A phase III randomized, double-blind, placebo-controlled study of sorafenib (S) in combination with capecitabine (C) was conducted in patients with HER2-negative, locally advanced or metastatic breast cancer. The primary endpoint was progression-free survival (PFS) per independent review. Secondary endpoints included overall survival (OS), time to progression (TTP), objective response rate (ORR), disease control rate (DCR) and safety.

Methods: Patients resistant to prior taxane and resistant to prior anthracycline or for whom further anthracycline was not indicated, and having received no more than one prior regimen for advanced disease were randomized 1:1 to placebo (PLC) or S (600 mg daily, po, 21-day schedule) in combination with C (1000 mg/m², bid, po, 14/7 days on/off). Results: A total of 537 patients were randomized: 266 to S + C and 271 to PLC + C. The two arms were generally well balanced; median age 54 years; 69% hormone receptor positive and 31% triple negative; and 43%/57% having received 0/1 prior lines of chemotherapy for metastatic disease. Median PFS was 5.5 mo for S + C and 5.4 mo for PLC + C; HR 0.973 (95% CI: 0.779, 1.217; one-sided p-value = 0.406). Median OS was 18.9 mo for S + C and 20.3 mo for PLC + C; HR 1.195 (95% CI: 0.943, 1.513; one-sided p-value = 0.930). There were no differences in TTP, ORR or DCR. The incidence of grade 3 AEs was 58.5% vs 39.3%, grade 4 AEs 5.8% vs 4.5%, and grade 5 AEs 6.2% vs 4.5%, S + C vs PLC + C arms, respectively. The most commonly reported grade 3 AEs included palmar-plantar erythrodysesthesia syndrome (16% vs 2%), fatigue (7% vs 3%) diarrhea (4% vs 6%), neutropenia (4% vs