Emerging clinical information provides new options for the management of postmenopausal women with recurrent or metastatic breast cancer, both in terms of the identification of patients who are candidates for hormone-based therapy and the type and sequence of hormone therapy used. These issues are discussed in the context of recent randomized clinical trial evidence that is most relevant for current clinical practice.


text

For patients with advanced breast cancer, the choice of systemic therapy is based largely on consideration of hormone receptor status, human epidermal growth factor 2 (HER2) status, previous systemic therapy, and whether the patient has a visceral crisis or is in need of rapid symptom control. In this regard, the criteria for identification of patients who are likely to respond to hormone-targeted interventions is currently undergoing revision. Conventionally, women with either estrogen receptor–positive (ER+) or progesterone receptor–positive (PR+) tumors are considered candidates for hormone therapy. The EBCTCG (Early Breast Cancer Trialist Cooperative Group) recently updated overview analyses of all randomized adjuvant therapy trials of 5 years of tamoxifen vs. no therapy. Although PR status remained of prognostic value, PR status was not at all predictive of tamoxifen benefit. As a result, in the advanced-disease setting, patients with such staining positivity is based on a low percentage of immunohistochemical staining giving results in femtomoles per milligram (fmol/mg) protein. With >12,000 women randomized, women with breast cancer with the lowest but still measurable ER levels (<9 fmol/mg protein) did not benefit from adjuvant tamoxifen use compared with women with ER levels >10 fmol/mg protein. More recently, the concept that extremely low immunohistochemical receptor staining identifies tumors likely to be hormone sensitive has been further challenged by molecular studies. In a recent report of 465 cases from MD Anderson Cancer Center, only a small minority of breast cancers with 1% to 9% cells positive for ER by immunohistochemical testing as being candidates for hormone therapy. This concept was largely based on a series of 777 patients with early-stage breast cancer treated with tamoxifen reported by Allred et al. Tumors with even 1% staining for ER that was at least intermediate in intensity (Allred score of >3) had recurrence outcome similar to tumors with a larger percentage of staining for ER. However the concept that such extremely low levels of staining signaled hormone responsiveness has been challenged by findings, again from the EBCTCG. In randomized trials comparing tamoxifen to no therapy in the adjuvant setting, ER was measured by quantitative density-grading centrifugation giving results in femtomoles per milligram (fmol/mg) protein. With >12,000 women randomized, women with breast cancer with the lowest but still measurable ER levels (<9 fmol/mg protein) did not benefit from adjuvant tamoxifen use compared with women with ER levels >10 fmol/mg protein. More recently, the concept that extremely low immunohistochemical receptor staining identifies tumors likely to be hormone sensitive has been further challenged by molecular studies. In a recent report of 465 cases from MD Anderson Cancer Center, only a small minority of breast cancers with 1% to 9% cells positive for ER by immunohistochemical analysis showed molecular features similar to those of tumors more strongly estrogen receptor positive.

In summary, although hormone therapy can still be used in patients with PR+ but ER− breast cancer and in patients in whom ER positivity is based on a low percentage of immunohistochemical staining, emerging results indicate a low expectation of clinical benefit. As a result, in the advanced-disease setting, patients with such tumor characteristics who are receiving hormone therapy should be closely monitored for disease progression after therapy initiation.

After early reports, larger studies now indicate that breast cancers may alter their hormone receptor and HER2 status throughout tumor progression. In a Karolinska University Hospital population, a change in status from primary tumor to relapse was seen in 32.4% for ER (P < .001) and 14.5% for HER2 (P = .44). Thus recurrent breast cancers should be biopsied to determine receptor status.

Also influencing the decision regarding hormone therapy in advanced breast cancer is tumor HER2 status. Of the ER+ cases, ap-
86% are HER2-12. Hormone-based therapies have been used together with HER2-targeted therapies,13,14 and results should be compared with those using chemotherapy and HER2-targeted agents, a topic that is beyond the scope of the current report.

As initial therapy for postmenopausal women with advanced breast cancer that is hormone receptor–positive and HER2-, hormone therapy is favored in most settings given its low toxicity profile, convenience, and good quality of life compared with chemotherapy.1,15 Although evidence from randomized trials directly comparing initial endocrine therapy to chemotherapy for advanced breast cancer is limited, a Cochrane review found no survival differences but found more toxicity with initial chemotherapy.16 In addition, hormone therapy can be associated with long-term disease control extending not uncommonly for more than a year. Nonetheless, there remains an unmet need in postmenopausal women with advanced breast cancer and ERdisease because resistance will develop in almost all patients and ultimately disease progression will ensue.

Current Hormone Therapy

Currently, available interventions for hormone receptor–positive advanced breast cancers in postmenopausal women use several distant mechanisms of action.12,17 Tamoxifen binds to the ER, which dimerizes and influences transcription at the nuclear level. Fulvestrant also binds to the ER but receptor dimerization is prevented and accelerated receptor degradation occurs. Aromatase inhibitors decrease estrogen circulatory levels by interfering with androgen-to-estrogen conversion in peripheral tissues.

Although not generally recommended in an adjuvant setting, in advanced disease reduction of estrogen levels by use of gonadotropin releasing hormone analogues and/oophorectomy can be used in combination with tamoxifen;18 aromatase inhibitors,19 or fulvestrant,20 albeit with limited support from full-scale clinical trials. Additive hormone use with progestins, estradiol, and androgens (fluoxymesterone) has some activity, but more general use is limited by unfavorable toxicity profiles.17 Finally, the recent approval of the combination of the aromatase inhibitor exemestane with the mTOR inhibitor everolimus for hormone receptor–positive, HER2- advanced breast cancer represents the first approval of a new intervention for hormone receptor–positive HER2-, advanced breast cancer since fulvestrant was approved in 200221 (Figure 1).

Despite development of resistance to initial hormone therapy, patients with disease progression may respond to another hormone therapy. However the optimal sequence for hormone therapy use has not been defined.15

Hormone Therapy in the First-Line Setting

Although randomized clinical trials have compared various hormone therapies in first-line treatment in advanced breast cancer management, straightforward interpretation of results is complicated by changes in the standards of adjuvant hormone therapy use over time, resulting in differential previous hormone therapy exposure, entry of patients with hormone receptor–negative or unknown tumor status into early trials, influences of crossover after progression to the comparator agent, and use of suboptimal drug dosages and schedules.

Drug dosage is especially an issue for fulvestrant in which initial evaluation was with a dose of 250 mg intramuscularly every 28 days.22 Later, studies of fulvestrant involved an amended loading dose schedule that involved adding 250 mg intramuscularly on day 1 and day 14 to the regimen of 250 mg every 28 days. In contrast, a 500-mg schedule using 500 mg intramuscularly on days 1, 14, and 28 and subsequently every 28 days demonstrated a statistically significantly improved time to progression when compared with the 250-mg schedule.23 This finding brings into question the relevance of earlier clinical studies done with a less effective fulvestrant regimen.24,25

In early first-line phase III studies of hormone therapy for advanced breast cancer, aromatase inhibitors were superior to tamoxifen for endpoints involving disease progression but did not significantly increase overall survival.26-29 Median time to progression (months) favored anastrozole (10.7 months) vs. tamoxifen (6.4 months).
months), time to progression favored letrozole (9.4 months) vs. tamoxifen (6.0 months), and progression-free survival favored exemestane (9.9 months) vs. tamoxifen (5.8 months). In the first-line setting, fulvestrant in a 250-mg schedule had similar efficacy as tamoxifen, with median time to progression (months) with fulvestrant being 8.2 months and tamoxifen being 8.3 months.

The potential influence of crossover on overall survival in these studies can be seen in a trial reported by Mouridsen et al in which 907 postmenopausal women with advanced breast cancer with hormone receptor–positive or unknown status were treated with hormone therapy for advanced disease. Both time to progression and overall response rate were statistically significantly in favor of letrozole compared with tamoxifen, whereas overall survival did not differ between randomization groups (letrozole, 34 months vs. tamoxifen, 30 months (median); $P = .53$). However the survival outcome favored letrozole over tamoxifen through the first 24 months ($P = .02$), and the difference was lost with longer follow-up, likely representing an effect of crossover to letrozole in women randomized to initial tamoxifen use. First-line phase III studies examining fulvestrant in a 250-mg loading schedule plus anastrozole vs. anastrozole have produced mixed results (Figure 2). In SWOG S0226, in a trial involving 694 randomized postmenopausal women with advanced breast cancer, the addition of fulvestrant improved median progression-free survival (months) (15.0 vs. 13.3 months; $P = .007$) and median overall survival (weeks) (47.7 vs. 41.3; $P = .049$). However in the similarly designed FACT trial, which randomized 514 postmenopausal women with advanced or locally recurrent breast cancer, the addition

**Figure 2** First-Line Hormone Therapy Trials in Advanced Breast Cancer With Fulvestrant 250 mg (Loading Schedule)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>N</th>
<th>Postmenopausal women</th>
<th>HR+ advanced breast cancer, untreated with HT for advanced disease</th>
<th>ANASTROZOLE 1 mg q day*</th>
<th>*Crossover to fulvestrant 500 mg allowed after progression</th>
<th>*Previous adjuvant tamoxifen = 40%</th>
<th>PFS (mo)</th>
<th>OS (mo) median</th>
<th>HR</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG S0226 Phase III Trial of Anastrozole + Fulvestrant 250 (loading) vs. Anastrozole Alone</td>
<td>FUL + ANA, n = 355</td>
<td>ANA, n = 352</td>
<td>15.0</td>
<td>13.5</td>
<td>0.80</td>
<td>0.007</td>
<td>ANASTROZOLE 1 mg q day*</td>
<td>PFS (mo)</td>
<td>OS (mo) median</td>
<td>47.7</td>
<td>41.3</td>
</tr>
<tr>
<td>FACT: Phase III Trial of Anastrozole + Fulvestrant 250 (loading) vs Anastrozole Alone</td>
<td>FUL + ANA, n = 256</td>
<td>ANA, n = 254</td>
<td>10.8</td>
<td>10.2</td>
<td>0.72</td>
<td>0.91</td>
<td>ANASTROZOLE 1 mg q day*</td>
<td>TTP (mo)</td>
<td>OS (mo) median</td>
<td>37.8</td>
<td>38.2</td>
</tr>
</tbody>
</table>

*Abbreviations: ANA = anastrozole; CBR = clinical benefit rate; FUL = fulvestrant; HR = hazard ratio; HR+ = hormone receptor positive; HT = hormone therapy; ORR overall response rate; OS = overall survival; PFS = progression-free survival; q = every; SWOG = Southwest Oncology Group; TTF = time to failure; TTP = time to progression.
of fulvestrant to anastrozole had no effect on progression-free survival or overall survival (Figure 2).32 These differences could be related to previous tamoxifen use. In subgroup analyses in the SWOG trial, the effect of adding fulvestrant was greater in the 60% of participants without previous tamoxifen exposure (median progression-free survival, 17.0 vs. 13.5 months, respectively),31 whereas only 30% of the FACT trial participants had no previous tamoxifen use.32 Such a hypothesis would require prospective evaluation but with the current higher dose fulvestrant regimen.

These mixed findings for the use of a fulvestrant 250-mg loading schedule are in contrast to a first-line trial evaluating fulvestrant as single agent in the higher 500-mg schedule. In the FIRST (Fulvestrant First-Line Study Comparing Endocrine Treatment) randomized phase II trial involving 205 postmenopausal women with hormone receptor–positive advanced breast cancer previously untreated for advanced disease, the clinical benefit rate and overall response rate were comparable for fulvestrant 500 mg given intramuscularly on days 1, 14, 28 and every 28 days thereafter to anastrozole 1 mg daily orally. However, median time to progression was substantially longer in the fulvestrant group (23.4 months vs. 13.1 months; hazard ratio [HR]; 0.66, 95% confidence interval [CI], 0.47-0.92; \( P = .01 \)),33,34 with half of the women in the fulvestrant group going nearly 2 years without disease progression (Figure 3).

**Hormone Therapy in a Second-Line Setting**

In a combined analysis of 2 randomized trials, use of the aromatase inhibitor anastrozole as second-line therapy after progression on ta-
moxifen resulted in a significant survival advantage over megestrol acetate. More pertinent to contemporary practice—in which most postmenopausal women in the United States with hormone receptor–positive advanced breast cancer will have received an aromatase inhibitor in the adjuvant setting—are trials examining use of hormone therapy after progression on nonsteroidal aromatase inhibitors (anastrozole or letrozole).

Two phase III randomized trials with 851 postmenopausal women with advanced breast cancer compared fulvestrant 250 mg intramuscularly monthly to anastrozole 1 mg orally daily after progression on previous endocrine therapy. No differences in clinical benefit rate or time to progression were seen. The use of the fulvestrant 250-mg loading schedule (adding 250 mg intramuscular doses on days 1 and 14) was evaluated in EFECT (Evaluation of Faslodex vs. Exemestane Trial), in which 693 postmenopausal women with advanced hormone receptor–positive breast cancer were randomized to fulvestrant or exemestane 25 mg daily orally after failure of nonsteroidal aromatase inhibitor therapy, and no differences in clinical outcome were seen, with median time to progression being a modest 3.7 months in both groups. Similarly, in the SoFea (Study of Faslodex, Exemestane, and Arimidex) trial, fulvestrant in a 250-mg loading schedule with or without anastrozole had results comparable to those of exemestane when evaluated in the same setting, with progression-free survival ranging between 3.4 and 4.8 months in the 3 groups.

The CONFIRM (Comparison of Faslodex in Recurrent or Metastatic Breast Cancer) trial compared the then-current label dose of fulvestrant 250 mg intramuscularly every 28 days to a fulvestrant 500-mg schedule given on days 1, 14, and 28 and thereafter every 28 days. In 736 postmenopausal women with advanced hormone receptor–positive breast cancer entered after failure of previous endocrine therapy, median progression-free survival was significantly improved by the higher dosage (fulvestrant 500 mg, 6.5 months vs. fulvestrant 250 mg, 5.5 months; \( P = .004 \)), and there were fewer deaths in the fulvestrant 500-mg group (HR, 0.84; 95% CI, 0.69-1.03), but the later difference was not statistically significant (\( P = .09 \)) (Figure 3). Similar trends were seen in a phase II randomized trial. As a result, the 500-mg fulvestrant schedule is now the standard regimen for fulvestrant (Figure 3).

In summary, based on the randomized clinical trial evidence for advanced hormone receptor–positive breast cancer, we expect about a 10- to 11-month time to progression for hormone therapy in the first-line setting and between a 3- and 6-month time to progression for use after previous aromatase inhibitor therapy. Although long-duration breast cancer control can be achieved with hormone therapy, results for even second-line hormone therapy are not particularly favorable. In the National Comprehensive Cancer Network guidelines it is recommended that for women without visceral crisis with hormone receptor–positive, HER2–advanced breast cancer, hormone therapy should be continued until no clinical benefit is seen after 3 consecutive endocrine therapy regimens. Although this is a reasonable approach, even second-line hormone therapy use requires close monitoring for potential early progression.

**Hormone Therapy Resistance**

Given these results, focused attention during the past decade has addressed the issue of mechanism of endocrine resistance. The PI3K/akt/mTOR pathway has been identified as playing a potential major role in this problem. The evidence suggests that the PI3K/akt/mTOR pathway becomes activated in hormone-resistant breast cancers and activation of mTOR, described as the cell master regulator, allows tumor cells to survive despite concurrent hormone therapy. As a result, targeting the mTOR pathway could provide benefit for patients with advanced breast cancer who demonstrate resistance to hormone therapy.

Against this background, everolimus has emerged as a potential mTOR kinase inhibitor. Preclinical findings suggest that everolimus inhibits mTOR through binding to the mTOR C-1 complex. Additional activities associated with everolimus use include reduction in angiogenesis by vascular endothelial growth factor and HIF-1 expression, another pathway with known involvement in hormone therapy endocrine resistance.

**Hormone Therapy Combined With Everolimus**

Most recently, everolimus has been approved in Europe and the United States for the treatment of postmenopausal women with hormone receptor–positive advanced breast cancer after failure of previous treatment with a nonsteroidal aromatase inhibitor.

A signal of everolimus benefit in the advanced-disease setting came from a randomized, phase II clinical trial, the TAMRAD (tamoxifen and RAD001-Everolimus) study (Figure 4). The trial included 211 postmenopausal women with hormone receptor–positive, HER2–advanced breast cancer previously treated with a nonsteroidal aromatase inhibitor in the adjuvant or metastatic setting. Randomization was to tamoxifen 20 mg/d vs. tamoxifen plus the addition of everolimus 10 mg/d. All medications were taken orally. The primary study endpoint was the rate of clinical benefit at 6 months, which favored the everolimus plus tamoxifen combination (61% vs. 42%, respectively; \( P = .045 \)), as did time to progression (months) (8.6 vs. 4.5, respectively). In addition, the addition of everolimus also increased overall survival by 55% (HR, 0.45; 95% CI, 0.28-0.81; exploratory log-rank \( P = .007 \)).

Everolimus increased toxicities previously reported for its use, including stomatitis, fatigue, rash, and diarrhea, with most being grade 1 and 2. Dose reductions because of adverse events were 28% in the everolimus combination group vs. none in the tamoxifen-alone group. In this phase II setting, the addition of everolimus to tamoxifen improved clinical outcome at a cost of an increase in limiting grade 3 toxicities.

A role of everolimus in advanced breast cancer management was established by findings from the phase III BOLERO-2 (Breast Cancer Trials of Oral Everolimus-20) study (Figure 4). In this randomized double-blind multicenter study, exemestane 25 mg plus placebo was compared with exemestane 25 mg plus everolimus 10 mg, both given daily in postmenopausal women with ER+, HER2–advanced breast cancer with recurrence or progression after previous therapy with letrozole or anastrozole. Randomization was 2:1 in favor of the everolimus arm (n = 485) with n = 239 in the placebo arm. The central assessment of time to progression favored the everolimus combination (10.6 vs. 4.1 months, respectively; HR, 0.36; 95% CI, 0.27-0.47; \( P < .001 \)), as did the clinical benefit rate (51.3% vs. 26.4%, respectively). It is noteworthy that at the first assessment at 6 weeks after entry, there was about 20% greater progression-free survival in the everolimus combination group.
Overall survival results are not mature, but there were fewer deaths in the everolimus groups (10.6% vs. 13.0%, respectively).

Toxicity was greater in the everolimus group. Stomatitis including oral ulceration was common, seen in 67% of participants, with 8% grade 3 and grade 1/2 diarrhea and nausea seen in 33% and 29% of patients, respectively.46 Pneumonitis was reported in 12% of patients, with 3% having a grade 3 event.46 A recent review outlines a decision tree addressing available information on diagnosis, monitoring, and management of mTOR inhibitor–associated noninfectious pneumonitis.47 As a result of the moderate potential for the development of grade 3 toxicities, the use of the everolimus combination requires careful toxicity monitoring with appropriate dose adjustments. Both the TAMRAD and BOLERO-2 trials were conducted in women with previous nonsteroidal aromatase inhibitor exposure. Further studies are needed to determine whether previous aromatase inhibitor exposure (or perhaps even progression while receiving aromatase inhibitors) are prerequisites for everolimus effect.

Although detailed mechanism of action consideration is beyond the scope of the present report, everolimus is a recognized inhibitor of mTOR.48 In addition, emerging evidence indicates that activation of the mTOR pathway is a key adaptive change driving resistance to endocrine and HER2-targeted therapies.49 As a result, an active program of research is exploring the potential role for everolimus in a wide range of breast cancer settings. ClinicalTrials.gov lists 41 ongoing or completed but not reported breast cancer clinical trials that incorporate everolimus, including BOLERO-1 and BOLERO-3, which are evaluating everolimus in addition to chemotherapy plus trastuzumab in patients with breast cancer with HER2+ metastatic
disease as well as planned adjuvant trials for patients with hormone receptor–positive disease.

Based on currently available results, when used in combination with exemestane, everolimus can slow progression of advanced breast cancer in patients with hormone receptor–positive, HER2 disease in whom therapy with anastrozole or letrozole has failed. The toxicity caused by the addition of everolimus requires careful monitoring but should be balanced against the associated improved clinical outcome. The current US Federal Drug Administration’s label indication for exemestane and letrozole supports first-line use for recurrence after adjuvant therapy with anastrozole or letrozole.

Conclusion

Therapy of advanced breast cancer is based on tumor receptor status (ER and HER2), previous adjuvant therapy exposure, and patient symptoms and extent of disease. Initial hormone therapy represents the standard of care for patients with ER+, HER2– advanced breast cancer without visceral crisis. The optimal sequence for use of the available therapies—including tamoxifen, nonsteroidal aromatase inhibitors (anastrozole, letrozole), the steroidal aromatase inhibitor exemestane, fulvestrant, and now exemestane plus everolimus—is not established.

Currently, most patients with advanced breast cancer will be diagnosed after recurrence while receiving or after completing adjuvant nonsteroidal aromatase inhibitor therapy. In that setting, the EFECT trial results suggest that fulvestrant 250 mg and exemestane represent equivalent therapies. The phase II FIRST trial results suggest that fulvestrant 500 mg may be superior to nonsteroidal aromatase inhibitor use and the SWOG SO226 trial also supports potential for fulvestrant use in the first-line setting. Results from the recently reported BOLERO-2 phase III trial identify everolimus in combination with exemestane as a new therapeutic option for hormone receptor–positive disease in patients with advanced breast cancer after failure of nonsteroidal aromatase inhibitors. The sequencing decision for first-line therapy in advanced disease for the common situation of previous adjuvant nonsteroidal aromatase inhibitor treatment between fulvestrant or the exemestane plus everolimus combination requires consideration of both the therapeutic efficacy and toxicity profiles of these regimens.

Disclosure

Dr. Chlebowski is a consultant for Novartis, AstraZeneca, and Pfizer. He has received honorarium from Novartis and grant funding from Amgen.

References


