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The BOLERO-6 Randomized Clinical Trial

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Everolimus Plus Exemestane vs Everolimus or Capecitabine Monotherapy for Estrogen Receptor–Positive, HER2-Negative Advanced Breast Cancer
The BOLERO-6 Randomized Clinical Trial

Guy Jerusalem, MD, PhD; Richard H. de Boer, MBBS, FRACP; Sara Hurvitz, MD; Denise A. Yardley, MD; Elena Kovalenko, MD; Bent Ejlertsen, MD; Sibel Blau, MD; Mustafa Özgüroğlu, MD; László Landherr, PhD; Marianne Ewertz, MD; Tetiana Taran, MD; Jenna Fan, MD, PhD; Florence Noel-Baron, PhD; Anne-Laure Louveau, MS; Howard Burris, MD

**IMPORTANCE** Everolimus plus exemestane and capecitabine are approved second-line therapies for advanced breast cancer.

**OBJECTIVE** A postapproval commitment to health authorities to estimate the clinical benefit of everolimus plus exemestane vs everolimus or capecitabine monotherapy for estrogen receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer.

**DESIGN** Open-label, randomized, phase 2 trial of treatment effects in postmenopausal women with advanced breast cancer that had progressed during treatment with nonsteroidal aromatase inhibitors.

**INTERVENTIONS** Patients were randomized to 3 treatment regimens: (1) everolimus (10 mg/d) plus exemestane (25 mg/d); (2) everolimus alone (10 mg/d); and (3) capecitabine alone (1250 mg/m² twice daily).

**MAIN OUTCOMES AND MEASURES** Estimated hazard ratios (HRs) of progression-free survival (PFS) for everolimus plus exemestane vs everolimus alone (primary objective) or capecitabine alone (key secondary objective). Safety was a secondary objective. No formal statistical comparisons were planned.

**RESULTS** A total of 309 postmenopausal women were enrolled, median age, 61 years (range, 32–88 years). Of these, 104 received everolimus plus exemestane; 103, everolimus alone; and 102, capecitabine alone. Median follow-up from randomization to the analysis cutoff (June 1, 2017) was 37.6 months. Estimated HR of PFS was 0.74 (90% CI, 0.57–0.97) for the primary objective of everolimus plus exemestane vs everolimus alone and 1.26 (90% CI, 0.96–1.66) for everolimus plus exemestane vs capecitabine alone. Between treatment arms, potential informative censoring was noted, and a stratified multivariate Cox regression model was used to account for imbalances in baseline characteristics; a consistent HR was observed for everolimus plus exemestane vs everolimus (0.73; 90% CI, 0.56–0.97), but the HR was closer to 1 for everolimus plus exemestane vs capecitabine (1.15; 90% CI, 0.86–1.52). Grade 3 to 4 adverse events were more frequent with capecitabine (74%; n = 75) vs everolimus plus exemestane (70%; n = 73) or everolimus alone (59%; n = 61). Serious adverse events were more frequent with everolimus plus exemestane (36%; n = 37) vs everolimus alone (29%; n = 30) or capecitabine (29%; n = 30).

**CONCLUSIONS AND RELEVANCE** These findings suggest that everolimus plus exemestane combination therapy offers a PFS benefit vs everolimus alone, and they support continued use of this therapy in this setting. A numerical PFS difference with capecitabine vs everolimus plus exemestane should be interpreted cautiously owing to imbalances among baseline characteristics and potential informative censoring.

**TRIAL REGISTRATION** ClinicalTrials.gov identifier: NCT01783444

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Everolimus Plus Exemestane vs Everolimus or Capecitabine Monotherapy for Advanced Breast Cancer

Key Points

**Question** What is the estimated clinical benefit of everolimus plus exemestane vs everolimus or capecitabine monotherapies for endocrine therapy–resistant, estrogen receptor–positive advanced breast cancer?

**Findings** This randomized clinical trial of 309 patients found a progression-free survival (PFS) benefit for everolimus plus exemestane over everolimus alone and a numerical PFS difference favoring capecitabine over combination therapy (note that imbalances among baseline parameters and potential informative censoring might have contributed to the PFS outcomes observed with capecitabine). No new safety signals were observed with the combination regimen.

**Meaning** Everolimus plus exemestane combination therapy offers an efficacy benefit vs everolimus alone, but the efficacy difference between combination therapy and capecitabine alone is still uncertain.

Methods

**Study Design and Setting**

BOLERO-6 was an open-label, phase 2, randomized clinical trial conducted at 83 medical centers across 18 countries (eTable 1 in Supplement 1). The combined trial protocol and statistical analysis plan are provided in Supplement 2. Patients were enrolled between March 4, 2013, and November 24, 2014. All patients provided written informed consent before enrollment. Study conduct adhered to Good Clinical Practice guidelines, local regulations, and the Declaration of Helsinki, and was approved by the institutional review boards, independent ethics committee, and/or research ethics boards at each study center.

**Participants**

Patients were postmenopausal women with ER-positive, HER2-negative metastatic or recurrent breast cancer, or locally advanced breast cancer not amenable to curative surgery or radiotherapy, whose disease had recurred or progressed during treatment with letrozole or anastrozole. Patients were required to have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) or bone lesions (lytic or mixed), and Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. Patients who received more than 1 prior line of chemotherapy for advanced breast cancer, prior treatment with exemestane or inhibitors of mammalian target of rapamycin (mTOR), phosphatidylinositol 3-kinase (PI3K), or protein kinase B, or with known hypersensitivity to mTOR inhibitors, capecitabine (or any of its components), or fluorouracil, were excluded. Further eligibility criteria are provided in eMethods in Supplement 1.

**Procedures**

The primary objective was to estimate the HR of PFS for everolimus plus exemestane vs everolimus alone. The primary end point was PFS, defined as the time from randomization to first documented progression or death due to any cause. The key secondary objective was to estimate the HR of PFS for everolimus plus exemestane vs capecitabine. Additional secondary end points included overall survival (OS), overall response rate (ORR), clinical benefit rate (CBR), and safety.

Tumors were investigator-assessed per RECIST, version 1.1 with computed tomography or magnetic resonance imaging at screening and every 6 weeks after randomization until disease progression, loss to follow-up, withdrawal of consent, or investigator decision.

Safety was assessed by adverse event (AE) frequency, graded per the CTCAE (Common Terminology Criteria for Adverse Events), version 4.0. Patients were followed up for safety up to 30 days after receiving the last dose of study treatment. The first antineoplastic therapy initiated after discontinuation of the study treatment was recorded in the patients' electronic case report form.

Patients were randomized 1:1:1 to receive 1 of the following treatments: (1) oral everolimus, 10 mg/d (two 5-mg tablets) plus oral exemestane (25 mg/d); (2) oral everolimus alone (10 mg/d); or (3) oral capecitabine alone (1250 mg/m² twice daily for 14 days of a 21-day cycle). Randomization was stratified by visceral disease status. Randomization procedures are detailed in eMethods in Supplement 1.
Patients received treatment until disease progression, unacceptable toxic effects, withdrawal of consent, or investigator decision. Patients randomized to everolimus plus exemestane who discontinued either treatment for reasons other than disease progression could continue receiving the combination partner as a monotherapy. Dose adjustments were permitted (eMethods in Supplement 1).

Statistical Analysis

Efficacy was analyzed in all randomized patients (full analysis set). Safety was analyzed in all patients who received 1 or more doses of study treatment, and 1 or more postbaseline safety assessments (safety set).

The BOLERO-6 trial was designed to provide estimates of treatment effect and not powered to perform statistical comparisons between study arms. A Cox regression model stratified by visceral disease status was used to estimate the HR of PFS and OS. Accompanying 90% CIs were preplanned to align with the sample size calculation, which was based on the precision of the estimate (width of the 90% CI of the HR) (eMethods in Supplement 1); 95% CIs are provided in eTables 4-5 in Supplement 1. Additional stratified multivariate Cox regression models of PFS and OS were adjusted on treatment on the following prognostic and baseline covariates where imbalances between arms were observed: bone-only lesions at baseline (yes vs no); prior chemotherapy use (yes vs no); ECOG performance status (0 vs 1-2); organs involved (2 vs 1, and ≥3 vs 1); race (white vs nonwhite); age (<65 vs ≥65 years).

Median PFS and median OS were estimated using the Kaplan-Meier method and presented with 90% CIs. The PFS was censored at the date of the last adequate tumor assessment for the following reasons: no PFS event was observed by the analysis cutoff; loss to follow-up; consent withdrawal; adequate assessment no longer available; documentation of an event after 2 or more missing tumor assessments; initiation of a new anticancer therapy. The OS was censored at the date of last contact if no death was observed by the analysis cutoff or if the patient was lost to follow-up. The ORR and CBR were estimated using the Clopper-Pearson method and presented with 90% CIs. Time to treatment failure (TTF) defined as the time from randomization to progression, discontinuation of treatment for other reasons than protocol deviation or administrative problems, or death, whichever occurred first, was analyzed using the Kaplan-Meier method and stratified Cox model to estimate the HRs.

An interim PFS analysis was conducted to allow early termination of the everolimus monotherapy arm in the event of far inferior efficacy vs everolimus plus exemestane (eMethods in Supplement 1). Confidence intervals were not adjusted for this interim PFS analysis.

Results

A total of 309 patients were randomized to receive everolimus plus exemestane (n = 104), everolimus alone (n = 103), or capecitabine alone (n = 102) (Figure 1). Overall, median patient age was 61 years (range, 32-88 years). Baseline characteristics are summarized in eTable 2 in Supplement 1. A larger proportion of patients in the capecitabine arm vs the everolimus plus exemestane and everolimus alone arms were white (n = 91, 89% vs n = 78, 75% and n = 85, 83%, respectively), younger than 65 years (n = 69, 68% vs n = 65, 63% and n = 64, 62%), had ECOG performance status of 0 (n = 57, 56% vs n = 54, 52% and n = 48, 47%), or had bone-only metastases (n = 24, 24% vs n = 13, 13% and n = 16, 16%), while fewer patients in the capecitabine arm had 3 or more metastatic sites (n = 45, 44% vs n = 52, 50% and n = 47, 46%).

Median follow-up from randomization to the analysis cutoff (June 1, 2017) was 37.6 months. At the analysis cutoff, treatment was ongoing in 7 patients in the everolimus plus exemestane arm (7%) and 1 patient in the capecitabine arm (1%). Median exposure was 27.5 weeks with everolimus plus exemestane, 20.0 weeks with everolimus, and 26.7 weeks with capecitabine. Median relative dose intensities of everolimus and exemestane in the combination arm were 0.92 and 1.00, respectively. Median relative dose intensities of everolimus and capecitabine in the monotherapy arms were 0.98 and 0.78, respectively.

Primary reasons for treatment discontinuation across the 3 arms were disease progression (n = 203, 66%) and AEs (n = 47, 15%) (Figure 1). Discontinuations owing to disease progression were more frequent with everolimus plus exemestane (n = 73, 70%) vs everolimus alone (n = 66, 64%) and capecitabine (n = 64, 63%). Discontinuations owing to AEs were more frequent with everolimus alone (n = 20, 19%) and capecitabine (n = 19, 19%) vs everolimus plus exemestane (n = 8, 8%). Eight patients receiving everolimus plus exemestane discontinued everolimus owing to AEs, resulting in 17% of patients (n = 18) reporting an AE leading to discontinuation for 1 or more of the study treatments in the combination arm.

There were 154 PFS events between the everolimus plus exemestane (n = 80) and everolimus alone (n = 74) arms. In the primary analysis, median PFS was 8.4 months with everolimus plus exemestane vs 6.8 months with everolimus alone, corresponding to an estimated 26% reduction of risk of disease progression or death (HR, 0.74; 90% CI, 0.57-0.97) (Figure 2). A stratified multivariate Cox regression model was used to account for baseline imbalances in patient characteristics and adjusted for known prognostic factors; a consistent HR was observed (0.73; 90% CI, 0.56-0.97). Compared with the everolimus plus exemestane arm, censoring was more frequent in the everolimus arm, especially for initiating new antineoplastic therapies (n = 19, 18% vs n = 9, 9%). Median TTF, considering all reasons for stopping treatment as an event, was 5.8 months with everolimus plus exemestane vs 4.2 months with everolimus alone (HR, 0.66; 90% CI, 0.52-0.84).

There were 148 PFS events between the everolimus plus exemestane (n = 80) and capecitabine (n = 68) arms. Median PFS was 8.4 months with everolimus plus exemestane vs 9.6 months with capecitabine (HR, 1.26; 90% CI, 0.96-1.66) (Figure 2). Compared with the everolimus plus exemestane arm, censoring was more frequent in the capecitabine arm (n = 34, 33% vs n = 24, 23%), especially for initiating new antineoplastic therapies (n = 20, 20% vs n = 9, 9%). Among patients censored owing to initiating antineoplastic therapies in...
the capecitabine arm, 65% discontinued treatment for safety reasons (n = 13 of 20). Median TTF was 5.8 months with everolimus plus exemestane vs 6.2 months with capecitabine (HR, 1.03; 90% CI, 0.81-1.31). A stratified multivariate Cox regression model of PFS, adjusted on prognostic factors and baseline characteristics where imbalances between arms were observed, produced an HR closer to 1 for everolimus plus exemestane vs capecitabine (HR, 1.15; 90% CI, 0.86-1.52).
Median OS was 23.1 months with everolimus plus exemestane vs 29.3 months with everolimus alone (HR, 1.27; 90% CI, 0.95-1.70) and 25.6 months with capecitabine (HR, 1.33; 90% CI, 0.99-1.79) (Figure 3). A stratified multivariate Cox regression model, adjusted on prognostic factors and baseline characteristics where imbalances between arms were observed, produced an HR of 1.27 (90% CI, 0.94-1.70) for everolimus plus exemestane vs everolimus alone and an HR closer to 1 for everolimus plus exemestane vs capecitabine (HR, 1.19; 90% CI, 0.88-1.62). On treatment discontinuation, antineoplastic therapies were initiated by 81 patients (78%) receiving everolimus plus exemestane and 83 patients (81%) receiving everolimus alone, with capecitabine the most common therapy that was given first in each arm (n = 20; 19% each). Eighty-one patients (79%) receiving capecitabine also initiated antineoplastic therapies, with everolimus plus exemestane the most common therapy that was given first (n = 12, 12%) (eTable 3 in Supplement 1). The ORR and CBR are detailed in eTable 4 in Supplement 1.

All patients were assessed for safety, and dose interruptions and reductions are detailed in eTable 6 in Supplement 1. All-grade and grade 3 to 4 AEs regardless of causality are listed in the Table. The most common all-grade AEs were stomatitis with everolimus plus exemestane (n = 51, 49%) and everolimus alone (n = 47, 46%), and palmar-plantar erythrodysesthesia (PPE) syndrome (n = 62, 61%) and diarrhea (n = 55, 54%) with capecitabine. The most common grade 3 to 4 AEs were anemia with everolimus plus exemestane (n = 13, 13%),

### Table. Adverse Events Regardless of Causality*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Patients, No. (%)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Everolimus + Exemestane (n = 104)</td>
<td>Everolimus (n = 103)</td>
<td>Capecitabine (n = 102)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3-4</td>
<td>Any Grade</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Total</td>
<td>104 (100)</td>
<td>73 (70)</td>
<td>101 (98)</td>
<td>61 (59)</td>
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<tr>
<td>Stomatitis</td>
<td>51 (49)</td>
<td>9 (9)</td>
<td>47 (46)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>39 (38)</td>
<td>8 (8)</td>
<td>32 (31)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36 (35)</td>
<td>5 (5)</td>
<td>34 (33)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Anemia</td>
<td>33 (32)</td>
<td>13 (13)</td>
<td>26 (25)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Elevated γ-GGT</td>
<td>16 (15)</td>
<td>9 (9)</td>
<td>16 (16)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>16 (15)</td>
<td>7 (7)</td>
<td>14 (14)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (14)</td>
<td>6 (6)</td>
<td>8 (8)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>13 (13)</td>
<td>4 (4)</td>
<td>18 (17)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>11 (11)</td>
<td>7 (7)</td>
<td>9 (9)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4 (4)</td>
<td>0</td>
<td>4 (4)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>PPE syndrome</td>
<td>3 (3)</td>
<td>1 (1)</td>
<td>3 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: AST, aspartate aminotransferase; γ-GGT, gamma-glutamyl transferase; PPE, palmar-plantar erythrodysesthesia.

* Reported are grade 3 to 4 adverse events with higher than 5% incidence in any of the treatment arms. Some patients have more than 1 adverse event.
elevated γ-glutamyl transferase with everolimus alone (n = 12, 12%), and PPE syndrome with capecitabine (n = 28, 27%). Serious AEs regardless of causality are detailed in eTable 7 in Supplement 1; the most common were pneumonia with everolimus plus exemestane (n = 8, 8%), pneumonia and acute kidney injury with everolimus alone (n = 4, 4%, each), and deep vein thrombosis (n = 4, 4%) with capcitabine. The AEs leading to study drug discontinuation regardless of causality are detailed in eTable 8 in Supplement 1; the most common were pneumonitis with everolimus plus exemestane (n = 3, 3%) and everolimus alone (n = 5, 5%) and PPE syndrome with capcitabine (n = 5, 5%).

Overall, 188 patients died during the study: 71 in the everolimus plus exemestane arm, 59 in the everolimus arm, and 58 in the capcitabine arm, with disease progression the most common reason in each arm. Sixteen of these deaths occurred during treatment (<30 days after end of treatment): 9 in the everolimus plus exemestane arm, 5 in the everolimus alone arm, and 2 in the capcitabine arm. Disease progression was the most common reason for death in the everolimus plus exemestane arm (n = 6); AEs were the most common reason in the monotherapy arms: acute kidney injury, cardiorespiratory arrest, and respiratory failure—1 event each—in the everolimus monotherapy arm; and cerebrovascular accident and septic shock—1 event each—in the capcitabine monotherapy arm (eTable 9 in Supplement 1).

Discussion

This was an open-label, phase 2 study conducted to fulfill a postapproval regulatory commitment to the US FDA and EMA. Median PFS with everolimus plus exemestane in patients with ER-positive, HER2-negative advanced breast cancer was 8.4 months (90% CI, 6.6-9.7 months), consistent with that reported in the BOLERO-2 study (7.8 months). It was also numerically longer than that with everolimus alone in this study (6.8 months; 90% CI, 5.5-7.2 months), corresponding to an estimated 26% reduction of risk of disease progression or death (HR, 0.74; 90% CI, 0.57-0.97). Median PFS with everolimus alone was numerically longer than that reported in a small phase 2 study (3.5 months; 95% CI, 1.9-5.5 months), although this outcome was observed in just 19 patients.

A numerical PFS difference in favor of capecitabine (median 9.6 months; 90% CI, 8.3-15.1 months) vs everolimus plus exemestane should be interpreted cautiously because the capecitabine outcome was inconsistent with previous capecitabine studies (PFS range, 4.1-7.9 months). The PFS difference between the 2 arms might also be attributed to informative censoring in the context of an open-label study as well as imbalances in prognostic factors and baseline characteristics. More patients were censored owing to initiating antineoplastic therapies who received capecitabine (20%) than everolimus plus exemestane (9%). Such patients may not have the same PFS prognosis as those censored for other reasons and thus could bias the PFS estimate. The TTF was found to be similar between everolimus plus exemestane and capecitabine (HR, 1.03; 90% CI, 0.81-1.31), supporting the assumption of informative censoring in the PFS analysis favoring the capecitabine arm.

The median OS observed with everolimus plus exemestane (23.1 months; 90% CI, 19.5-28.0 months; 95% CI, 18.9-29.5 months) was inconsistent with the BOLERO-2 study (31.0 months; 95% CI, 28.0-34.6 months), with a similar median follow-up time (approximately 4 years). A random effect due to the small sample size in this study (n = 104 vs n = 485 in BOLERO-2) cannot be ruled out. Another contributing factor may have been different patterns of antineoplastic therapies initiated between the 2 studies after treatment discontinuation; however, any analysis is limited by documentation of only the first-line antineoplastic therapy initiated by patients in both studies. In BOLERO-2, more patients had an ECOG performance status of 0, and fewer had 3 or more metastatic sites than in the present study, although these factors were not found to have influenced the results. Median OS with everolimus plus exemestane was also numerically shorter vs everolimus alone (29.3 months; 90% CI, 24.3-31.8 months) and capecitabine (25.6 months; 90% CI, 23.8-33.4 months) in the present study. While no clear reasons were apparent to explain the discrepancy between the PFS and OS results with everolimus plus exemestane vs everolimus alone, the median OS with capecitabine in the present study was consistent with previous capecitabine studies (18.6-29.4 months). These results should also be interpreted cautiously because there were some potential imbalances in baseline characteristics that may have been influential.

Regarding safety, incidences of AEs and on-treatment deaths due to AEs (ie, AE-related deaths occurring up to 30 days after the end of treatment) were comparable among the 3 treatment arms. Stomatitis and the related AE of mouth ulceration were more common with everolimus plus exemestane and everolimus alone than with capecitabine, although stomatitis is a class effect of mTOR inhibitors and everolimus-associated stomatitis has been well documented. The incidence and severity of stomatitis would likely be lower using current practices because BOLERO-6 was designed prior to the results of the SWISH study, which supported initiation of topical treatment with dexamethasone mouthwash when starting everolimus treatment. The safety profile of everolimus plus exemestane was therefore consistent with BOLERO-2, and no new safety signals were observed; the overall benefit-risk profile of this combination remains unchanged. Everolimus in combination with other endocrine therapies also demonstrated a similar safety profile and no new safety signals. The incidence of PPE syndrome observed in the capecitabine arm was consistent with previous studies of capecitabine monotherapy.

Limitations

This was not a phase 3 confirmatory study, and any interpretation of the results must consider the limited sample size and open-label design. Insights are required from other studies comparing endocrine therapy and targeted therapy combinations with capecitabine for ER-positive advanced breast cancer, such as the ongoing phase 3 PEARL study (NCT02028507).
Conclusions

The treatment landscape for HR-positive, HER2-negative advanced breast cancer now includes cyclin-dependent kinase 4/6 inhibitors and endocrine therapy combinations. However, with the optimal sequence of endocrine agents following first-line endocrine therapy still uncertain, postapproval studies continue to provide valuable insights. The results of the present study suggest that mTOR inhibitor and endocrine therapy combinations remain important for aromatase inhibitor-refractory disease. Safety and PFS with everolimus plus exemestane in this study were consistent with BOLERO-2 and are now supported by real-world evidence. The PFS with capecitabine in this study was inconsistent with historical data, while real-world data are also lacking. Both PFS and OS for everolimus plus exemestane vs capecitabine may have been confounded by baseline imbalances favoring capecitabine and by informative censoring. The unchanged benefit-risk profile shown by everolimus plus exemestane in this study therefore supports retention of this combination as an option for patients with advanced breast cancer.


20. Kornblum N, Manola J, Klein P, et al. PRECOG 0102: a randomized, double-blind, phase II trial of fulvestrant plus everolimus or placebo in post-menopausal women with hormone receptor (HR)-positive, HER2-negative metastatic breast cancer (MBC) resistant to aromatase inhibitor (AI) therapy [abstract S1-02]. Presented at: San Antonio Breast Cancer Symposium; December 6-10, 2016; San Antonio, TX.

