# Endocrine Therapy for Advanced Breast Cancer

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**Abstract:** The demonstrated efficacy of pharmacologic antiestrogen therapy in treating hormone receptor–positive breast cancer has changed the landscape of treatment for the majority of women with metastatic disease, providing them with a well-tolerated therapeutic alternative to surgical oophorectomy and chemotherapy. A multitude of clinical trials have evaluated the various endocrine agents alone or in combination. Studies have established ovarian suppression as key for the management of premenopausal metastatic breast cancer patients, and aromatase inhibitor therapy as first-line treatment for their postmenopausal counterparts. Fulvestrant (Faslodex, AstraZeneca) has also been found to be efficacious and has been studied in the first-line and second-line settings. De novo and acquired endocrine therapy resistance represent a major challenge to the ongoing treatment of patients with hormone receptor–positive disease; strategies to circumvent or delay resistance, including the use of combination endocrine therapy and endocrine therapy with agents targeting various growth-factor signaling pathways, represent an active area of investigation. This review provides a summary of the various landmark trials that have established our current standards of practice in the management of patients with hormone receptor–positive metastatic breast cancer. A discussion of future directions and ongoing studies is also provided.

## Introduction

Approximately 75% of metastatic breast cancers (MBCs) are positive for expression of the estrogen and/or progesterone receptors.[1] As MBC remains largely incurable, goals of therapy include symptom palliation and prolongation of survival. To this end, consideration of quality of life and long-term tolerability of the treatments is essential. Endocrine therapy represents a well-tolerated and effective treatment option for these patients and is generally utilized in the first-line setting for hormone receptor–positive (HR+) MBC unless tumor burden warrants consideration of more rapidly acting cytotoxic agents.[2] Historically, the use of oophorectomy as a treatment

for breast cancer paved the way for development of early pharmacologic antiestrogens. The oral selective estrogen receptor modulators (SERMs), tamoxifen, toremifene (Fareston, ProStrakan) and raloxifene (Evista, Lilly), demonstrate tissue-specific estrogen antagonism or agonism; their activity in breast cancer is attributed to estrogen receptor antagonism in breast tissue. The progestin megestrol acetate (Megace, Bristol-Myers Squibb) is thought to act by downregulating and/or inhibiting the synthesis of estrogen receptors, and having a direct cytotoxic effect on breast cancer cells.[3] After comparison between tamoxifen and megestrol acetate demonstrated similar efficacy but a more favorable side effect profile with tamoxifen,[4,5] SERMs became the standard endocrine therapy for HR+ MBC. Because of notable toxicity, particularly weight gain,[4] megestrol acetate remains a fourth-line treatment option. It is generally used after disease progression on aromatase inhibitors, SERMs, and selective estrogen receptor downregulators.

The advent of other endocrine therapies has broadened the antiestrogen armamentarium. Ovarian suppression can be achieved by subcutaneous injections of leuprolide or goserelin, which provide nonpulsatile (nonphysiologic) stimulation of gonadotropin-releasing hormone (GnRH) receptors in the pituitary gland. These GnRH agonists ultimately result in downregulation of estrogen production. Aromatase inhibitors (AIs) function by inhibition of the enzyme responsible for conversion of androgens to estrogens. Aminoglutethimide, a first-generation AI, demonstrated efficacy, but rash, cytopenias, and the need for concomitant hydrocortisone[6,7] limited its utility. After demonstrating superiority to megestrol acetate and subsequently to tamoxifen,[8-12] third-generation AIs became the standard of care for treatment of postmenopausal women with HR+ MBC. Letrozole (Femara, Novartis) and anastrozole (Arimidex, AstraZeneca) are nonsteroidal AIs that reversibly and competitively bind aromatase, whereas exemestane, a steroidal AI, irreversibly deactivates the enzyme. Finally, fulvestrant is an intramuscular, selective estrogen receptor downregulator that results in estrogen receptor degradation.[13]

A significant body of research has examined optimal agents, sequences, and combinations to be utilized in the management of HR+ MBC. In addition, de novo and acquired resistance to endocrine therapy have been the focus of recent investigation. The present review serves to summarize current recommendations with regard to endocrine therapy in advanced breast cancer (ABC, including metastatic and locally advanced unresectable disease) as well as the scientific rationale behind these recommendations; particular attention will be focused on more recent studies of combination antiestrogen therapy as well as endocrine therapy in combination with targeted agents.

## Premenopausal Patients

Endocrine therapy for premenopausal patients requires antagonism of high levels of circulating estrogens. Pharmacologic castration using GnRH (luteinizing hormone–releasing hormone [LHRH]) nonpulsatile agonists demonstrated clinical benefit in HR+ MBC similar to that of oophorectomy but without necessitating surgery.[14,15] Subsequently, ovarian suppression was studied in combination with tamoxifen to induce maximal estrogen blockade.[16-19] Early trials suggested a benefit of combination ovarian ablation and tamoxifen,[16,17] leading to a randomized phase 3 study to confirm these findings. A 3-arm, randomized, prospective European Organisation for Research and Treatment of Cancer (EORTC) study evaluated 161 premenopausal patients with ABC treated with buserelin, tamoxifen, or both and confirmed that combined treatment demonstrated improved response rate, progression-free survival (PFS), and overall survival (OS).[18] (See the table for an overview of trials.) In a 2001 meta-analysis[19] including the above 3 studies and more than 500 patients, maximal estrogen blockade with the combination of tamoxifen and an LHRH agonist resulted in improved OS, PFS, and objective response rate (ORR) compared with ovarian suppression alone.

After the above findings provided evidence for the use of tamoxifen with ovarian suppression in premenopausal women with ABC, and AIs demonstrated efficacy in postmenopausal women, the combination of goserelin and anastrozole was evaluated. Based on multiple clinical trials demonstrating efficacy of ovarian suppression with an AI[20,21] or with fulvestrant,[22] the National Comprehensive Cancer Network currently recommends that in premenopausal women with MBC without previous exposure to an antiestrogen, initial treatment may be with an antiestrogen alone, or ovarian suppression or ablation plus endocrine therapy. In premenopausal women with recurrent disease within 1 year of antiestrogen exposure, surgical, radiotherapeutic, or pharmacologic ovarian suppression is recommended with oral antiestrogen therapy.

## AI Therapy in Postmenopausal Patients

In postmenopausal women, as in premenopausal women, tamoxifen remained for some time the first-line endocrine therapy option; third-generation AIs were initially approved in the second-line MBC setting, after progression while taking tamoxifen. However, in 2000 two studies compared anastrozole vs tamoxifen as first-line treatment of postmenopausal women with advanced disease, with practice-changing results.[8,10,23] In the North American study,[10] 353 postmenopausal women with estrogen receptor–positive (ER+) (89%) or estrogen

receptor–unknown (11%) status who had received no prior therapy for MBC were randomly assigned to receive tamoxifen or anastrozole. Primary endpoints were time to progression (TTP), objective response (OR), and tolerability. Median TTP was 11.1 months for patients in the AI group and 5.6 months for patients in the tamoxifen group (hazard ratio [HR] for progression, 1.44; lower limit of 95% CI, 1.16; *P*=.005). Anastrozole was at least as effective as tamoxifen in terms of OR, and both treatments were relatively well tolerated. Clinical benefit rate (CBR, including complete response, partial response, and stable disease) was 59% with anastrozole and 46% with tamoxifen (*P*=.0098). A larger but similarly designed and simultaneously published trial, the TARGET (Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability) study,[8] confirmed these findings. Six hundred sixty-eight patients received anastrozole or tamoxifen. After a median of 19 months of follow-up, anastrozole was equivalent to tamoxifen in terms of the primary endpoints—median TTP, ORR, and tolerability—with a lower incidence of thromboembolic events and vaginal bleeding. Findings from both the North American study and the TARGET study reinforced the role of anastrozole as first-line therapy for postmenopausal women with ABC.[23]

The other AIs have also been compared with tamoxifen. Letrozole was compared with tamoxifen as first-line treatment for postmenopausal women with HR+ breast cancer.[9] Nine hundred seven evaluable patients were randomly assigned to receive either the AI or the SERM. Letrozole conferred a prolonged TTP (9.4 months vs 6.0 months; *P*<.0001) and ORR (32% vs 21%, odds ratio, 1.78; *P*=.0002). Three hundred seventy-one patients were enrolled in a phase 3 trial comparing exemestane vs tamoxifen as first-line treatment for MBC[24]; ORR was greater with exemestane than with tamoxifen (46% vs 31%; odds ratio, 1.85 [95% CI, 1.21-2.82]; *P*=.005). However, no longer-term benefit was seen in PFS, and no OS difference was seen. These 2 studies,[9,24] as well as a 2006 meta-analysis that demonstrated an OS benefit with an AI,[25] support the use of third-generation AIs in the first-line treatment of ABC.

Bertelli and colleagues addressed the issue of cross-resistance between steroidal and nonsteroidal AIs.[26] Additional AI therapy after prior disease progression (exemestane after progression with a nonsteroidal AI, or a nonsteroidal AI after progression with exemestane) demonstrated efficacy, indicating partial non–cross-resistance between steroidal and nonsteroidal AIs. Optimal sequencing remains unclear.

## Fulvestrant

Fulvestrant is a "pure" estrogen antagonist with a mechanism of action distinct from that of the AIs, as it results in estrogen receptor degradation. Two parallel phase 3 trials compared fulvestrant with anastrozole in previously endocrine-treated ABC patients, the vast majority of whom had previously received tamoxifen.[27,28] Howell and colleagues in the United Kingdom randomly assigned 451 patients with prior sensitivity to hormonal therapy or HR+ ABC to receive fulvestrant 250 mg (no loading dose) or anastrozole.[27] The primary endpoint was TTP. After a median follow-up of 14.4 months, fulvestrant was as effective as anastrozole, with a median TTP of 5.5 months vs 5.1 months, respectively, and no statistically significant differences in CBR or ORR. Interestingly, response duration was significantly longer in the fulvestrant group. In a North American phase 3 study,[28] 400 postmenopausal women were treated in the second-line setting with either fulvestrant or anastrozole. After a median 16.8 months of follow-up, the 2 groups were similar in terms of the primary endpoint of TTP, as well as time to treatment failure, OR, and CBR. Again, median duration of response was significantly greater with fulvestrant than with anastrozole (12.9 months vs 10.9 months). Both of the above study protocols specified that OS would be analyzed when more than 50% of the patients died; therefore, no formal statistical analyses were conducted in either study. A prospective combined analysis of these 2 studies[29] noted that the vast majority of patients (96% in the fulvestrant group and 97% in the anastrozole group) had been previously treated with tamoxifen, and concurred with the conclusion that fulvestrant is at least as effective as anastrozole in the second-line treatment of HR+ ABC. Of note, the dose of fulvestrant used in these studies (250 mg monthly) was less than the current standard dose (500 mg monthly, with biweekly loading dose in the first month).

In the EFECT (Evaluation of Faslodex Versus Exemestane Clinical Trial) trial, fulvestrant was compared with exemestane in postmenopausal patients with HR+ breast cancer whose disease had recurred or progressed after prior treatment with a nonsteroidal AI.[30] In this phase 3 trial, 693 women were randomly assigned to receive either fulvestrant or exemestane. Both agents demonstrated efficacy after the use of a nonsteroidal AI, with a CBR of 32.2% with fulvestrant and 31.5% with exemestane. Efficacy in terms of TTP (primary endpoint), ORR, CBR, and median duration of clinical benefit was similar, and tolerability was favorable with both agents. This protocol specified that time to death (OS) was to be analyzed when more than 50% of the patients had died across both treatment groups. At the time of data analysis, this point was not reached so no formal statistical analyses were conducted. As in prior studies, the dose of fulvestrant studied was less than the current standard dose. In addition, although hormone receptor positivity was an inclusion criterion for this study, the majority of women relapsed within 6

**Table.** Key Clinical Trials Involving Endocrine Therapy in Advanced or Metastatic Breast Cancer

| | Study Design | Significance |
|---|---|---|
| **Premenopausal** | | |
| Klijn,[18] 2000 (EORTC) | Phase 3 | Tamoxifen in combination with buserelin demonstrated improved PFS, ORR, and OS compared with either agent alone. |
| **Postmenopausal, first-line setting** | | |
| Bonneterre,[8] 2000 (TARGET) | Phase 3 | Anastrozole demonstrated equivalence to tamoxifen in terms of median TTP, ORR, and tolerability, with a lower incidence of thromboembolic events and vaginal bleeding. |
| Nabholtz,[10] 2000 | Phase 3 | Anastrozole demonstrated significantly longer TTP and a better CBR than tamoxifen, and was at least equivalent in terms of OR. |
| Mouridsen,[9] 2003 | Phase 3 | Letrozole conferred a prolonged TTP and superior ORR compared with tamoxifen. |
| Paridaens,[24] 2008 (EORTC) | Phase 3 | Exemestane conferred a greater ORR than tamoxifen, with no significant difference in PFS or OS. |
| **Fulvestrant, first-line setting** | | |
| Robertson,[31] 2009 (FIRST) | Phase 2 | Standard-dose fulvestrant (500 mg/mo + 500 mg in month 1, day 14) compared with anastrozole provided a similar CBR and ORR. TTP was significantly longer with fulvestrant, and duration of response numerically favored fulvestrant. |
| NCT01602380 (FALCON) | Phase 3 | Fulvestrant vs anastrozole in an endocrine therapy–naive population; ongoing. |
| **Fulvestrant, second-line setting** | | |
| Howell,[27] 2002 | Phase 3 | In a population heavily pretreated with tamoxifen, fulvestrant (250 mg, no loading dose) was as effective as anastrozole in terms of TTP, CBR, and ORR, with longer response duration in the fulvestrant group. |
| Osborne,[28] 2002 | Phase 3 | In a population heavily pretreated with tamoxifen, fulvestrant and anastrozole conferred similar TTP, time to treatment failure, OR, and CBR, and fulvestrant conferred a longer duration of response. |
| Chia,[30] 2008 (EFECT) | Phase 3 | After progression on a nonsteroidal AI, fulvestrant and exemestane both demonstrated efficacy, with similar TTP, ORR, CBR, and median duration of benefit, as well as favorable tolerability. |
| **Fulvestrant, optimal dose** | | |
| Di Leo,[32] 2010 (CONFIRM) | Phase 3 | Low-dose (250 mg/mo) and high-dose (500 mg/mo + 500 mg in month 1, day 14) fulvestrant were compared, with longer PFS in the higher-dose group and no difference in tolerability. Established current dose of fulvestrant as 500 mg/mo + 500 mg on day 14. |
| **Combination endocrine therapy, first-line setting** | | |
| Bergh,[33] 2012 (FACT) | Phase 3 | Anastrozole plus fulvestrant (250 mg/mo) was compared with anastrozole alone in patients who had received prior endocrine therapy in the adjuvant setting, treated at first relapse. There were no significant differences in TTP, OR, time to treatment failure, duration of response, CBR, or OS. More patients discontinued therapy owing to adverse effects in the combination group. |
| Mehta,[34] 2012 (SWOG S0226) | Phase 3 | Anastrozole plus fulvestrant (500 mg on month 1, day 1; 250 mg on day 14; 250 mg/mo thereafter) was compared with anastrozole alone in the first-line setting. Allowed for fulvestrant dose adjustment to 500 mg after CONFIRM study data were reported. Allowed for crossover from anastrozole-only to fulvestrant at progression. Median PFS was 1.5 months longer in the combination group, with better 6-month OS survival and similar toxicity. |
| Goss,[36] 2007 | Phase 3 | Letrozole was compared with atamestane in combination with toremifene in a largely treatment-naive population. TTP, time to treatment failure, OR, and tolerability were similar in the 2 groups. |

*(continued on page 218)*

**Table.** Key Clinical Trials Involving Endocrine Therapy in Advanced or Metastatic Breast Cancer *(continued)*

| | | |
|---|---|---|
| **Combination endocrine therapy, second-line setting** | | |
| Johnston,[38] 2013 (SOFEA) | Phase 3 | Patients who progressed with nonsteroidal AI therapy were randomly assigned to receive fulvestrant plus anastrozole, fulvestrant plus placebo, or exemestane. All regimens had efficacy, and there were no statistically significant differences in PFS. |
| **Endocrine therapy with HER2-directed therapy** | | |
| Kaufman,[40] 2009 (TANDEM) | Phase 3 | Trastuzumab with anastrozole conferred significantly improved PFS, TTP, CBR, and ORR compared with anastrozole alone in women with HR+, HER2+ MBC treated in the first-line setting. |
| Johnston,[41] 2009 | Phase 3 | In women with HR+, HER2+ MBC, lapatinib with letrozole conferred significantly improved PFS compared with letrozole alone, although with grades 3 to 4 diarrhea. |
| **Endocrine therapy with PI3K/Akt/mTOR inhibition, first-line setting** | | |
| Wolff,[44] 2013 (HORIZON) | Phase 3 | In an AI-naive population, letrozole plus oral temsirolimus was compared with letrozole alone. Toxicity was more frequent in the combination arm, and the study was stopped prior to reaching its primary endpoint of PFS. |
| **Endocrine therapy with PI3K/Akt/mTOR inhibition, second-line setting** | | |
| Baselga,[42] 2012 (BOLERO-2) | Phase 3 | After progression on a nonsteroidal AI, exemestane and everolimus conferred significant improvement in PFS and response rate compared with exemestane alone, although with notable toxicity in the combination arm. |
| Bachelot,[43] 2012 (TAMRAD) | Phase 2 | After progression following AI therapy, tamoxifen plus everolimus conferred an improved CBR and TTP compared with tamoxifen alone, although with notable toxicity in the combination arm. |
| **Endocrine therapy with antiangiogenic agents, first-line setting** | | |
| Martin,[45] 2012 (LEA) | Phase 3 | Patients were randomly assigned to receive endocrine therapy (letrozole or fulvestrant) alone or with bevacizumab. There was no statistically significant improvement in PFS with bevacizumab, but there was increased toxicity. |
| NCT00601900 (CALGB 40503) | Phase 3 | Tamoxifen or letrozole with or without bevacizumab; ongoing. |

AI, aromatase inhibitor; CBR, clinical benefit rate; HR+, hormone receptor–positive; HER2+, human epidermal growth factor receptor 2 positive; MBC, metastatic breast cancer; OR, objective response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

months of initiation of endocrine therapy, suggesting that many patients enrolled in this trial in fact had hormone-insensitive disease, potentially decreasing the power of the study and masking true therapeutic benefit in the relevant population. Given these data, either exemestane or fulvestrant has efficacy after progression on a nonsteroidal AI.

Fulvestrant has more recently been compared with anastrozole for use in the first-line setting for MBC. In the phase 2, randomized, FIRST (Fulvestrant First-Line Study Comparing Endocrine Treatments) study,[31] fulvestrant (current standard dose, 500 mg/mo + 500 mg on day 14 of month 1) was compared with anastrozole in postmenopausal patients with HR+ ABC. The primary efficacy endpoint, CBR, and ORR were similar for both study groups. TTP was significantly longer with fulvestrant than with anastrozole, and duration of OR numerically favored fulvestrant. A phase 3 study (FALCON [*Fulvestrant and Anastrozole Compared in Hormonal Therapy Naïve Advanced Breast Cancer*]; NCT01602380) evaluating fulvestrant vs anastrozole in an endocrine therapy–naive population is ongoing.

The phase 3 CONFIRM (Comparison of Faslodex in Recurrent or Metastatic Breast Cancer) study[32] established 500 mg as the standard dose of fulvestrant. In this trial, more than 700 patients with ER+ disease whose disease had progressed with prior endocrine therapy were randomized to receive either fulvestrant 250 mg monthly or fulvestrant 500 mg monthly with an additional 500 mg loading dose on day 14 of month 1. Significantly longer PFS was noted in the higher-dose group (HR, 0.80 [95% CI, 0.68-0.94]; *P*=.006), and there was no difference in tolerability.

## Combination Endocrine Therapy

The studies above demonstrate the efficacy of pharmacologic endocrine therapy in treating MBC; however, clinical experience shows that HR+ tumors eventually grow despite tamoxifen, fulvestrant, and the AIs. This observed resistance to endocrine therapy prompted investigation into strategies to prolong responses and evade or delay treatment resistance. In the phase 3, randomized, FACT (Fulvestrant and

Anastrozole Combination Therapy) trial,[33] 514 women received anastrozole plus fulvestrant 250 mg monthly or anastrozole alone. Approximately two-thirds of women had received adjuvant endocrine therapy, though as this trial was largely conducted prior to approval of adjuvant AI use in the recruiting countries, only 8 women had received AIs. Women were treated at first relapse following primary treatment of localized disease.

With a median follow-up of 8.9 months, the primary endpoint of TTP was not statistically different between groups (10.8 months with the combination vs 10.2 months with the single agent). There were no significant differences in ORR, time to treatment failure, duration of response, CBR, or OS. More patients in the combination arm, 6.3%, discontinued treatment owing to adverse effects, compared with 3.1% in the anastrozole-only arm. The authors concluded that combination therapy offered no value over anastrozole monotherapy.

Mehta and colleagues of the Southwest Oncology Group (SWOG) Cooperative Group performed a similar phase 3 trial (SWOG S0226) in which 694 patients with HR+ MBC were randomly assigned to receive either anastrozole with fulvestrant (500 mg on day 1 of month 1, 250 mg on day 14, and 250 mg monthly thereafter) or anastrozole alone in the first-line setting.[34] However, the SWOG trial encouraged women in the anastrozole-only arm to receive fulvestrant monotherapy after progression. In addition, after approval of fulvestrant 500 mg, the SWOG protocol was amended to allow patients in either group to receive the 500 mg dose after progression, though the proportion of patients who received high-dose fulvestrant is not clear. Median PFS, the primary endpoint of this trial, was 13.5 months in the AI-alone group and 15.0 months in the combination therapy group ($P$=.007). OS was significantly improved in the combination arm (47.7 months vs 41.3 months; $P$=.049). Toxicity was similar. The SWOG authors suggested that the OS difference indicated an increase in efficacy with combination therapy vs sequential anastrozole and fulvestrant, noting that 41% of patients in the anastrozole-alone group crossed over to the fulvestrant-alone group (a population of patients felt to have good-prognosis disease that did not warrant immediate chemotherapy).

The reasons for disparate results from the FACT and SWOG trials are not fully understood. Allowance of crossover in the SWOG trial may have confounded OS analysis, as the AI-alone arm used for survival analyses was more accurately a mixed population. Furthermore, the percentage of individuals from each group in the SWOG trial who received low- vs high-dose fulvestrant is unclear. Both the FACT and SWOG studies evaluated treatment in the first-line setting. However, while 39% of patients in the SWOG trial had MBC at initial presentation and therefore endocrine therapy–naive disease, approximately two-thirds of patients in the FACT trial had received prior adjuvant endocrine therapy for localized disease (the vast majority were previously treated with tamoxifen); one could thus argue that the FACT study population may have been relatively more endocrine therapy–resistant than the SWOG trial population. Finally, the question of concurrent vs sequential use of these agents remains. These 2 studies were evaluated in a recent meta-analysis and the authors concluded that there is not solid evidence that the addition of fulvestrant 250 mg monthly is better than anastrozole alone.[35]

Goss and colleagues conducted a randomized phase 3 trial comparing single-agent letrozole with the combination of atamestane, a steroidal AI, and toremifene, a SERM.[36] The study population was 865 women with HR+ ABC who completed adjuvant therapy more than 12 months prior to study entry, and had received no prior endocrine therapy in the ABC or MBC setting. Approximately 80% of patients were treatment-naive with reference to both chemotherapy and endocrine therapy. No significant differences were seen in TTP, time to treatment failure, OR, tolerability, adverse events, or adherence. Analogous to the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial in the adjuvant setting,[37] these findings speak to the fact that no additional benefit has been seen with the combination of an AI and a SERM as compared with an AI alone.

Most recently, the phase 3 SOFEA (Fulvestrant With or Without Anastrozole or Exemestane Alone in Treating Postmenopausal Women With Locally Advanced or Metastatic Breast Cancer) trial evaluated more than 700 postmenopausal patients with HR+ breast cancer that progressed with nonsteroidal AI therapy.[38] Patients were randomly assigned to receive either fulvestrant (500 mg intramuscular injection on day 1, 250 mg on days 15 and 29, then 250 mg every 28 days) plus daily oral anastrozole; or fulvestrant (same dosage) plus placebo; or daily oral exemestane. The primary endpoint, PFS, was 4.4 months in patients who received fulvestrant and anastrozole, 4.8 months in those who received fulvestrant and placebo, and 3.4 months in those who received exemestane. There were no statistically significant differences in PFS between patients treated with fulvestrant plus anastrozole and those treated with fulvestrant plus placebo (HR, 1.00 [95% CI, 0.83-1.21]; $P$=.98) or between those treated with fulvestrant plus placebo and those treated with exemestane (HR, 0.95 [95% CI, 0.78-1.14]; $P$=.56). No difference in OS was recorded between patients who received fulvestrant plus anastrozole and those who received fulvestrant plus placebo, or between those who received fulvestrant plus placebo and those who received exemestane. Thus, in patients whose disease progressed with nonsteroidal AIs,

fulvestrant 250 mg combined with a nonsteroidal AI was not superior to either fulvestrant or exemestane alone. Consistent with the EFECT trial results,[30] these findings confirmed that either exemestane or fulvestrant alone is a treatment option after progression with a nonsteroidal AI.

## Endocrine Therapy + HER2–Targeted Therapy

Crosstalk between hormone and growth factor signaling pathways including the human epidermal growth factor receptor 2 (HER2) pathway is implicated in endocrine therapy resistance. After a phase 2 trial demonstrated that trastuzumab (Herceptin, Genentech) and letrozole were effective in combination for postmenopausal women with HER2 and hormone receptor–copositive MBC,[39] parallel phase 3 trials evaluated combination therapy.[40,41]

In the TANDEM (Trastuzumab and Anastrozole Directed Against ER-Positive HER2-Positive Mammary Carcinoma) trial,[40] 207 postmenopausal women with HR+ and HER2+ MBC were randomly assigned to receive trastuzumab plus anastrozole or anastrozole alone for the first-line treatment of MBC. The primary endpoint, PFS, as well as TTP, CBR, and ORR, were significantly improved with the combination as compared with anastrozole alone, with reversible toxicity. In addition, there was a nonstatistically significant increase in median OS in the trastuzumab plus anastrozole arm as compared with anastrozole alone (34.1 months vs 28.6 months; *P*=.451). However, median PFS—2.4 months in the anastrozole arm and 4.8 months in the combination arm—was shorter than expected in both study groups. In the approximately 70% of patients in both arms with centrally confirmed HR+ disease, the PFS for the combination arm was 5.6 months vs 3.8 months in the AI-only group.

Johnston and colleagues[41] performed a phase 3 study using lapatinib (Tykerb, GlaxoSmithKline), a dual tyrosine kinase inhibitor that targets HER2 as well as epidermal growth factor receptor. The researchers enrolled 1286 HR+ MBC patients in order to accrue a population of HR+, HER2+ patients (n=219) to address the primary hypothesis of this study. Patients were treated in the first-line setting for MBC with either letrozole alone or letrozole and lapatinib. This study also demonstrated benefit from combination therapy in the women with HER2 and hormone receptor–copositive MBC. The primary endpoint, PFS, was 8.2 months in the combination arm and 3.0 months with letrozole alone, though no PFS improvement was seen for the larger population of HER2-negative women included in the study. The combination arm had significantly more grade 3 or 4 diarrhea than did the letrozole-only arm (10% vs 1%, *P*<.05). No differences in OS were noted. Based on these studies, combination endocrine and HER2-targeted therapies are approved for HER2+, HR+ MBC, with the trastuzumab and anastrozole regimen more utilized owing to tolerability.

## Inhibition of the PI3K/Akt/mTOR Pathway

In addition to combination endocrine therapy and targeting the HER2 pathway, an additional potential mechanism of endocrine therapy resistance involves the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway. Three recent randomized trials evaluated hormonal therapy with pathway inhibitors.[42-44] The BOLERO-2 (Breast Cancer Trial of Oral Everolimus 2) study[42] was an international, multicenter, phase 2, randomized trial in which 724 patients with HR+, HER2-nonamplified ABC were randomly assigned in a 2:1 ratio to receive either exemestane and everolimus (Afinitor, Novartis) or exemestane alone (exemestane plus placebo). All patients' disease had recurred or progressed while receiving previous therapy with a nonsteroidal AI, in the adjuvant setting and/or to treat advanced disease, and many had received tamoxifen (48%), fulvestrant (16%), or prior chemotherapy (68%). Eighty-four percent of the patients had prior sensitivity to endocrine therapy. Patients with prior treatment with exemestane or mTOR inhibitors were excluded. The primary endpoint was PFS.

A preplanned interim analysis demonstrated an investigator-assessed PFS of 6.9 months with both agents and 2.8 months with exemestane alone (HR for progression or death, 0.43 [95% CI, 0.35-0.54]; *P*<.001). Central review observed a median PFS of 10.6 months for the combination and 4.1 months for exemestane alone (HR, 0.36 [95% CI, 0.27-0.47]; *P*<.001). Response rates were 9.5% and 0.4% in the combination therapy and exemestane-alone groups, respectively (*P*<.001). Of note, the combination arm had more toxicity, including grade 3 toxicities of stomatitis (8% in the everolimus arm vs 1% in the placebo arm), anemia (6% vs <1%), dyspnea (4% vs 1%), hyperglycemia (4% vs <1%), fatigue (4% vs 1%), and pneumonitis (3% vs 0%). Nineteen percent of patients discontinued everolimus owing to adverse events, whereas 4% of patients discontinued placebo.

The TAMRAD (Tamoxifen Plus Everolimus [RAD001]) study[43] was a multicenter, open-label phase 2 trial in which 111 postmenopausal women with HR+, HER2-negative MBC and relapse after stopping treatment with an AI were assigned to receive tamoxifen plus everolimus or tamoxifen alone. The primary endpoint of 6-month CBR was 61% (95% CI, 47%-74%) with tamoxifen plus everolimus and 42% (95% CI, 29-56) with tamoxifen alone. TTP was longer with the combination than with tamoxifen alone (8.6 months vs 4.5 months, respectively; HR, 0.54 [95% CI, 0.36-0.81]). Response

rates were similar. As in the BOLERO-2 trial, the combination arm had more toxicity and an accordingly higher rate of treatment discontinuation owing to adverse effects. Overall, the TAMRAD and BOLERO-2 trials support the combination of the mTOR inhibitor everolimus with endocrine therapy in previously endocrine-resistant disease, although they are indicative of everolimus toxicity and decreased tolerability of this regimen.

In the HORIZON (Study Evaluating CCI-779 and Letrozole in Post-menopausal Women With Breast Cancer) study, Wolff and colleagues studied letrozole, a nonsteroidal AI, plus oral temsirolimus (Torisel, Wyeth) as first-line endocrine therapy in postmenopausal women with ABC.[44] In this phase 3 randomized trial, 1112 postmenopausal women with HR+ ABC were randomly assigned to receive letrozole alone or letrozole with temsirolimus. This study population was AI-naive; no patients had received an AI as part of their treatment for ABC, and patients were ineligible if prior adjuvant AI therapy was administered within 12 months before the study. The study was terminated early (median follow-up, 9.5 months; range, 0-27.2 months) after the Independent Data Monitoring Committee concluded that the study was unlikely to reach its primary endpoint of PFS. In addition, grades 3 and 4 treatment-emergent adverse events were more common in the temsirolimus arm than in the letrozole-only arm (37% vs 24%), and more patients in the temsirolimus arm had a permanent dose reduction owing to adverse effects than in the letrozole-alone arm.

Unlike BOLERO-2 and TAMRAD, the HORIZON study showed no benefit in the primary endpoint of PFS, nor in ORR or OS. Additionally, no PFS benefit was seen in the 40% of patients who had received prior adjuvant endocrine therapy. However, an exploratory analysis examining patients ages 65 years and younger demonstrated improved PFS with the combination therapy (9.0 months vs 5.6 months; HR, 0.75 [95% CI, 0.60-0.93]; *P*=.009). The authors concluded that external confirmation of this benefit seen in younger postmenopausal patients is warranted. The authors also considered dosing or administration of temsirolimus as a cause for potentially decreased efficacy, noting that if toxicity was felt to be a surrogate for pharmacodynamic effects, toxicity of temsirolimus in the HORIZON trial was somewhat lower than previously observed.

The disparate findings in BOLERO-2 and TAMRAD as compared with HORIZON are likely in part attributable to the characteristics of included patients. BOLERO-2 and TAMRAD included patients with endocrine-resistant disease, whereas HORIZON included patients with largely AI-naive disease. This observation is interesting in light of the concept of adaptive upregulation of growth signaling pathways, including the PI3K/Akt/mTOR pathway, in endocrine-resistant disease; the addition of mTOR pathway inhibitors may be of particular benefit in patients for whom upregulation of this pathway adaptively develops in the setting of prior hormone therapy.

## Endocrine Therapy and Inhibition of Angiogenesis

After early indications that high vascular endothelial growth factor (VEGF) levels in breast tumors are associated with decreased endocrine therapy responsiveness, Martin and colleagues conducted a phase 3 trial evaluating the VEGF inhibitor bevacizumab (Avastin, Genentech) with endocrine therapy in the first-line setting for postmenopausal patients with HR+, HER2-negative ABC.[45] In this study (the LEA study [Bevacizumab + Endocrine Treatment vs Endocrine Treatment as First Line Treatment in Postmenopausal Patients With Advanced or Metastatic Breast Cancer]), 380 patients were randomly assigned to receive endocrine therapy alone or in combination with bevacizumab. Of the patients, 342 received endocrine therapy with letrozole and 38 with fulvestrant. Results presented at the 2012 San Antonio Breast Cancer Symposium demonstrated no statistically significant improvement in the primary endpoint, PFS, with bevacizumab added to endocrine therapy (18.4 months vs 13.8 months; HR, 0.83; *P*=.14) and no significant difference in OS with bevacizumab added to endocrine therapy (41 months vs 42 months; HR, 1.18; *P*=.469).[46] However, increased toxicity consistent with the known toxicity profile of bevacizumab was seen. Results of a second phase 3, randomized trial of endocrine therapy (tamoxifen or letrozole) with or without bevacizumab in patients with ABC are also awaited (Cancer and Leukemia Group B [CALGB] 40503; NCT00601900).

## Conclusion and Future Directions

Endocrine therapy is the mainstay of therapy for women with ER+ MBC, and affords patients an effective and well-tolerated treatment option. Over the past 2 decades, significant advances have been made in defining effective agents; the optimal sequence of therapy after the second line remains unclear, in part owing to developing standards of care, which evolved while many critical phase 3 trials were ongoing. More recently, efforts are being focused on understanding, preventing, and evading treatment resistance.[47]

ER-targeted therapy is being studied in combination with agents that may inhibit mechanisms of endocrine therapy resistance. PI3K activation has been noted to promote antiestrogen resistance, and PI3K inhibitors are undergoing active investigation. Two ongoing phase 3 trials are examining BKM-120 (buparlisib), an

oral pan-PI3K inhibitor, vs placebo in combination with fulvestrant in postmenopausal women with HR+, HER2-negative metastatic breast cancer. BELLE-2 (NCT01610284) is studying this combination in MBC that is refractory to aromatase inhibitor therapy, and BELLE-3 (NCT01633060) is examining the combination in patients whose disease progressed on or after mTOR inhibition. Other PI3K inhibitors, including isoform-specific agents, are in earlier-phase trials. Cyclin-dependent kinase 4/6 (CDK4/6) hyperactivation or retinoblastoma (Rb) protein loss may result in cell-cycle deregulation that confers antiestrogen resistance. Phase 2 data presented at the 2012 San Antonio Breast Cancer Symposium reported that the addition of the CDK4/6 inhibitor PD-0332991 (PD-991) to letrozole conferred a dramatic PFS improvement (26.1 months vs 7.5 months) and was relatively well tolerated.[48] Phase 3 studies are under way. As treatment of HR+ cancers evolves, so does the molecular landscape of the tumors themselves; new mechanisms of endocrine therapy resistance emerge. Continued efforts will be aimed at therapeutic exploitation of promising targets in endocrine resistance.

## References


1. Rugo HS. The breast cancer continuum in hormone-receptor-positive breast cancer in postmenopausal women: evolving management options focusing on aromatase inhibitors. *Ann Oncol.* 2008;19(1):16-27.
2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines)®: Breast Cancer. Version 1.2014. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed December 18, 2013.
3. Russell CA, Green SJ, O'Sullivan J, et al. Megestrol acetate and aminoglutethimide/hydrocortisone in sequence or in combination as second-line endocrine therapy of estrogen receptor-positive metastatic breast cancer: a Southwest Oncology Group phase III trial. *J Clin Oncol.* 1997;15(7):2494-2501.
4. Muss HB, Case LD, Atkins JN, et al. Tamoxifen versus high-dose oral medroxyprogesterone acetate as initial endocrine therapy for patients with metastatic breast cancer: a Piedmont Oncology Association study. *J Clin Oncol.* 1994;12(8):1630-1638.
5. Sedlacek SM. An overview of megestrol acetate for the treatment of advanced breast cancer. *Semin Oncol.* 1988;15(2)(suppl 1):3-13.
6. Lipton A, Harvey HA, Santen RJ, et al. A randomized trial of aminoglutethimide versus tamoxifen in metastatic breast cancer. *Cancer.* 1982;50(11):2265-2268.
7. Smith IE, Harris AL, Morgan M, et al. Tamoxifen versus aminoglutethimide in advanced breast carcinoma: a randomized cross-over trial. *Br Med J (Clin Res Ed).* 1981;283(6304):1432-1434.
8. Bonneterre J, Thürlimann B, Robertson JF, et al. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. *J Clin Oncol.* 2000;18(22):3748-3757.
9. Mouridsen H, Gershanovich M, Sun Y, et al. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *J Clin Oncol.* 2003;21(11):2101-2109.
10. Nabholtz JM, Buzdar A, Pollak M, et al; Arimidex Study Group. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. *J Clin Oncol.* 2000;18(22):3758-3767.
11. Paridaens R, Dirix L, Lohrisch C, et al; European Organization for the Research and Treatment of Cancer (EORTC)—Investigational Drug Branch for Breast Cancer (IDBBC). Mature results of a randomized phase II multicenter study of exemestane versus tamoxifen as first-line hormone therapy for postmenopausal women with metastatic breast cancer. *Ann Oncol.* 2003;14(9):1391-1398.
12. Gibson L, Lawrence D, Dawson C, Bliss J. Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. *Cochrane Database Syst Rev.* 2009;(4):CD003370.
13. Wakeling AE, Dukes M, Bowler J. A potent specific pure antiestrogen with clinical potential. *Cancer Res.* 1991;51(15):3867-3873.
14. Harvey HA, Lipton A, Max DT, Pearlman HG, Diaz-Perches R, de la Garza J. Medical castration produced by the GnRH analogue leuprolide to treat metastatic breast cancer. *J Clin Oncol.* 1985;3(8):1068-1072.
15. Brambilla C, Escobedo A, Artioli R, Lechuga MJ, Motta M, Bonadonna G. Medical castration with zoladex: a conservative approach to premenopausal breast cancer. *Tumori.* 1991;77(2):145-150.
16. Boccardo F, Rubagotti A, Perrotta A, et al. Ovarian ablation versus goserelin with or without tamoxifen in pre-perimenopausal patients with advanced breast cancer: results of a multicentric Italian study. *Ann Oncol.* 1994;5(4):337-342.
17. Jonat W, Kaufmann M, Blamey RW, et al. A randomised study to compare the effect of the luteinising hormone releasing hormone (LHRH) analogue goserelin with or without tamoxifen in pre- and perimenopausal patients with advanced breast cancer. *Eur J Cancer.* 1995;31A(2):137-142.
18. Klijn JG, Beex LV, Mauriac L, et al. Combined treatment with buserelin and tamoxifen in premenopausal metastatic breast cancer: a randomized study. *J Natl Cancer Inst.* 2000;92(11):903-911.
19. Klijn JG, Blamey RW, Boccardo F, Tominaga T, Duchateau L, Sylvester R; Combined Hormone Agents Trialists' Group and the European Organization for Research and Treatment of Cancer. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. *J Clin Oncol.* 2001;19(2):343-353.
20. Forward DP, Cheung KL, Jackson L, Robertson JF. Clinical and endocrine data for goserelin plus anastrozole as second-line endocrine therapy for premenopausal advanced breast cancer. *Br J Cancer.* 2004;90(3):590-594.
21. Carlson RW, Theriault R, Schurman CM, et al. Phase II trial of anastrozole plus goserelin in the treatment of hormone receptor-positive, metastatic carcinoma of the breast in premenopausal women. *J Clin Oncol.* 2010;28(25):3917-3921.
22. Bartsch R, Bago-Horvath Z, Berghoff A, et al. Ovarian function suppression and fulvestrant as endocrine therapy in premenopausal women with metastatic breast cancer. *Eur J Cancer.* 2012;48(13):1932-1938.
23. Bonneterre J, Buzdar A, Nabholtz JM, et al; Arimidex Writing Committee; Investigators Committee Members. Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma. *Cancer.* 2001;92(9):2247-2258.
24. Paridaens RJ, Dirix LY, Beex LV, et al. Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. *J Clin Oncol.* 2008;26(30):4883-4890.
25. Mauri D, Pavlidis N, Polyzos NP, Ioannidis JP. Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in advanced breast cancer: meta-analysis. *J Natl Cancer Inst.* 2006;98(18):1285-1291.
26. Bertelli G, Garrone O, Merlano M, et al. Sequential treatment with exemestane and non-steroidal aromatase inhibitors in advanced breast cancer. *Oncology.* 2005;69(6):471-477.
27. Howell A, Robertson JF, Quaresma Albano J, et al. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. *J Clin Oncol.* 2002;20(16):3396-3403.
28. Osborne CK, Pippen J, Jones SE, et al. Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. *J Clin Oncol.* 2002;20(16):3386-3395.
29. Robertson JF, Osborne CK, Howell A, et al. Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: a prospective combined analysis of two multicenter trials. *Cancer.* 2003;98(2):229-238.
30. Chia S, Gradishar W, Mauriac L, et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. *J Clin Oncol.* 2008;26(10):1664-1670.
31. Robertson JF, Llombart-Cussac A, Rolski J, et al. Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: results from the FIRST study. *J Clin Oncol.* 2009;27(27):4530-4535.
32. Di Leo A, Jerusalem G, Petruzelka L, et al. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. *J Clin Oncol.* 2010;28(30):4594-4600.

33. Bergh J, Jönsson PE, Lidbrink EK, et al. FACT: an open-label randomized phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer. *J Clin Oncol*. 2012;30(16):1919-1925.
34. Mehta RS, Barlow WE, Albain KS, et al. Combination anastrozole and fulvestrant in metastatic breast cancer. *N Engl J Med*. 2012;367(5):435-444.
35. Tan PS, Haaland B, Montero AJ, Lopes G. A meta-analysis of anastrozole in combination with fulvestrant in the first line treatment of hormone receptor positive advanced breast cancer. *Breast Cancer Res Treat*. 2013;138(3):961-965.
36. Goss P, Bondarenko IN, Manikhas GN, et al. Phase III, double-blind, controlled trial of atamestane plus toremifene compared with letrozole in postmenopausal women with advanced receptor-positive breast cancer. *J Clin Oncol*. 2007;25(31):4961-4966.
37. Baum M, Budzar AU, Cuzick J, et al; ATAC Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet*. 2002;359(9324):2131-2139.
38. Johnston SR, Kilburn LS, Ellis P, et al; SoFEA investigators. Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial. *Lancet Oncol*. 2013;14(10):989-998.
39. Marcom PK, Isaacs C, Harris L, et al. The combination of letrozole and trastuzumab as first or second-line biological therapy produces durable responses in a subset of HER2 positive and ER positive advanced breast cancers. *Breast Cancer Res Treat*. 2007;102(1):43-49.
40. Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. *J Clin Oncol*. 2009;27(33):5529-5537.
41. Johnston S, Pippen J Jr, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J Clin Oncol*. 2009;27(33):5538-5546.
42. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med*. 2012;366(6):520-529.
43. Bachelot T, Bourgier C, Cropet C, et al. Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO study. *J Clin Oncol*. 2012;30(22):2718-2724.
44. Wolff AC, Lazar AA, Bondarenko I, et al. Randomized phase III placebo-controlled trial of letrozole plus oral temsirolimus as first-line endocrine therapy in postmenopausal women with locally advanced or metastatic breast cancer. *J Clin Oncol*. 2013;31(2):195-202.
45. Martin M, Loibl S, von Minckwitz G, et al; GEICAM (Spanish Breast Cancer Research Group) and GBG (German Breast Group). Phase III trial evaluating the addition of bevacizumab to endocrine therapy as first-line treatment for advanced breast cancer – first efficacy results from the LEA study [SABCS abstract S1-7]. *Cancer Res.* 2012;72(24)(suppl 3).
46. Martin M, von Minckwitz G, Morales S, et al. Phase III trial evaluating the addition of bevacizumab to endocrine therapy as first-line treatment for advanced breast cancer – first efficacy results from the LEA study. Slide presentation at: 35th Annual CTRC-AACR San Antonio Breast Cancer Symposium; December 4-8, 2012; San Antonio, TX. http://www.researchtopractice.com/5MJCSABCS2013/1/4#. Accessed December 17, 2013.
47. Miller TW. Endocrine resistance: what do we know? *Am Soc Clin Oncol Educ Book*. 2013:37-42.
48. Finn RS, Crown JP, Lang I, et al. Results of a randomized phase 2 study of PD 0332991, a cyclin-dependent kinase (CDK) 4/6 inhibitor, in combination with letrozole vs letrozole alone for first-line treatment of ER+ /HER2– advanced breast cancer (BC) [SABCS abstract S1-6]. *Cancer Res*. 2012;72(24)(suppl 3).