Review

# Optimizing Endocrine Therapy for Breast Cancer

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**Abstract**

Endocrine therapy has significantly improved outcomes for patients with early- and advanced-stage hormone-receptor (HR)–positive breast cancer. Despite the success of adjuvant endocrine therapy, some patients with early-stage disease will experience relapse. Additionally, all patients with advanced disease will eventually experience disease progression on endocrine therapy due to resistance. Improved understanding of the mechanisms associated with resistance to endocrine agents has recently led to the approval of new therapeutics. Multiple questions remain unanswered, including the optimal duration of adjuvant therapy, the role of ovarian ablation in early-stage breast cancer in premenopausal women, and how to best incorporate targeted agents with endocrine therapy in the metastatic setting. This article reviews the optimization of endocrine therapy in patients with HR-positive breast cancer, focusing on these controversial areas. (J Natl Compr Canc Netw 2015;13:e56–e64)

Approximately two-thirds of breast cancers express either the estrogen receptor (ER), progesterone receptor (PR), or both, and this expression is predictive of benefit from endocrine therapies.[1] The use of available endocrine agents has markedly improved outcomes for patients with all stages of hormone receptor (HR)–positive breast cancer. However, despite the marked success of endocrine therapy in the treatment of HR-positive breast cancers, many patients will experience relapse and all patients with advanced disease will ultimately experience disease progression, due to intrinsic or acquired resistance to endocrine therapy. The mechanisms underlying intrinsic and acquired resistance to endocrine agents are complex and likely similar, and include activation of growth factor pathways resulting in changes in coregulators of the ER.[2–5]

Molecular profiling has allowed a better understanding of the biology of HR-positive breast cancers. Analysis of these breast cancers using the intrinsic gene set has identified at least 2 distinct subtypes, luminal A and luminal B, each of which has a unique biology and recurrence pattern. Luminal B cancers appear to harbor intrinsic resistance to endocrine therapy, which likely results in their high recurrence rate within the first 5 years of diagnosis.[6] Other molecular assays, such as the 21-gene recurrence score and the 70-gene signature,[7,8] provide prognostic information for patients with early-stage HR-positive breast cancers, and the use of the 21-gene recurrence score assay has allowed thousands of women with node-negative HR-positive breast cancer to avoid systemic chemotherapy, with all its inherent toxicities.

Despite the success with using targeted agents in HR-positive breast cancer, several critical questions remain. The use of molecular profiling has clearly allowed a more tailored approach to treating patients with early-stage HR-positive breast cancer, but has not been used to determine which patients truly benefit from endocrine therapy, or how long this treatment should be given. Whether a subset of premenopausal women with HR-positive early-stage breast cancer should receive ovarian ablation in combination with tamoxifen remains unclear. In the metastatic setting, although everolimus has been shown to improve outcome, the optimal timing at which to introduce mTOR inhibition remains unclear. This article reviews the optimization of endocrine therapy in patients with HR-positive breast cancer, with a specific focus on some of these controversial areas.

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## Early-Stage Breast Cancer

### Premenopausal Women

For patients who are premenopausal at the time of diagnosis of early-stage breast cancer, the current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer recommend that premenopausal women receive tamoxifen with or without ovarian suppression.[9] The role of ovarian ablation via surgery, radiation, or suppression with luteinizing hormone–releasing hormone agonists has not been clearly defined. A meta-analysis of trials comparing ovarian ablation or suppression versus no adjuvant therapy showed improved outcomes; however, patients did not receive chemotherapy or tamoxifen.[10] Other trials investigating the role of ovarian suppression in the adjuvant setting have yielded mixed results.

The Suppression of Ovarian Function Trial (SOFT; ClinicalTrials.gov identifier: NCT00066690) randomized women who were premenopausal and did not receive chemotherapy, or who remained premenopausal after completion of chemotherapy, to 5 years of either endocrine therapy with tamoxifen alone, tamoxifen plus ovarian suppression, or exemestane plus ovarian suppression. The Tamoxifen and Exemestane Trial (TEXT) compared tamoxifen plus ovarian suppression versus exemestane plus ovarian suppression. With a median follow-up of 68 months, a combined analysis of 4690 patients enrolled on SOFT and TEXT showed an improved 5-year disease-free survival (DFS) rate with exemestane plus ovarian suppression compared with tamoxifen plus ovarian suppression (91.1% vs 87.3%; hazard ratio [HR], 0.72; $P<.001$).[11] Results of the tamoxifen-alone arm from SOFT were not included in this analysis.

The Austrian Breast & Colorectal Cancer Study Group trial 12 (ABCSG-12) was a smaller study of 1803 premenopausal women with HR-positive breast cancer randomized to either anastrozole plus ovarian suppression or tamoxifen plus ovarian suppression, with or without zoledronic acid. In contrast to the combined analysis of SOFT and TEXT, after a median follow-up period of 62 months, no significant difference in DFS was seen in ABCSG-12 (HR, 1.08; $P=.591$).[12] The differing results could be a result of the smaller study size in ABCSG-12. Based on the combined analysis of SOFT and TEXT, an aromatase inhibitor (AI) plus ovarian suppression represents a new option for patients. Multiple questions remain, such as the timing of ovarian suppression with chemotherapy (concurrently, as on TEXT vs sequentially, as on SOFT). For patients with chemotherapy-induced menopause, it is unknown whether similar benefit would be observed by switching from tamoxifen to an AI after postmenopausal status is confirmed, thereby eliminating the need for 5 years of ovarian suppression. Although the reported adverse events were similar between the 2 groups, subjects dropped out of the exemestane arm more frequently (16% vs 11%). The results of the tamoxifen-alone arm in SOFT are also anticipated to provide additional insight into the optimal management of early-stage HR-positive breast cancer in premenopausal patients.

### Postmenopausal Women

In postmenopausal women, estrogen is synthesized when androgenic substrates produced by the adrenal glands are converted to estradiol by the aromatase enzyme.[13] AIs suppress plasma estrogen levels in postmenopausal women. The ATAC trial (Arimidex, Tamoxifen, Alone or in Combination) was a landmark study of more than 9000 patients comparing 5 years of anastrozole with 5 years of tamoxifen, and showed improved DFS with anastrozole compared with tamoxifen.[14] Similarly, the Breast International Group 1-98 (BIG 1-98) trial also showed improved DFS with 5 years of letrozole compared with 5 years of tamoxifen.[15] Several trials have investigated the benefit of switching to an AI after tamoxifen for 2 to 3 years compared with completing 5 years of tamoxifen, showing improved DFS.[16–19] Overall, all available trials demonstrate a benefit to using AIs as adjuvant therapy for HR-positive early-stage breast cancer in postmenopausal women, but whether an upfront AI is superior to tamoxifen for 2 to 5 years followed by an AI is unclear (Table 1). The Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial compared 5 years of exemestane versus sequential therapy with tamoxifen followed by exemestane, and showed no significant difference in long-term outcome.[20] The NCCN Guidelines recommend that postmenopausal patients receive an AI upfront for 5 years; or in sequence before or after 2 to 3 years of tamoxifen; or as extended adjuvant therapy after 5 years of tamoxifen.[9] For women with a contraindication or intolerance to an AI, 5 years of tamoxifen, or consideration of up to 10 years, is recommended.[9]

**Table 1 Trials of Aromatase Inhibitors as Initial Adjuvant Therapy or in Sequence With Tamoxifen for Postmenopausal Patients With Early-Stage Breast Cancer**

| Trial | Drugs | Number of Subjects | Median Follow-up (y) | Disease-Free Survival | Hazard Ratio (95% CI)[a] |
|---|---|---|---|---|---|
| ATAC[14] | Anastrozole<br>Tamoxifen | 3125<br>3116 | 10 | 69.5%<br>67.2% | 0.91 (0.83–0.99)<br>*P*=.04 |
| BIG 1-98[15] | Letrozole<br>Tamoxifen<br>Letrozole → Tamoxifen<br>Tamoxifen → Letrozole | 2463<br>2459<br>1540<br>1548 | 8.1 | 76.4%<br>72.0%<br>77.8%<br>77.3% | 0.82 (0.74–0.92)<br>*P*=.0002[a] |
| IES[17,19] | Tamoxifen<br>Tamoxifen → Exemestane | 2305<br>2294 | 7.6 | 82.4%<br>84.7% | 0.81 (0.71–0.92)<br>*P*=.001 |
| ITA[16] | Tamoxifen<br>Tamoxifen → Anastrozole | 225<br>223 | 5.3 | 72%<br>82.5% | 0.57 (0.38–0.85)<br>*P*=.005 |
| ABCSG 8/ ARNO 95[18] | Tamoxifen<br>Tamoxifen → Anastrozole | 1606<br>1618 | 2.3 | 93.2%<br>95.6% | 0.60 (0.44–0.81)<br>*P*=.0009 |
| TEAM[20] | Exemestane<br>Tamoxifen → Exemestane | 4875<br>4904 | 5.1 | 86%<br>85% | 0.97 (0.88–1.08)<br>*P*=.60 |

Abbreviations: ABCSG, Austrian Breast & Colorectal Cancer Study Group; ARNO, Arimidex-Nolvadex; ATAC, Arimidex, Tamoxifen, Alone or in Combination; BIG 1-98, Breast International Group 1-98; IES, Intergroup Exemestane Study; ITA, Italian Tamoxifen Anastrozole; TEAM, Tamoxifen Exemestane Adjuvant Multinational.
[a]Hazard ratio for letrozole versus tamoxifen arms.

## Duration of Endocrine Therapy

Unlike other subtypes of breast cancer, late recurrences are a hallmark of a subset of HR-positive cancers. The recommendation to stop endocrine therapy at 5 years was based primarily on data from the NSABP (National Surgical Adjuvant Breast and Bowel Project) B-14 trial that demonstrated a higher recurrence rate in patients with node-negative HR-positive breast cancer who received 10 years, compared with 5 years, of tamoxifen.[21] However, several trials have shown the benefit of extending adjuvant endocrine therapy to 10 years (Table 2).[22,23] The National Cancer Institute of Canada (NCIC) MA.17 trial demonstrated a significant improvement in DFS in patients who received up to 5 years of letrozole after 5 years of tamoxifen, compared with placebo.[24] The benefit of extended adjuvant therapy with letrozole was especially notable in patients with node-positive cancers and cancers that expressed both ER and PR.[25] The Adjuvant Tamoxifen—To Offer More? (aTTom) and Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trials both compared 5 versus 10 years of tamoxifen. Both trials demonstrated reduced risk of recurrence and mortality with longer treatment. Among the almost 7000 subjects with ER-positive disease on the ATLAS trial, the risk of recurrence in years 5 to 14 was 21.4% in the group taking tamoxifen for 10 years compared with 25.1% in the control group.[26] Similar improvements in long-term outcome were observed among nearly 7000 patients who received 10 years of tamoxifen on the aTTom trial.[27] Interestingly, in the ATLAS and aTTOM trials, most of the benefit was seen after subjects completed 10 years of tamoxifen, most likely because of a carryover effect of the 5 years of tamoxifen. The risks for development of endometrial cancer and venous thromboembolic events were increased in the women who received 10 years of tamoxifen.[26,27] Both of these studies included premenopausal and postmenopausal patients. The different results seen in NSABP B-14 perhaps may be explained by the larger number of patients with higher-risk disease on the ATLAS and aTTom trials. No data are currently available regarding the use of adjuvant AIs beyond 5 years, and results of the NSABP B-42 trial, in which patients who have received either 5 years of an AI or tamoxifen for 2 years followed by an AI for 3 years, are awaited (ClinicalTrials.gov identifier: NCT00382070). A re-randomization of the MA.17 trial will evaluate durations of endocrine therapy longer than 10 years (ClinicalTrials.gov identifier: NCT00754845).

**Table 2 Recent Trials of Extended Adjuvant Endocrine Therapy Beyond 5 Years of Tamoxifen in Patients With Early-Stage Breast Cancer**

| Trial | Duration of Therapy (y) | Number of Subjects | Median Follow-up (y)[a] | Disease-Free Survival | Hazard Ratio (95% CI) |
|---|---|---|---|---|---|
| MA.17[24,25] | Tamoxifen x 5<br>Tamoxifen x 5 → Letrozole x 5 | 2582<br>2575 | 2.4 | 94.0%<br>96.4% | 0.58 (0.45–0.76)<br>*P*=.00004 |
| NSABP B-33[23] | Tamoxifen x 5<br>Tamoxifen x 5 → Exemestane x 5 | 779<br>783 | 2.5 | 88%<br>91% | 0.68<br>*P*=.07 |
| ABCSG 6A[22] | Tamoxifen x 5<br>Tamoxifen x 5 → Anastrozole x 3 | 469<br>387 | 5.2 | 88.2%<br>92.9% | 0.62 (0.40–0.96)<br>*P*=.031 |
| ATLAS[26] | Tamoxifen x 5<br>Tamoxifen x 10 | 3418<br>3428 | 7.6 | 74.9%<br>78.6% | *P*=.002 |
| aTTom[27] | Tamoxifen x 5<br>Tamoxifen x 10 | 3485<br>3468 | 10 | 80.7%<br>83.3% | 0.85 (0.76–0.95)<br>*P* =.003 |

Abbreviations: ABCSG, Austrian Breast & Colorectal Cancer Study Group; ATLAS, Adjuvant Tamoxifen: Longer Against Shorter; aTTom, Adjuvant Tamoxifen—To Offer More?; NSABP, National Surgical Adjuvant Breast and Bowel Project.
[a]Median follow-up beyond initial 5 years of tamoxifen.

Although these trials all show an advantage to continuing endocrine therapy to 10 years, a critical issue is determining which patients need extended adjuvant therapy. Given the fact that luminal A cancers have a low rate of recurrence during the 5 years following diagnosis[28] and seem to be sensitive to endocrine agents, one could hypothesize that this is the subset of breast cancers most likely to have late recurrences. However, at least up to 10 years after diagnosis, luminal B cancers continue to have a higher recurrence rate than luminal A cancers.[29] The Breast Cancer Index (BCI), which includes the HOXB13:IL8R (H/I) gene expression ratio and the Molecular Grade Index, identifies 2 distinct subsets of ER-positive breast cancer with different rates of recurrence 5 to 10 years post-diagnosis.[30] In multivariate analysis, BCI, which is now available in the United States, remained significant in predicting recurrences 5 to 10 years after diagnosis, whereas the 21-gene recurrence score and IHC4 assay, which is based on quantitative assessment of ER, PR, HER2, and Ki67, did not.[30] The H/I index has been demonstrated to be predictive of benefit from extended adjuvant AI therapy from a subset of the NCIC MA.17 trial.[31] Other molecular assays, including the PAM50 risk-of-recurrence score, which includes 46 genes from the intrinsic subset and tumor size, and the EndoPredict assay, have been shown to be predictive of recurrences beyond 5 years.[32,33] Interestingly, looking at individual gene sets in the EndoPredict assay, genes associated with proliferation seem to be predictive of recurrences within 5 years, whereas genes associated with ER signaling are predictive of later recurrences.[33] Apart from BCI, none of these assays have been evaluated in trials in which patients received extended adjuvant therapy, and given that BCI was evaluated in a relatively small subset from the MA.17 trial, further validation would be appropriate before its widespread use to decide which patients need longer durations of endocrine therapy. Additionally, the ability of these assays to predict very late recurrences, which occur beyond 10 years, is currently unknown.

Taken together, it is reasonable to consider extended adjuvant therapy on an individual patient basis. If a patient remains premenopausal after completing 5 years of tamoxifen, one should consider extending tamoxifen treatment for an additional 5 years based on results of the ATLAS and aTTom trials.[9] If a patient becomes definitively postmenopausal during the first 5 years of tamoxifen, switching to an AI for 5 additional years is a reasonable option, although this has not been compared with continuing tamoxifen for a total of 10 years.[34] In postmenopausal women treated with upfront AIs or with tamoxifen followed by an AI, the long-term safety and efficacy of extending an AI beyond 5 years is not known and is currently under investigation. Until definitive data are available, extending therapy may be reasonable in patients with high-risk disease, particularly if they are tolerating treatment well.

## Metastatic Breast Cancer

### First-Line Therapy

Before the development of third-generation AIs, tamoxifen was the standard of care for first-line treatment of HR-positive metastatic breast cancer (MBC). Based on the favorable toxicity profile of AIs and at least equivalent efficacy results compared with megestrol in patients whose disease had progressed on first-line tamoxifen,[35–38] studies were initiated to evaluate AIs as first-line therapy for MBC. The largest trial randomized more than 900 patients with advanced breast cancer to either tamoxifen or letrozole. At a median follow-up of 32 months, letrozole was superior to tamoxifen, with a time to progression of 9.4 months versus 6 months for tamoxifen ($P<.0001$).[39,40] Similar trials comparing anastrozole and tamoxifen have also shown improved long-term outcomes with an AI in the first-line setting.[41,42]

Fulvestrant is a steroidal analogue of 17-beta-estradiol and binds to the ER. This prevents receptor dimerization and downregulates ER. Fulvestrant is the only available agent in this class, and is administered as an intramuscular injection because of poor oral bioavailability. Fulvestrant was initially compared with anastrozole in patients with MBC who had progressed on first-line tamoxifen. These studies showed that fulvestrant was equivalent to anastrozole in time to progression, response rate, and clinical benefit rate. Based on these trials, fulvestrant was approved by the FDA for use in postmenopausal women with MBC who have progressed on previous hormonal therapy.[43–45] Fulvestrant was subsequently compared with tamoxifen in the first-line setting, but showed equivalent outcome.[46] Initial trials of fulvestrant used a monthly 250-mg injection; however, pharmacokinetic data showed that it could take 3 to 6 months to reach steady-state level.[47] Subsequent trials were designed to evaluate alternative dosing schedules. Based on improved median progression-free survival (PFS) and median overall survival (OS) using a 500-mg loading dose on days 0, 14, and 28, the FDA updated the fulvestrant approval, recommending the 500-mg loading and therapeutic dose schedule, although this trial was not performed in the first-line setting.[48] Fulvestrant at the higher dose schedule was demonstrated to be superior to anastrozole in the first-line treatment of HR-positive MBC, with median time to progression of 23 months compared with 13 months.[49]

The combination of fulvestrant and anastrozole in the first-line setting has also been compared with sequential therapy with anastrozole followed by fulvestrant in 2 trials with somewhat conflicting results. The SWOG trial showed improved median PFS in the combination arm compared with the sequential arm (13.5 vs 15.0 months; HR, 0.80; $P=.007$).[50] In contrast, the Fulvestrant and Anastrozole Combination Therapy (FACT) trial did not show a significant improvement in median time to progression with the combination (10.8 vs 10.2 months; $P=.99$).[51] The conflicting results in these 2 trials may be attributed to differences in size of the trials and differences in patient populations, with the SWOG trial having more patients with de novo MBC. Median PFS was longer in the anastrozole-only arm of the SWOG trial, compared with the FACT trial, suggesting that a higher proportion of patients in the SWOG trial had endocrine-sensitive disease.

The addition of targeted agents to first-line endocrine therapy is currently being evaluated. Palbociclib is an oral inhibitor of cyclin-dependent kinase 4 and 6 (CDK4/6), which are proteins involved in regulating cell cycle progression.[52] Overexpression of cyclin D1 has been observed in more than one-third of breast cancers.[53] Cyclin D1 activates CDK4 and its continued activity plays a key role in maintaining breast tumorigenesis.[54] Preclinical data showed activity of palbociclib in HR-positive breast cancer cells.[55] PALOMA-1 was a randomized phase II trial that randomized 165 patients to either letrozole alone or combination palbociclib and letrozole as first-line therapy for HR-positive advanced breast cancer. Median PFS was 20.2 months in the combination arm compared with 10.2 months in the letrozole arm (HR, 0.49; $P=.0004$).[56] Based on these promising results, a phase III randomized trial is currently underway (ClinicalTrials.gov identifier: NCT01740427).

Preclinical data have supported a role of the ER-Src axis in the development of resistance to endocrine therapy.[57] The addition of dasatinib, a Src tyrosine kinase inhibitor, to letrozole as first-line treatment for HR-positive MBC improved PFS from 10 to 20 months in a randomized phase II trial.[58]

In the absence of a clinical trial, decisions on optimal first-line endocrine therapy for patients with HR-positive disease should be made based on prior therapy in the adjuvant setting. The combination of fulvestrant and anastrozole is reasonable but should

probably be reserved for patients with de novo MBC, or those who have a long disease-free interval from initial diagnosis.

## Prior Treatment With Nonsteroidal AIs

In the EFECT trial, patients with HR-positive MBC who had received prior therapy with a nonsteroidal AI were randomized to either exemestane or fulvestrant (Table 3). Time to progression was identical at just under 4 months in each arm, and no significant difference was seen in any of the other trial end points.[59] This trial suggests that no single endocrine agent is superior to another in this setting. Additionally, the time to progression of less than 6 months suggests that most of the patients, all of whom had received at least a nonsteroidal AI previously, had endocrine-resistant disease. The EFECT trial has been used subsequently to design trials evaluating the addition of other targeted agents to endocrine therapy in patients with HR-positive MBC who were previously treated with nonsteroidal AIs.

Endocrine resistance is a critical issue for patients with HR-positive MBC. Some tumors harbor intrinsic resistance to endocrine agents and do not benefit from endocrine therapy; in the metastatic setting, all tumors ultimately acquire resistance to endocrine therapy. The mechanisms underlying resistance to endocrine therapy are complex. However, enhanced signaling through growth factor receptor pathways has been demonstrated in preclinical and clinical studies. Activation of the PI3K/Akt/mTOR pathway can lead to estrogen-independent activation of ER and has been associated with resistance to endocrine therapy.[60,61] Preclinical data showed that mTOR inhibition can restore sensitivity to endocrine therapy and induce apoptosis in breast cancer cells.[62,63]

BOLERO-2 was a randomized phase III trial evaluating the addition of the mTOR inhibitor everolimus to exemestane in patients with MBC whose disease had progressed or recurred after treatment with a nonsteroidal AI. The addition of everolimus to exemestane led to significant improvements in PFS (6.9 vs 2.8 months by local assessment, $P<.001$; 10.6 vs 4.1 months by central assessment, $P<.001$). Recent OS data showed a nonsignificant improvement in OS from 26.6 months with exemestane alone to 31 months with exemestane plus everolimus (HR, 0.89; $P=.1426$).[64] However, the addition of everolimus was associated with increased toxicities.[65] The most common grade 3 or 4 adverse events were stomatitis, fatigue, hyperglycemia, anemia, and pneumonitis.[66] Based on the results of BOLERO-2, the FDA approved everolimus in combination with exemestane for postmenopausal patients with advanced breast cancer. Everolimus has been studied in combination with other endocrine agents. The TAMRAD trial was a phase II trial that compared combination tamoxifen and everolimus with tamoxifen alone. The clinical benefit rate was significantly improved in the combination arm (61% vs 42%; $P=.045$), as was the time to progression (8.6 vs 4.5 months). The toxicities observed in TAMRAD were similar to those seen in BOLERO-2.[67] A single-

**Table 3 Trials of Endocrine Therapy Among Patients With Hormone Receptor–Positive Advanced Breast Cancer After Progression on a Nonsteroidal Aromatase Inhibitor**

| Trial | Drugs | Number of Subjects | Progression-Free Survival (mo) | Hazard Ratio (95% CI) |
|---|---|---|---|---|
| EFECT[59] | Exemestane<br>Fulvestrant | 342<br>351 | 3.7<br>3.7 | 0.963 (0.82–1.13)<br>*P*=.6531 |
| BOLERO-2[64] | Exemestane<br>Exemestane + everolimus | 239<br>485 | 4.1[a]<br>10.6 | 0.36 (0.27–0.47)<br>*P*<.001 |
| TAMRAD[67] | Tamoxifen<br>Tamoxifen + everolimus | 57<br>54 | 4.5<br>8.6 | 0.54 (0.36–0.81)<br>*P*=.0021 |
| ENCORE[70] | Exemestane<br>Exemestane + entinostat | 66<br>64 | 2.3<br>4.3 | 0.73 (0.50–1.07)<br>*P*=.055 |

Abbreviations: BOLERO, Breast Cancer Trials of Oral Everolimus; EFECT, Evaluation of Faslodex versus Exemestane Trial; ENCORE, Entinostat Combinations Overcoming Resistance; TAMRAD, Tamoxifen Plus Everolimus.
[a]Progression-free survival reported according to central assessment.

arm phase II trial of fulvestrant and everolimus in postmenopausal women who experienced disease progression or relapse on a nonsteroidal AI showed a median time to progression of 7.4 months and a clinical benefit rate of 49%.[68]

Preclinical data support the concept that histone deacetylase (HDAC) inhibitors may play a role in reversing resistance to endocrine therapy.[69] The Entinostat Combination Overcoming Resistance (ENCORE) trial evaluated the addition of entinostat, a HDAC inhibitor, to exemestane in patients with HR-positive MBC who experienced prior disease progression on nonsteroidal AIs. Although no significant improvement was seen in PFS, a significant improvement in OS was noted.[70] The FDA has designated entinostat as a Breakthrough Therapy, and results of the ENCORE trial will be confirmed in the ongoing ECOG 2112 trial.

At the time of disease progression on exemestane and everolimus, whether the cancer has developed resistance to the endocrine agent, everolimus, or both is unclear. Studies are underway to evaluate the potential benefit of continuing everolimus beyond progression with an alternative endocrine agent. Inhibition of PI3K signaling upstream of mTOR is currently being evaluated among patients who experience disease progression on everolimus. BELLE-3 (ClinicalTrials.gov identifier: NCT01633060) is an ongoing phase III trial randomizing patients to either fulvestrant or combination fulvestrant and BKM-120, an oral pan-class PI3K inhibitor. The addition of everolimus to adjuvant endocrine therapy is also being evaluated in patients with high-risk HR-positive breast cancer. A phase III trial comparing endocrine therapy alone versus endocrine therapy plus 1 year of everolimus is being conducted among patients with 4 or more positive axillary lymph nodes or a 21-gene recurrence score greater than 25.

Although everolimus is approved for patients with HR-positive MBC who have received prior nonsteroidal AIs in the adjuvant or metastatic setting, given available preclinical data it seems likely that mTOR inhibition may be more effective in the endocrine-resistant setting. This hypothesis is supported by the fact that the addition of temsirolimus to letrozole did not improve outcomes in the first-line setting.[71] Unfortunately there is no definitive way of determining whether a patient with MBC has endocrine-sensitive or endocrine-resistant disease without assessing the benefit of endocrine therapy in the metastatic setting. Given the additional toxicity of everolimus, it will be important to determine which line of therapy is optimal in patients with HR-positive metastatic disease.

## Conclusions and Future Directions

The standard of care for adjuvant endocrine therapy for early-stage HR-positive breast cancer has evolved in recent years with the use of AIs in addition to tamoxifen for postmenopausal women. Although all postmenopausal women without a contraindication should be recommended to take an AI during adjuvant therapy, both the upfront AI use and sequential approach after tamoxifen are reasonable options. Several studies have shown benefit for extending adjuvant hormonal therapy to 10 years. Currently, no evidence supports extending therapy with an AI beyond 5 years, but the results of NSABP B-42 (ClinicalTrials.gov identifier: NCT00382070) addressing this question are eagerly anticipated. Molecular profiling should help define which patients require longer durations of adjuvant endocrine therapy.

Intrinsic resistance and the development of acquired resistance remain a significant challenge in the management of patients with HR-positive MBC. An improved understanding of the mechanisms of resistance to endocrine therapy has led to the development and approval of targeted therapies, such as everolimus in combination with endocrine therapy for patients with advanced breast cancer. Agents that target multiple growth factor receptors and signaling cascades are currently being developed with the goal of improving long-term outcomes.

Agents with proven efficacy in the metastatic setting should be considered for evaluation in patients with early-stage HR-positive breast cancer. Studies investigating the addition of everolimus to adjuvant endocrine therapy are currently ongoing. Because the addition of targeted agents to endocrine therapy is likely to increase toxicity, determining which patients are at higher risk for recurrence and most likely to benefit will be critical to improving long-term outcomes for early-stage HR-positive breast cancer.

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