastatic breast cancer previously treated with bevacizumab.[34] Median PFS (3.4 vs. 2.7 months; HR, 0.65; $P = .02$) and time to progression (TTP; 3.6 vs. 2.7 months; HR, 0.64; $P = .02$) were significantly longer in the combination group, although median OS and ORR did not differ.

The efficacy observed in these 2 randomized phase II trials provided the basis for this phase III multinational, double-blind, randomized, placebo-controlled study, RESILIENCE (tRial comparing capecitabinE in combination with SorafenIb or pLacebo for treatment of locally

advanced or metastatic HER2-Negative breast CancEr). We report herein the results of this study, in which the combination of sorafenib with first- or second-line capecitabine treatment were assessed [NCT01234337].

## Patients and Methods

### Study Population

The design of RESILIENCE has been described.[35] Briefly, the population included adults aged 18 years or older with a life expectancy of ≥ 12 weeks and histologically or cytologically confirmed HER2-negative locally advanced or metastatic breast cancer. Patients were resistant or intolerant to previous taxane and anthracycline treatment or had a contraindication for further anthracycline therapy. No more than 1 previous chemotherapy regimen for metastatic disease was allowed.

Previous adjuvant or neoadjuvant therapy, including hormonal therapy, for locally advanced or metastatic disease was allowed. All patients had measurable or nonmeasurable disease, radiologically evaluable according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST), and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Patients were excluded if they had HER2-positive disease or unknown estrogen receptor and progesterone receptor status; had previously been treated with a VEGF inhibitor; had symptomatic brain metastases or a Grade ≥ 3 hemorrhage/bleeding event within the previous 4 weeks; had experienced thrombotic, embolic, venous, or arterial events within the previous 6 months; had major surgery < 4 weeks before study entry; or had uncontrolled hypertension or active or clinically significant cardiac disease.

This study was conducted in accordance with Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and applicable local laws and regulations. All patients provided written informed consent.

### Treatment

Patients were randomized 1:1 to capecitabine 1000 mg/m$^2$ orally b.i.d. for days 1 to 14 of every 21-day cycle with oral sorafenib 600 mg/d (200 mg in the morning and 400 mg in the evening) or placebo. Patients were stratified according to hormone receptor status of their tumors (estrogen- and/or progesterone-receptor–positive vs. estrogen-and protesterone receptor–negative), number of previous lines of chemotherapy for metastatic breast cancer (0 vs. 1), and geographic region (North America vs. Europe vs. other [Israel, South Africa, South America, Japan, China, and Australia]).

The daily dosage of sorafenib or matching placebo could be increased to 800 mg/d if the 600 mg/d dosage was well tolerated, defined as no greater than Grade 1 fatigue, dermatologic toxicities, or gastrointestinal toxicities after a 21-day cycle. Patients who had undergone dose escalation and were well tolerant of 800 mg/d sorafenib or placebo were permitted an increase in capecitabine dosage to 1250 mg/m$^2$ b.i.d. during subsequent treatment cycles. After dose reductions, re-escalations were allowed for sorafenib/placebo but not for capecitabine. The dosing algorithm was designed to mitigate dermatologic and other toxicities.

Treatment was discontinued for documented clinical or radiological disease progression according to RECIST, investigator decision, or intolerable toxicities, withdrawal of consent, or noncompliance with study treatment. Patients who required discontinuation of sorafenib or placebo were allowed to continue to receive capecitabine alone, however, those who required discontinuation of capecitabine also were discontinued from sorafenib/placebo treatment.

## Study Procedures

At the beginning of each treatment cycle, patients were evaluated using electrocardiography, blood tests, patient health-related quality of life (HRQoL) questionnaires, a complete physical examination, and ECOG PS. During the first 6 weeks of treatment, patients were monitored weekly for vital signs and underwent skin examinations for palmar-plantar erythrodysesthesia (PPE) syndrome and other toxicities.

Pharmacokinetic assessments were for exposure to 5-FU, the active metabolite of capecitabine, and sorafenib. Five blood samples were collected from each of approximately 200 patients before and 0.5, 1, 2, and 4 hours after the capecitabine dose on day 14 of cycle 2. Sorafenib exposure was estimated from 1 of these 5 blood samples.

Patient-reported outcomes included breast cancer symptom evaluation using the Functional Assessment of Cancer Therapy-Breast Symptoms Index (FBSI-8; 8 items)[36,37] and HRQoL using the EuroQoL 5-Dimension Questionnaire (EQ-5D).[38]

## Study Design and Data Analysis

The primary end point was PFS according to independent central review (RECIST criteria) of a computed tomography and/or magnetic resonance imaging scan and a bone scan if clinically indicated at the time of screening every 6 weeks from the day of randomization for the first 36 weeks, and every 9 weeks thereafter. The secondary end points were OS, TTP, ORR, disease control rate (DCR), duration of response, and safety. During the study, the performance of the central independent blinded reader panel was assessed regularly in a blinded manner by the imaging vendor. An unexpectedly high rate of discordance between local and central readers raised concerns about the quality of the independent reads. After deliberations with the external Steering Committee, the entire central reader panel was replaced before database cutoff by a new panel of expert readers, and all patient scans were reread. Only the scan results from the second reader panel were used to analyze study end points. All reader performance assessments were performed in a completely blinded manner to eliminate any potential bias.

Sample size was determined according to calculations on the basis of PFS. In the original protocol, 363 events were required to detect a 66.7% increase in PFS, assuming a 1-sided $\alpha$ of 0.005 with a power of 98.9%. Subsequently, the protocol was amended to assume a 1-sided $\alpha$ of 0.005 with a power of 92.8%, requiring 250 PFS events, including progression according to central radiology review and death from any cause, to detect a 66.7% increase in PFS. At the time of the amendment, study accrual had been completed and 537 patients randomized.

Efficacy outcomes were analyzed for the intention to treat (ITT) population, defined as all randomized patients. PFS, OS, and TTP were estimated using the Kaplan–Meier method and compared using log rank tests, with patients stratified according to hormone receptor status of their tumors, number of lines of previous chemotherapies for metastatic disease, and geographic region. The primary end point, PFS, was analyzed with a 2-sided α of 0.01. All secondary time to event end points were analyzed with a 2-sided α of 0.05. In the final PFS analysis, an interim OS analysis was performed using an O'Brien–Fleming type α spending function. Cochran–Mantel–Haenzel tests with the randomization factors as strata were used to compare DCR and ORR in the 2 study arms.

## Results

Patient recruitment for RESILIENCE began in November 2010. Of the 707 patients who provided informed consent, 537 completed screening and were randomized: 271 to placebo with capecitabine and 266 to sorafenib with capecitabine (Figure 1). The 2 arms were well balanced; their baseline patient characteristics (ITT population) are summarized in Table 1. The median patient age was 54.0 years, and more than half had received more than 1 previous chemotherapy regimen for metastatic disease. Most patients had hormone receptor-positive tumors and visceral disease.

At data cutoff, 285 patients had died (145 randomized to sorafenib with capecitabine and 140 to placebo with capecitabine), and 323 PFS events (in 148 and 175 patients, respectively) had occurred. Per study protocol, patients who discontinued or withdrew from treatment, including for adverse events (AEs), without documented disease progression, were followed-up until the date of last evaluable tumor assessment, for determination of PFS, or death, for OS. The number of PFS events was higher than expected before replacement of the central reader panel, which occurred after event requirements were changed according to amendment.

In Table 2 study drug administration, including overall treatment duration, dose density, and treatment modification, is summarized. The mean daily doses of capecitabine in the placebo with capecitabine and sorafenib with capecitabine arms were 1913.5 mg/m$^2$ (87.4% of planned dose) and 1734.1 mg/m$^2$ (75.5% of planned dose), respectively. The mean daily doses of placebo and sorafenib were 654 mg/d (92.9% of planned dose) and 566 mg/d (79.9% of planned dose), respectively. Median overall placebo/sorafenib treatment durations were 24.0 and 18.1 weeks, respectively.

Per study protocol, doses of sorafenib and placebo were escalated to 800 mg/d in 72 patients (27.7%) in the sorafenib with capecitabine arm and 130 (48.7%) in the placebo with capecitabine arm, respectively. Subsequently, capecitabine doses were increased to 2500 mg/m$^2$ in 30 (11.5%) sorafenib with capecitabine-treated patients and in 64 (24.0%) placebo with capecitabine-treated patients.

### Efficacy

Compared with capecitabine with placebo, capecitabine with sorafenib did not significantly prolong PFS or OS. Median PFS estimated according to independent central review was 5.5

months for sorafenib with capecitabine versus 5.4 months for placebo with capecitabine, with an estimated HR of 0.973 (95% confidence interval [CI], 0.779–1.217; $P = .811$; Figure 2A). According to investigator assessment, the HR was 1.03 ($P = .777$).

Assessment of median PFS according to subgroup (Figure 3A) showed that none of the factors—age, race, region, ECOG PS, number of previous treatments, hormone receptor status, or visceral disease at baseline—had HRs that significantly favored one group over the other. Similarly, assessment of median OS according to subgroup (Figure 3B) showed that none of the factors had HRs significantly favoring either group. Median OS was shorter in the sorafenib with capecitabine group than in the placebo with capecitabine group (18.9 vs. 20.3 months; HR, 1.195; 95% CI, 0.943–1.513; $P = .140$; Figure 2B).

Best responses according to central assessment using RECIST criteria are summarized in Table 3. ORR, the sum of patients with complete response (CR) and partial response (PR), was similar in the sorafenib with capecitabine group and placebo with capecitabine group (13.5% vs. 15.5%; $P = .515$). DCR, the sum of patients with CR, PR, stable disease, and non-CR/nondisease progression, was also similar in these 2 groups (60.5% vs. 58.3%; $P = .569$).

## Safety and Tolerability

Table 4 shows the treatment-emergent AEs in the safety population (placebo with capecitabine, n = 267; sorafenib with capecitabine, n = 260), and Supplemental Table 1 in the online version shows the treatment-emergent AEs of frequency ≥ 10% in either group, differing ≥ 5% in the 2 groups, and the corresponding rates of Grade 3 and 4 AEs.

Toxicities of any Grade more frequent in the sorafenib with capecitabine group than in the placebo with capecitabine group included PPE syndrome (79.2% vs. 59.6%), diarrhea (47.3% vs. 37.8%), mucosal inflammation (15.4% vs. 6.7%), and hypertension (26.2% vs. 5.6%). Grade 3 to 4 toxicities differing in these 2 groups included PPE syndrome (15.4% vs. 7.1%), diarrhea (4.2% vs. 6.4%), and vomiting (3.5% vs. 0.7%).

All AEs, and the relationship of each to treatment and to each study drug, were reported on electronic case report forms by individual investigators. The safety of the trial was evaluated by an independent data monitoring committee, which determined whether an AE was treatment-emergent. On the basis of these criteria, 13 patients (5.0%) in the sorafenib with capecitabine group and 9 (3.4%) in the placebo with capecitabine group died from treatment-emergent AEs within 30 days after the last dose of study drug. There was 1 investigator-assessed, treatment-emergent death due to hepatic failure in the sorafenib with capecitabine group; this was the only death considered related to treatment with sorafenib and capecitabine.

## Pharmacokinetics

The pharmacokinetic parameters of capecitabine after administration of 1000 mg/m$^2$ capecitabine with placebo or sorafenib are shown in Supplemental Table 2 in the online version. Compared with placebo, sorafenib was found to increase capecitabine exposure; maximal concentration (mg/L) geometric least square mean was 1.29 (90% CI, 1.07–1.56).

Evaluation of the pharmacokinetic parameters of 5-FU after administration of 1000 mg/m$^2$ capecitabine with placebo or sorafenib showed that sorafenib had no effect on 5-FU exposure (see Supplemental Table 3 in the online version). The geometric mean concentration of sorafenib 4 hours after dose was 5.15 mg/L (see Supplemental Figure 1 in the online version).

### Quality of Life Measures

Mean FBSI-8 scores at baseline were 21.68 in the placebo with capecitabine group and 20.95 in the sorafenib with capecitabine group; mean scores at the end of treatment (EOT) visit were 19.99 and 19.36, respectively. Mean EQ-5D index scores in these 2 groups were 0.71 and 0.68, respectively, at baseline and 0.62 and 0.58, respectively, at EOT visit. Mean EQ-5D visual analogue scale scores in these 2 groups were 68.53 and 68.47, respectively, at baseline and 63.96 and 63.85, respectively at the EOT visit.

## Discussion

The RESILIENCE trial did not meet its primary end point, prolongation of PFS, or its secondary end points, OS and ORR, in patients with HER2-negative advanced breast cancer treated with sorafenib with capecitabine. Compared with placebo with capecitabine, sorafenib with capecitabine did not significantly prolong PFS (HR, 0.973; 95% CI, 0.779–1.217) or OS (HR, 1.195; 95% CI, 0.943–1.513). Similarly, subgroups of the 2 arms did not differ significantly in PFS and OS, and ORRs did not differ significantly ($P = .515$). Significant differences in quality of life measures were not observed.

Data from the phase IIB Spanish Breast Cancer Cooperative Group (SOLTI)-0701 study showed that the combination of sorafenib with capecitabine as first- or second-line treatment significantly improved median PFS (6.4 vs. 4.1 months; HR, 0.58; $P = .001$) but had no effect on median OS (22.2 vs. 20.9 months; HR, 0.86; $P = .42$) or ORR (38% vs. 31%; $P = .25$).[30] However, the sorafenib dosage in that trial, 800 mg/d, had unacceptable toxicities in many patients. Therefore, in RESILIENCE, the initial sorafenib dosage was 600 mg/d, with clear dose modification guidelines to manage toxicities. At the end of the trial, the average daily dose and duration of capecitabine treatment were lower in the sorafenib with capecitabine group than in the placebo with capecitabine group.

Although the AEs observed were consistent with the safety profiles of sorafenib and capecitabine, the rates of Grade 3 AEs and of dose modifications and discontinuations because of AEs were higher in the sorafenib with capecitabine arm. The reduced sorafenib dose in RESILIENCE and the overlapping toxicities of sorafenib and capecitabine might explain, at least in part, the reason that the efficacy observed in SOLTI-0701 was not confirmed by RESILIENCE.

Most women with metastatic breast cancer have HER2-negative tumors.[39] Standard treatment options include endocrine therapy and chemotherapy,[40] but there is no clearly superior approach or sequence to treating patients in the first- or second-line palliative setting.[39] Although effective new targeted therapies for HER2- negative disease are emerging, they have lagged compared with treatments for HER2-positive disease. Two

agents with different mechanisms of action approved to treat metastatic HER2-negative, hormone receptor-positive breast cancer are everolimus, a mammalian target of rapamyc inhibitor,[41,42] and palbociclib, an inhibitor of cyclin-dependent kinases 4 and 6.[7,8] Everolimus is administered with exemestane and palbociclib with letrozole, both aromatase inhibitors.

Metastatic breast cancer is a heterogeneous disease, and patient selection might have played a role in the negative results observed in RESILIENCE, perhaps because of timing of introduction of the tyrosine kinase inhibitor (TKI) in the course of the disease or the potential for differences in molecular subgroups. The results of this trial might have been affected by the molecular profile of the metastatic lesions relative to the molecular targets of sorafenib.[43] Furthermore, angiogenesis might not be as clinically relevant a target in metastatic breast cancer as previously thought.[9–15] Outcomes of this trial might have been improved by better preselection of patients.

The inconsistencies observed in data across studies with antiangiogenic agents might correspond to differences in these agents' mechanism of action and resistance, which have not been thoroughly assessed across breast cancer subtypes, selection of combination therapy, and differences in study design and patient populations.[30] Overall, however, antiangiogenic agents have not shown clinically significant efficacy to date in breast cancer patients, suggesting that these agents might be ineffective in these settings.[43] Alternatively, the efficacy of agents that block angiogenesis might be dependent on as yet unidentified patient or tumor characteristics, including biomarkers. Despite the absence of clear evidence showing that biomarker expression in metastatic lesions can predict response to treatment,[39] the potential value of sorafenib and other TKIs in advanced breast cancer might be better explored with improved target and patient selection.[44] Future studies might reveal optimal combinations of TKIs and chemotherapeutic agents with the greatest synergy and fewest overlapping toxicities.

## Conclusion

The RESILIENCE data showed that the combination of sorafenib with capecitabine did not significantly improve PFS or OS in patients with HER2-negative advanced breast cancer compared with capecitabine alone.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

We thank the patients for their contribution to this study. We thank the global investigators (Appendix A). Editorial support was provided by BelMed Professional Resources, Inc. This study was supported by Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals, an Amgen subsidiary.

Claudio Zamagni and Bohuslav Melichar have had consulting and advisory roles with Roche Pharma AG. Jonas Bergh has received research support for his institution from Amgen, Bayer, AstraZeneca, Merck, Roche, and Sanofi-Aventis. Bernando L. Rapoport has acted on the Speakers' Bureau of Roche. Lee S. Schwartzberg has had a consulting or advisory role with Genentech and has acted on the Speakers' Bureau of Genentech.

# Appendix A

## The RESILIENCE Trial Investigators

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### Clinical Practice Points

- Randomized phase II trials showed that the combination of the antiangiogenic multikinase inhibitor sorafenib with capecitabine or gemcitabine significantly increased median PFS in patients with HER2-negative advanced breast cancer.
- In the randomized, double-blind, placebo-controlled phase III RESILIENCE trial capecitabine (1000 mg/m$^2$ b.i.d. on days 1–14 of each 21-day cycle) with sorafenib (600 mg/d) or placebo were compared in 537 patients with HER2-negative locally advanced/metastatic breast cancer.
- The combination of sorafenib reduced the planned daily dose of capecitabine and shortened treatment duration.
- Compared with capecitabine with placebo, sorafenib with capecitabine did not significantly prolong median PFS (5.5 vs. 5.4 months; HR, 0.973; 95% CI, 0.779–1.217; $P = .811$) or OS (18.9 vs. 20.3 months; HR, 1.195; 95% CI, 0.943–1.513; $P = .140$) and did not enhance ORR (13.5% vs. 15.5%; $P = .515$) or DCR (60.5% vs. 58.3%; $P = .569$).
- All grade toxicities that were more frequent in the sorafenib than in the placebo group included PPE syndrome (79.2% vs. 59.6%), mucosal inflammation (15.4% vs. 6.7%), and hypertension (26.2% vs. 5.6%).
- Grade 3/4 toxicities more frequent in the sorafenib group included PPE syndrome (15.4% vs. 7.1%) and vomiting (3.5% vs. 0.7%).
- These findings showed that the combination of sorafenib with capecitabine did not significantly improve PFS or OS or enhance ORR or DCR in patients with HER2-negative advanced breast cancer compared with capecitabine alone.
- The combination of sorafenib with capecitabine is not warranted in patients with HER2-negative advanced breast cancer.

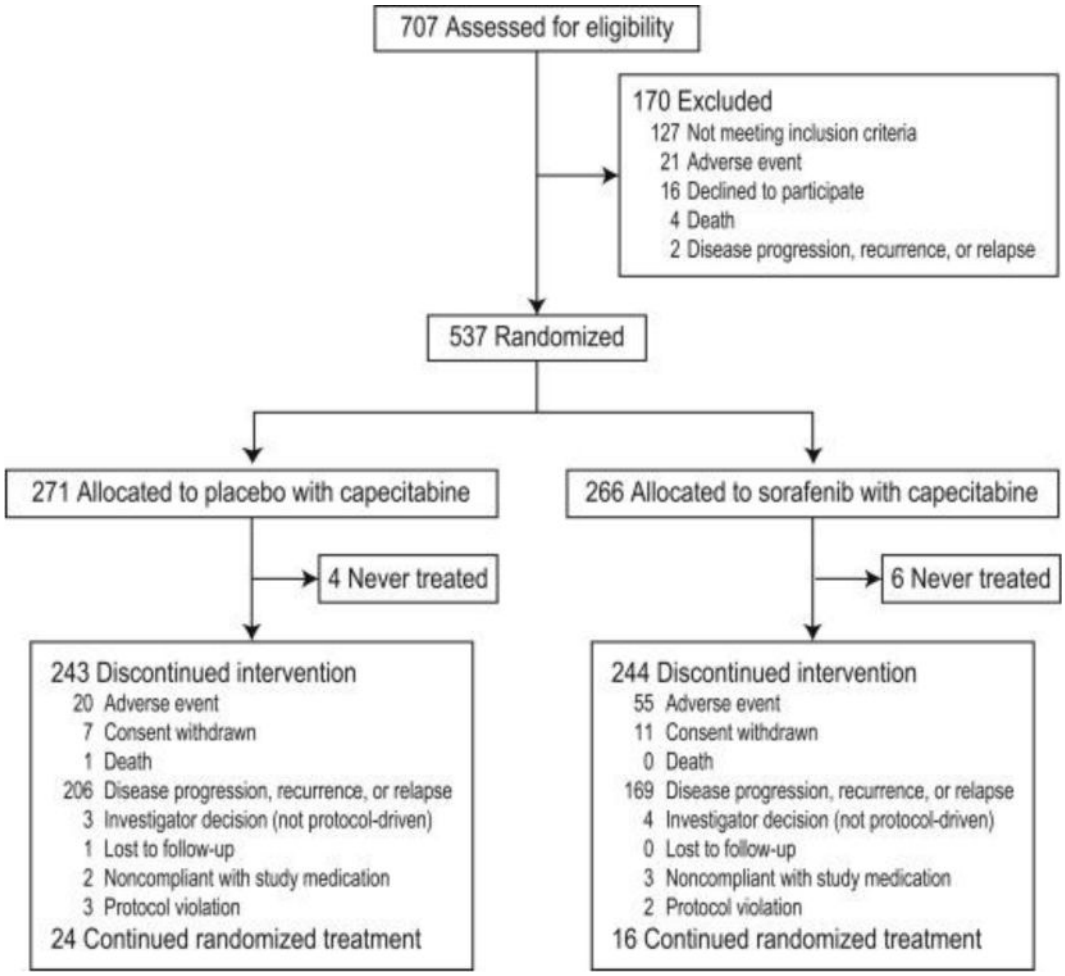


**Figure 1.**
Patient Disposition

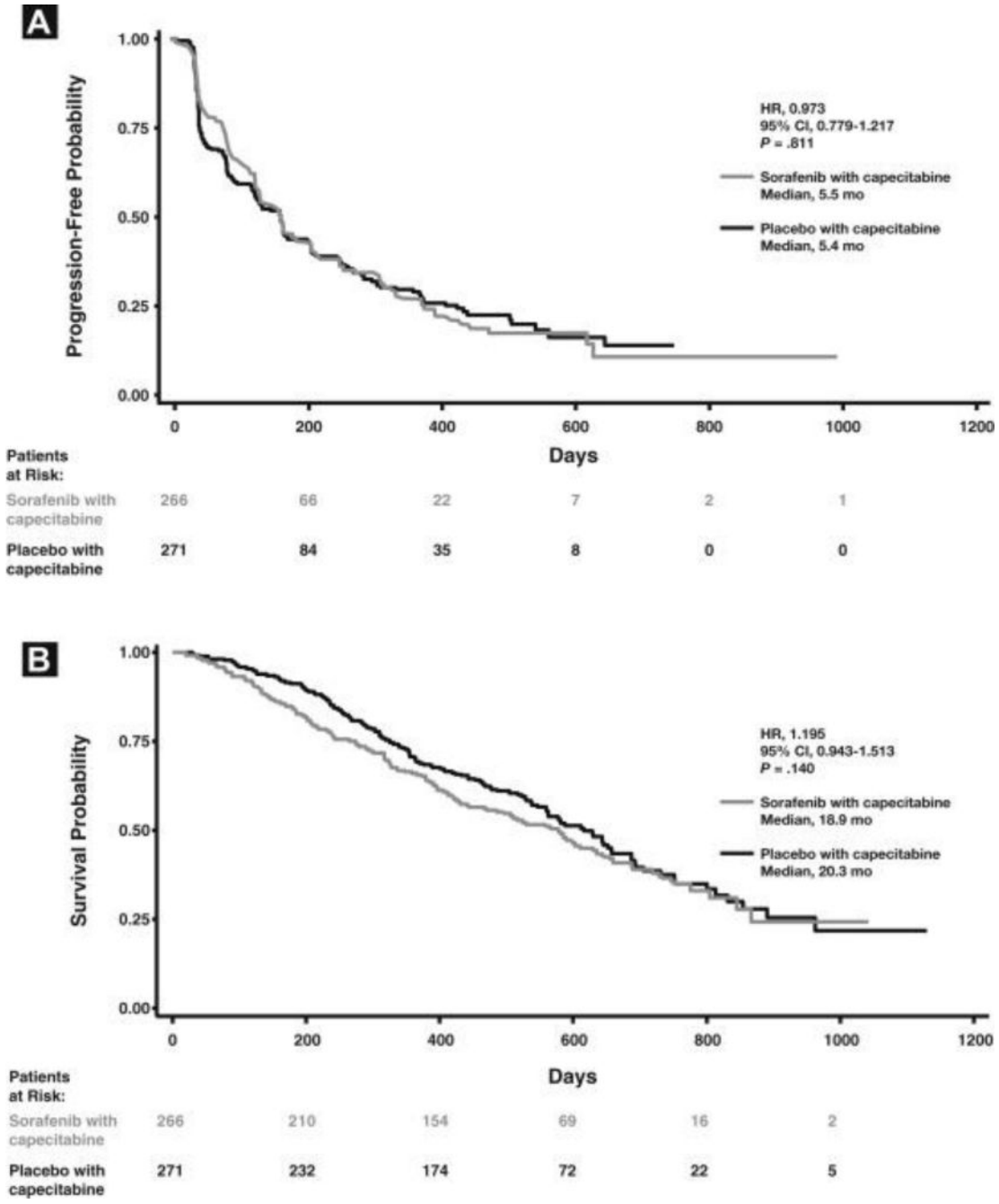


**Figure 2.**

Kaplan–Meier Plots of (A) Progression-Free Survival and (B) Overall Survival in Patients Treated With Sorafenib With Capecitabine or Placebo With Capecitabine

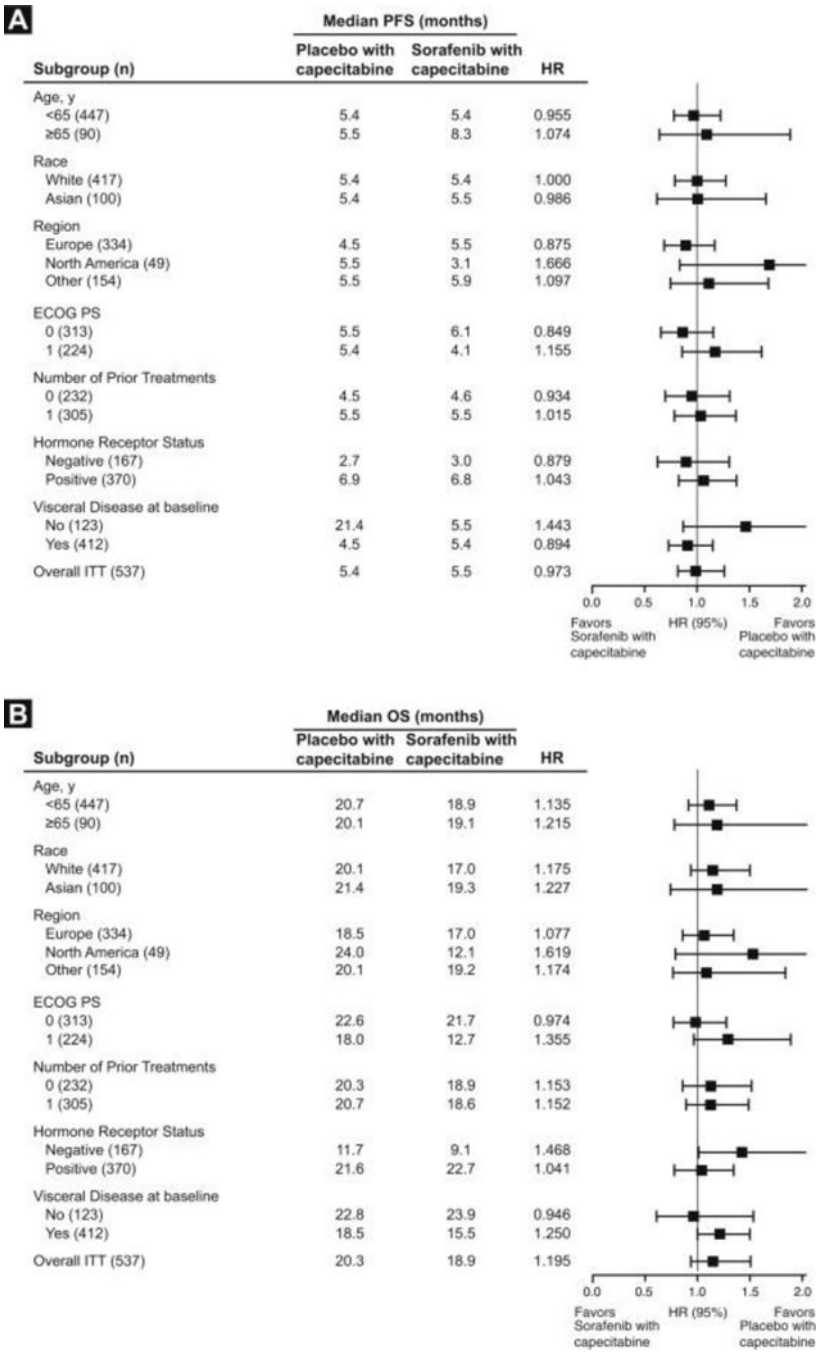


**Figure 3. Forest Plots of Factors Associated With (A) Progression-Free Survival (PFS) and (B) Overall Survival (OS) in Patients Treated With Sorafenib With Capecitabine or Placebo With Capecitabine**

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; ITT = intention to treat.

## Table 1

Baseline Characteristics (ITT Population)

| | Placebo/Capecitabine (n = 271), % | Sorafenib/Capecitabine (n = 266), % |
|---|---|---|
| **Median Age, y** | 55.0 | 53.0 |
| **Female Sex** | 98.9 | 99.6 |
| **Geographical Area** | | |
| Europe | 62.0 | 62.4 |
| North America | 9.6 | 8.6 |
| Others | 28.4 | 28.9 |
| **Previous Chemotherapies for Metastatic Disease** | | |
| 0 | 43.5 | 42.9 |
| 1 | 56.5 | 57.1 |
| **Hormone Receptor Status**[a] | | |
| Negative | 31.0 | 31.2 |
| Positive | 69.0 | 68.8 |
| **ECOG PS** | | |
| 0 | 59.4 | 57.1 |
| 1 | 40.6 | 42.9 |
| **Visceral Disease** | | |
| No | 21.0 | 24.8 |
| Yes | 78.6 | 74.8 |
| Missing | 0.4 | 0.4 |
| **Number of Organs Involved** | | |
| 1 | 25.1 | 25.9 |
| 2 | 38.7 | 35.3 |
| 3 | 22.5 | 18.8 |
| >3 | 13.3 | 19.5 |
| Missing | 0.4 | 0.4 |

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; ITT = intention to treat.

[a]Per interactive voice response system.

## Table 2

Study Drug Administration

| | Placebo With Capecitabine Group | | Sorafenib With Capecitabine Group | |
|---|---|---|---|---|
| | **Placebo (mg)** | **Capecitabine (mg/m$^2$)** | **Sorafenib (mg)** | **Capecitabine (mg/m$^2$)** |
| **Daily Dose** | | | | |
| Mean | 654 | 1913.5 | 566 | 1734.1 |
| Mean % planned | 92.9 | 87.4 | 79.9 | 75.5 |
| **Overall Treatment Duration, wk** | | | | |
| Median | 24.0 | 22.9 | 18.1 | 18.1 |
| Mean | 30.7 | 30.2 | 26.8 | 26.6 |
| **Cycles** | | | | |
| Mean | 10.0 | 10.0 | 8.7 | 8.9 |
| Median | 8.0 | 8.0 | 6.0 | 6.0 |
| **Treatment Modification, %** | | | | |
| Interruption | 47.6 | 28.8 | 68.1 | 46.5 |
| Reduction | 20.6 | 44.6 | 42.7 | 67.3 |

## Table 3

Summary of Best Response According to RECIST Criteria

| | Placebo With Capecitabine (n = 271) | Sorafenib With Capecitabine (n = 266) | *P* |
|---|---|---|---|
| **ORR (CR D PR)** | 42 (15.5) | 36 (13.5) | .515 |
| CR | 4 (1.5) | 0 (0.0) | |
| PR | 38 (14.0) | 36 (13.5) | |
| **SD** | 65 (24.0) | 80 (30.1) | |
| **Non-CR/Non-PD** | 51 (18.8) | 45 (16.9) | |
| **PD** | 89 (32.8) | 61 (22.9) | |
| **Unable to Evaluate** | 12 (4.4) | 19 (7.1) | |
| **Not Assessed** | 12 (4.4) | 25 (9.4) | |
| **Disease Control Rate (CR D PR D SD D Non-CR/Non-PD)** | 158 (58.3) | 161 (60.5) | .569 |

Data are presented as n (%) except where otherwise stated.

Abbreviation: RECIST = Response Evaluation Criteria in Solid Tumors.

## Table 4

Overview of Treatment-Emergent AEs in the Safety Population

| | Placebo/Capecitabine (n = 267) | Sorafenib/Capecitabine (n = 260) |
|---|---|---|
| **Any AE** | 257 (96.3) | 260 (100) |
| Grade 3 | 105 (39.3) | 152 (58.5) |
| Grade 4 | 12 (4.5) | 15 (5.8) |
| Grade 5 | 12 (4.5) | 16 (6.2) |
| **SAEs** | 67 (25.1) | 80 (30.8) |
| **AEs Leading to Dose Modification** | 160 (59.9) | 225 (86.5) |
| **AEs Leading to Permanent Discontinuation of Study Drug** | 28 (10.5) | 61 (23.5) |
| **Study Drug-Related Treatment-Emergent Deaths** | 0 (0.0) | 1 (0.4)[a] |

Data are presented as n (%).

Abbreviations: AE = adverse event; SAE = serious adverse event.

[a]Hepatic failure.