Hormone receptor-positive (HR+) breast cancer is the most prevalent subtype of breast cancer in both early- and advanced-stage disease. Moreover, the treatment of HR+ breast cancer has had the greatest global influence in improving disease-free survival and overall survival (OS) in early-stage disease, and in prolonging progression-free survival (PFS) and potentially extending OS in advanced-stage disease. Since Beatson first demonstrated surgical oophorectomy induced regressions in inoperable breast cancer over a century ago, the developmental strategies of hormone therapy for the treatment of breast cancer have led to the classes of selective estrogen-receptor modulators, selective estrogen-receptor downregulators, and AI. Only in the past few years have we started to see the promise of additional pathway-targeted therapy in combination with hormone therapy have an effect on clinical outcomes. In the current climate HR has become synonymous with ER. If renewed interest in targeting the androgen receptor succeeds in establishing clinical utility for this approach, then the accepted meaning of HR+ breast cancer may need to be redefined. This review will focus on the current treatment strategies and algorithms in the management of HR+ MBC on the basis of prior and recent randomized clinical trials and attempt to integrate the results into standard clinical practice.

FIRST-LINE HORMONE THERAPY IN HR+ MBC

Following seminal publications in the 1970s, tamoxifen became established as the preferred mode of endocrine manipulation for the treatment of HR+ MBC on the basis of its superior efficacy and toxicity profile. More than 25 years later, third-generation AIs have now demonstrated greater clinical efficacy in head-to-head trials with tamoxifen. However, interpreting the results of these and other first-line trials in the context of current practice can be challenging because of changing patterns and prevalence of adjuvant hormone therapy use, ER reporting, and possible discordant receptor status relative to the primary tumor, and increasing subsequent-line treatment options available. In two large studies comparing anastrozole with tamoxifen, there were notable differences in clinical outcomes. PFS (median) was...
significantly longer for anastrozole (11.1 vs. 5.6 months) in the smaller North American trial, although no difference was observed in the larger European TARGET study (8.3 months vs. 8.2 months). It should be noted that no OS difference was demonstrated in either of the trials. A higher percentage of known HR+ patients and patients who had received adjuvant tamoxifen in the North American study may have selected for an outcome favoring the AI. The two trials were also prospectively designed to facilitate a combined analysis in which no difference in PFS was demonstrated.

In the PO25 study, letrozole was associated with a significantly improved median time to progression (TTP) (9.4 months vs. 6 months for tamoxifen; hazard ratio \(= 0.72 \ p < 0.0001\)). The study design built in cross-over at the time of progression. There was no significant difference in median OS (hazard ratio = 0.96; 95% CI 0.84–1.09). The steroidal AI, exemestane, has also been shown to improve median PFS over tamoxifen (9.9 vs. 5.8 months), without an OS benefit (hazard ratio = 1.13; 95% CI 0.85–1.5).

Fulvestrant, an estrogen-receptor downregulator, was initially approved for use in the second-line setting at a dose of 250 mg monthly. Over the last 5 years there has been an evolution of the recommended dose and of its position within the treatment algorithm for HR+ MBC. An updated analysis of the FIRST trial (a randomized phase II study), comparing a higher dose (HD) of fulvestrant (500 mg days 1 and 14, followed by 500 mg monthly thereafter) with anastrozole, confirmed superior TTP for fulvestrant (23.4 months vs. 13.1 month) compared with anastrozole. It is noteworthy that a high proportion of patients in both study arms were endocrine-treatment naïve (71.6% fulvestrant arm and 77.7% anastrozole arm), which may make interpretation of these results confounded in those patients relapsing on an adjuvant hormonal regimen. Both treatments were well tolerated with no important differences in prespecified events. Notwithstanding the limitations of this as a phase II open-label study, the role of fulvestrant as first-line treatment for HR+ MBC is promising and the basis for a phase III randomized control trial (FALCON).

Historically, combination regimens have failed to demonstrate a benefit over single endocrine agents. Furthermore, in the adjuvant setting the combination arm of the ATAC trial failed to show efficacy over tamoxifen alone and was discontinued. A pharmacokinetic interaction whereby anastrozole concentrations were lower in the combination with tamoxifen has been proposed as an explanation for this finding. In preclinical studies fulvestrant is active in a low estrogen environment and has demonstrated efficacy in combination with an AI. Fulvestrant competes with estrogen for binding of the ER, and reducing estrogen levels might enhance efficacy by allowing increased fulvestrant-ER binding.

Clinical studies evaluating the efficacy of fulvestrant by using a loading dose (500 mg day 1, 250 mg days 14 and 28, and every 28 days thereafter) in combination with anastrozole compared with anastrozole alone have reported mixed results. In the SWOG S0226 study\(^6\) a PFS and OS benefit in favor of the combination arm were seen (PFS 15 vs. 13.5 months, hazard ratio = 0.80; 95% CI 0.68–0.94; \(p = 0.007\), OS 47.7 vs. 41.3 months, hazard ratio = 0.81; 95% CI 0.65–1.0; \(p = 0.049\)). In contrast, the similarly designed FACT trial found no statistically significant difference in either TTP or OS (TTP hazard ratio = 0.99; 95% CI 0.81–1.20; OS hazard ratio, 1.0; 95% CI, 0.76–1.32). The discordance between these studies may be partly explained by a higher proportion of patients with previous exposure to tamoxifen in the FACT study (67% compared with 40% in the SWOG trial) and the large proportion of patients with de novo metastatic disease (38.9%) in the SWOG study.

In the case of premenopausal women combining a gonadotropin-releasing hormone analog with tamoxifen was shown to be more effective than either agent alone in a three-arm study of 161 patients randomly assigned to either buserelin, tamoxifen (40 mg daily) or both. Less than 3% of the patients enrolled had received adjuvant tamoxifen. The combination arm demonstrated superior median PFS compared with the buserelin and tamoxifen arms (9.7, 6.3, and 5.6 months, respectively; \(p = 0.03\)). Median OS was also greater for the combination (3.7, 2.5, and 2.9 years; \(p = 0.01\)). Evidence for combining a gonadotropin-releasing hormone analog with an AI is less substantial (single-arm phase II trials only\(^1,12\)) and therefore this approach is best regarded as a second-line option.

The use of fulvestrant in premenopausal women is yet to be established. An observational study of fulvestrant in combination with ovarian suppression for MBC described a clinical benefit rate of 58%, suggesting that further investigation of
this combination is indicated. Modern trials including ovarian suppression with a gonadotropin-releasing hormone have commonly employed a 28-day schedule of goserelin or buserelin at 6 mg 6-weekly for two treatments and 8 mg every 8 weeks thereafter. There is no clinical data assessing the relative efficacy of various gonadotropin-releasing-hormone analogs or different dosing schedules. Despite this, it seems reasonable to substitute a long-acting agent once response has been established.

In the absence of impeding visceral crisis or knowledge of primary endocrine resistance, endocrine strategies remain the preferred first approach for the management of HR+ MBC. Recent studies have sought to establish which agent should be considered for this pole-position. One of the challenges in translating these findings into clinical practice stems from the influence of prior adjuvant endocrine therapy, particularly the increasing use of adjuvant AIs, on the choice of endocrine agent in the advanced setting. Because the majority of patients enrolled in the studies discussed above were either endocrine-treatment naïve or exposed to tamoxifen only, the “real-life” applicability of the evidence is unclear. Nonetheless the literature supports an advantage for AIs over tamoxifen in terms of the clinical end points of TTP and clinical benefit, although not in OS. Current data suggest fulvestrant may be a reasonable first-line option; however, further clinical trials are needed (which are ongoing) to more confidently establish its position.

**SECOND-LINE HORMONE THERAPY IN HR+ MBC**

In trials investigating third-generation AIs compared with megestrol for the treatment of HR+ MBC progressive on tamoxifen, the benefit for AIs appeared small, but their toxicity profile compared favorably, particularly with respect to the unintentional weight gain associated with megestrol. With longer-term follow-up a survival benefit for anastrozole over megestrol emerged. Although these agents have individually established efficacy in both first- and second-line trials, there is less data to support superiority of one AI agent over another. Preclinical data indicate that letrozole is a more potent inhibitor of aromatization. In a head-to-head trial comparing letrozole with anastrozole following progression on antiestrogen therapy there was no difference in TTP or OS, and as such clinically meaningful superiority for letrozole over the other AIs has not been definitively established.

Early second-line trials of fulvestrant in patients who had progressed on prior antiestrogen therapy demonstrated similar response rates and survival compared with AIs. A LD regimen (500 mg day 1, 250 mg day 14 and 28, and every 8 weeks thereafter) was tested in the CONFIRM study. Results support

### TABLE 1. First-Line Hormone Therapy Trials in HR+ MBC

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>HR+ %</th>
<th>Median TTP (months)</th>
<th>CBR%</th>
<th>Cross-over</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonneterre 2000 (TARGET)</td>
<td>Tam Ana</td>
<td>45</td>
<td>89</td>
<td>100</td>
<td>Not done</td>
<td>0.99</td>
</tr>
<tr>
<td>Nabholtz 2001</td>
<td>Tam Ana</td>
<td>80</td>
<td>100</td>
<td>100</td>
<td>51%</td>
<td>1.44</td>
</tr>
<tr>
<td>Bonneterre 2001 (Combined)</td>
<td>Tam Ana</td>
<td>80</td>
<td>100</td>
<td>100</td>
<td>51%</td>
<td>1.44</td>
</tr>
<tr>
<td>Mouridsen 2007 (PO25)</td>
<td>Tam Ana</td>
<td>80</td>
<td>100</td>
<td>100</td>
<td>51%</td>
<td>1.44</td>
</tr>
<tr>
<td>Paridaens 2008</td>
<td>Tam Ana</td>
<td>80</td>
<td>100</td>
<td>100</td>
<td>51%</td>
<td>1.44</td>
</tr>
<tr>
<td>Robertson 2009 (FIRST)</td>
<td>Tam Ana</td>
<td>80</td>
<td>100</td>
<td>100</td>
<td>51%</td>
<td>1.44</td>
</tr>
<tr>
<td>Mehta 2012 (SWOG S0226)</td>
<td>Tam Ana</td>
<td>80</td>
<td>100</td>
<td>100</td>
<td>51%</td>
<td>1.44</td>
</tr>
<tr>
<td>Bergh 2012 (FACT)</td>
<td>Tam Ana</td>
<td>80</td>
<td>100</td>
<td>100</td>
<td>51%</td>
<td>1.44</td>
</tr>
</tbody>
</table>

**Abbreviations:** Ana, anastrozole; Exe, exemestane; CBR, clinical benefit rate; Ful, fulvestrant; HR+, hormone-receptor positive; Let, letrozole; MBC, metastatic breast cancer; NR, not reported; PFS, progression-free survival; Tam, tamoxifen; TTP, time to progression.
the preferential use of the 500 mg regimen that demonstrated superior PFS (6.5 months vs. 5.5 months, hazard ratio = 0.80; 95% CI, 0.68 – 0.94; p = 0.006) without a significant increase in adverse events. A recent update from the study suggested an OS benefit for the higher dose of fulvestrant. How and where fulvestrant fits remains an area of active research. Although earlier trials demonstrated equivalence, more recent data has demonstrated that the 500 mg dose is the more efficacious dose therefore calling into question the validity of earlier studies done with a lesser-dose regimen.

Without specific sequencing trials it is not possible to establish the optimal order of exposure to hormonal agents in the advanced setting. Large PFS differences are seldom seen in either first-or second-line trials, and in the absence of significant OS benefits, the specific sequence may be less important that ensuring exposure to each class of agent over time as long the tumor(s) remain hormonally sensitive.

**THIRD-LINE AND BEYOND HORMONE THERAPY IN HR+ MBC**

There is little data on which to establish evidence-based recommendations for third-line hormonal treatment and beyond. On the basis of the EFECT study20 and the results of a review of cross-resistance between steroidal and nonsteroidal AIs,23 both fulvestrant and exemestane are reasonable options following progression on tamoxifen and a nonsteroidal AI as monohormone therapy. The preferred option, in options following progression on tamoxifen and a nonsteroidal AI, is exemestane, followed by fulvestrant (an mTOR inhibitor)—see below. Endocrine therapy with either progesterin or high-dose estrogen can be considered in selected cases.24 Suitability for further endocrine therapy following progression on two or more prior lines must be assessed with consideration of earlier individual drug exposures, disease burden, and previous duration of response (clinical benefit).

**HORMONE THERAPY IN COMBINATION WITH ADDITIONAL TARGETED AGENTS**

It is likely we have realized the majority of the benefit from our current hormonal agents given as monotherapy for the treatment of MBC. The major focus over the past decade has been the investigation of blocking signaling pathways that potentially cross-talk to the ER pathway and are thought to be involved in either intrinsic or acquired resistance. The pathways that have led to randomized clinical trials include the HER2 pathway, epidermal growth factor receptor (EGFR) pathway, insulin growth factor receptor pathway, and the phosphatidylinositol 3-kinase (PI3K)-Akt-mammalian target of mTOR pathway. Despite a quantitative inverse relationship between HER2 and ER (and progesterone receptor), approximately half of all HER2+ breast cancers are also HR+. HER2 overexpression confers a worse prognosis in breast cancer, regardless of the accompanying hormone-receptor status. Two phase III randomized controlled trials have been performed with the addition of targeted anti-HER2–therapy in combination with hormone therapy in HER2+ HR+ MBC. The TAnDEM study (207 patients) combined trastuzumab with anastrozole compared with anastrozole alone as first- or second-line hormone therapy in advanced stage disease.26 Prior tamoxifen as adjuvant or hormone therapy for MBC was allowed, though approximately 35% to 40% of patients were hormone-therapy naïve on enrollment. Although the addition of trastuzumab to an AI did have a statistically significant effect in improving the hazard ratio for PFS (hazard ratio = 0.63; 95% CI, 0.47 – 0.84), the absolute improvement was modest at best (median PFS 4.8 months vs. 2.4 months; log-rank p = 0.0016). Moreover, there was no difference in OS between the arms, with the authors stating a likely reason being that 70% of patients on the anastrozole-alone arm crossed over to receive a trastuzumab-containing regimen at some point in time postprogression. The second randomized controlled trial to mention is the phase III trial that compared the combination of letrozole plus lapatinib with letrozole with a placebo as first-line treatment of HR+ MBC, which included a population of known HER2+ tumors.27 In the HER2+ HR+ cohort (219 patients), the addition of lapatinib to letrozole improved PFS (hazard ratio = 0.71; 95% CI, 0.53 – 0.96), but again with no difference as of yet seen in OS (though less than 50% of deaths have occurred at time of analysis). Although additional targeted therapies have been the investigation of blocking signaling pathways that potentially cross-talk to the ER pathway and are thought to be involved in either intrinsic or acquired resistance.

**TABLE 2. Second-Line Hormone Therapy Trials in HR+ MBC**

<table>
<thead>
<tr>
<th>Buzdar 199821</th>
<th>Dombernowsky 199821</th>
<th>Kaufmann 200021</th>
<th>Rose 200321</th>
<th>Chia 200821</th>
<th>Johnston 201221</th>
<th>Di Leo 201021</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ana Meg Let 2.5 mg Meg Exe Meg Let Ana Ful Exe Ful Ful + Ana Exe Ful 500 Ful 250</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>263</td>
<td>253</td>
<td>174</td>
<td>189</td>
<td>366</td>
<td>403</td>
</tr>
<tr>
<td>CBR</td>
<td>35</td>
<td>32</td>
<td>37.4</td>
<td>34.6</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>TTP months</td>
<td>4.8</td>
<td>4.6</td>
<td>5.6</td>
<td>5.5</td>
<td>4.7</td>
<td>3.9</td>
</tr>
<tr>
<td>Significance</td>
<td>hazard ratio = 0.94; p = 0.07</td>
<td>hazard ratio = 0.63; p = 0.0370</td>
<td>hazard ratio = 0.98; p = 0.56</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Known HR | 26% | 42% | 68% | 49% | 98% | 100% | 100% | 100% |

Abbreviations: Ana, anastrozole; Exe, exemestane; Ful, fulvestrant; HR+, hormone-receptor positive; Let, letrozole; Meg, megestrol; MBC, metastatic breast cancer.
numerically the hazard ratio was less on this trial compared with the TANDEM trial, the absolute improvement in PFS was greater (median PFS 8.2 months vs. 3.0 months). Taken together, it would appear reasonable to offer a postmenopausal woman with HR+ HER2+ advanced breast cancer not medically fit to receive chemotherapy with trastuzumab, a combination of either lapatinib or trastuzumab with an AI, with the goal of prolonging PFS but uncertain of improving OS. The other reasonable scenario would be in patients on maintenance trastuzumab (and possibly pertuzumab as well) postcombination chemotherapy to add a hormonal agent to the antibody(s) with hopes again of prolonging PFS and delaying the time to the next chemotherapy regimen.

Preclinical data has suggested that cross-talk between growth-factor receptors and the ER pathway are involved in the development of endocrine resistance. Increased expression of EGFR, HER2 and IGF-1 receptors is associated with tamoxifen resistance via activation of downstream signaling pathways. Two randomized phase II studies have been performed of hormone therapy in combination with either an oral EGFR tyrosine kinase inhibitor (TKI) (gefitinib) or a placebo in HR+ MBC. In the smaller of the two studies (93 patients), the PFS was longer in the anastrozole and gefitinib arm compared with the anastrozole and placebo arm (hazard ratio = 0.55; 95% CI, 0.32–0.94) with a median PFS of 14.7 months versus 8.4 months, respectively. Numerically the hazard ratio was less on this trial compared with the anastrozole and placebo arm (hazard ratio 0.52–1.15) in favor of the gefitinib arm; however, in patients treated with prior tamoxifen or prior AIs, the hazard ratio was 0.78 (95% CI, 0.52–1.15) in favor of the gefitinib arm; however, in patients treated with prior tamoxifen or prior AIs, the hazard ratio in fact favored the placebo arms (hazard ratio 1.45, 95% CI 0.63–3.45; hazard ratio = 1.16, 95% CI 0.69–1.93, respectively). Because these studies having conflicting results to some degree), the phase II statistical design, relatively small sample sizes, and no demonstration of an effect on OS—it would not be advisable to prescribe gefitinib or any other EGFR TKI in combination with hormone therapy in HR+ MBC.

In the previously mentioned study by Johnston et al., there was a preplanned hypothesis to explore the role of lapatinib to overcome endocrine resistance in the cohort of HR+ and HER2+ patients experiencing a relapse on or less than 6 months since discontinuation of adjuvant tamoxifen. The premise being preclinical models demonstrating growth-factor activity is enhanced in association with endocrine resistance. Because lapatinib is a dual TKI against EGFR and HER2, the combination of lapatinib and letrozole would be ideal to test this hypothesis. In fact, there was a nonsignificant trend toward a prolonged PFS for lapatinib-letrozole in this cohort (200 patients), with a hazard ratio of 0.78 (95% CI, 0.57–1.07; p = 0.117) and median PFS of 8.3 months versus 3.1 months, respectively. Although it may be tempting to consider this combination in tamoxifen resistant scenarios, this was only an exploratory subgroup analysis, there are greater grade 3 and 4 toxicities (primarily diarrhea and rash) for the combination, and there is no evidence of a survival benefit to recommend this therapeutic strategy.

Perhaps the greatest promise realized so far in attempting to combine targeted agents to hormone therapy has been in blocking the PI3K-Akt-mTOR pathway. Preclinical data suggests a close interaction between this pathway and ER signaling, with a substrate of the mTOR complex 1 (mTORC1) having the ability to directly activate the ER in a ligand independent manner. In the landmark BOLERO-2 study, 724 postmenopausal women with HR+ MBC and prior exposure to a nonsteroidal AI were randomly assigned to either everolimus (a mTORC1 inhibitor) and exemestane or a placebo and exemestane. Despite the patient population being relatively heavily pretreated (100% prior nonsteroidal AI, approximately 50% prior tamoxifen, and 68% had received prior chemotherapy) there was an improvement in PFS with a median PFS of 6.9 months with everolimus plus exemestane compared with 2.8 months for the placebo and exemestane.

### TABLE 3. Targeting Additional Pathways in Addition to Hormone Therapy in HR+ MBC

<table>
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</thead>
<tbody>
<tr>
<td></td>
<td>Ana + Tras</td>
<td>Ana + Placebo</td>
<td>Ana + Lapatinib</td>
<td>Ana + Placebo</td>
<td>Tam + Placebo</td>
<td>Exe + Placebo</td>
</tr>
<tr>
<td>n</td>
<td>104</td>
<td>103</td>
<td>108</td>
<td>111</td>
<td>50</td>
<td>43</td>
</tr>
<tr>
<td>CBR</td>
<td>27.9%</td>
<td>42.7%</td>
<td>29%</td>
<td>48%</td>
<td>34%</td>
<td>49%</td>
</tr>
<tr>
<td>PFS (months)</td>
<td>3.8</td>
<td>5.6</td>
<td>3.0</td>
<td>8.2</td>
<td>8.4</td>
<td>14.7</td>
</tr>
<tr>
<td>OS (months)</td>
<td>23.9</td>
<td>28.5</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Significance</td>
<td>hazard ratio</td>
<td>hazard ratio</td>
<td>hazard ratio</td>
<td>hazard ratio</td>
<td>hazard ratio</td>
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</tr>
<tr>
<td></td>
<td>0.63 95% CI:</td>
<td>0.63 95% CI:</td>
<td>0.71 95% CI:</td>
<td>0.55 95% CI:</td>
<td>0.84 95% CI:</td>
<td>0.43 95% CI:</td>
</tr>
<tr>
<td></td>
<td>0.47–0.84</td>
<td>0.47–0.84</td>
<td>0.53–0.96</td>
<td>0.32–0.94</td>
<td>0.59–1.18</td>
<td>0.35–0.54</td>
</tr>
</tbody>
</table>

Abbreviations: Ana, anastrozole; CBR, clinical benefit rate; EGFR, epidermal growth factor receptor; Exe, exemestane; Fru, fulvestrant; HR+, hormone-receptor positive; Let, letrozole; Meg, megestrol; MBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; NR, not reported; PFS, progression-free survival; Tras, trastuzumab.
(hazard ratio = 0.43; 95% CI, 0.35–0.54; p < 0.001). This clinically relevant improvement in PFS unfortunately comes at the expense of associated greater toxicities in the everolimus arm, in particular increased grade 3 or 4 stomatitis (8%), anemia (6%), dyspnea (4%), fatigue (4%), hyperglycemia (4%), and pneumonitis (3%). Fortunately though, time to deterioration of performance status and quality of life (≥5%) was not statistically different between the treatment groups as measured on the study. OS data are not yet mature, with results expected within the next year. Subgroup analyses demonstrated the consistency of the results across all subgroups assessed. With these compelling results, it would be appropriate for clinicians to consider the combination of everolimus and exemestane as a standard option in HR+/postmenopausal MBC with prior exposure to nonsteroidal AI in medically fit individuals who would be followed closely by their oncologist, and whom are aware of the toxicity spectrum and management strategies associated with this mTOR inhibitor.

WHERE WILL PROGRESS BE POTENTIALLY MADE IN THE NEAR FUTURE?

Technology today is allowing us to perform genomic and transcriptomic analyses to support high-resolution in breast cancers in a timely and less-costly manner than ever before. We have now recognized from a molecular landscape not all HR+ breast cancers are identical, to now using subtype designations of luminal A and luminal B breast cancers.32 In a recent integrated clustering analysis of copy number and gene expression of close to 2,000 breast tumors, 10 novel subtypes (or clusters) were identified with distinct clinical outcomes.33 This included the discovery of a high-risk ER+ subgroup composed of 11q13/14 cis-acting luminal tumors. Several known and putative driver genes reside in this region, such as CCND1, EMSY, PAK1 and RSF1. A recent randomized phase II trial of an oral inhibitor of cyclin-dependent kinase 4/6 (PD 033299) in combination with letrozole demonstrated a significant improvement in PFS (p < 0.001) compared with letrozole alone, with preclinical studies suggesting a greater sensitivity in tumors with CCND1 amplification.34 The hope is that as the capacity increases to molecularly interrogate breast tumors on a real-time basis we can understand the mutational evolution that occurs with disease progression, identify potentially “actionable” genomic aberrations, and ultimately use the information to better select therapeutic agents more likely to be efficacious.

ER biology is inextricably linked to multiple cell-signaling pathways with known cross-talk and regulatory feedback loops between pathways. As a further example of linked pathway cross-talk, both preclinical and a clinical studies have demonstrated that blockade of mTOR can induce AKT activation and activation of IGF-1R (via induction of IRS-1) as a result of loss of a potent intrinsic-negative feedback loop.35 Thus further preclinical studies with human tumor samples and tissue-based pharmacodynamic studies will need to be performed to better understand the complexity of blocking a pathway and the resultant alterations in other linked pathways to move this field further forward. Only with this information will we have the knowledge of whether to block single or multiple pathways together with hormonal agents to delay or prevent the development of resistance to hormone therapy.

CONCLUSION

Hormonal-based treatment strategies are and will almost certainly remain the mainstay of therapy in the majority of breast cancers today and into the foreseeable future. At present it does not appear the sequence of hormonal agents effect OS rather using all of the agents available in a hormonally sensitive population is the important factor. It is likely prior exposure (duration of exposure and time from exposure) to adjuvant hormonal agent(s) and a greater understanding of the pathways involved in primary and acquired hormonal resistance will dictate the choice of the actual hormonal agent used. We are now starting to see the promise realized with blocking cross-talking growth factor pathways in addition to the ER pathway, with the greatest efficacy seen with the mTOR inhibitor everolimus in combination with exemestane and perhaps to a lesser extent anti-HER2-directed therapy in combination with an AI. Future gains will likely involve a greater understanding of the redundancy and compensation induced by blocking these pathways, trials involving blocking multiple pathways in addition to hormonal agents, and the molecular interrogation of the patient’s tumor in search of predictive biomarkers and “actionable” genomic aberrations to establish that individual’s treatment algorithm.
References


