The majority of invasive breast cancer patients present with hormone receptor-positive disease, and modulation of estrogen receptor (ER) activation is an essential component of systemic adjuvant therapy for these women. While tamoxifen has traditionally been the primary adjuvant endocrine therapy for all ER-positive women, recent trials evaluating the use of aromatase inhibitors (AIs) have challenged this standard in postmenopausal women, and ongoing trials are examining the optimal use of endocrine therapy in younger women. Issues regarding the optimal approach to endocrine therapy in both pre- and postmenopausal women are examined in this review.

Drs. Cianfrocca and Wolff have provided a thoughtful and thorough review of the current data regarding the use of endocrine therapy in women with hormone receptor-positive breast cancer. We have made significant progress in our understanding of the basic mechanisms of endocrine therapy and resistance, as well as improvements in the clinical care of women with hormone receptor-positive breast cancer. Many questions remain unanswered, however, and the recent progress should not give rise to complacency.

Uncertainties of Treating Premenopausal Women
We still know far less about endocrine therapy in younger women than in their older counterparts. In older women, we have entered a post-tamoxifen era, in which we have treatments that have proven to be better than tamoxifen alone. In contrast, a 5-year course of tamoxifen therapy remains standard in premenopausal women, and the role of additional treatment is still uncertain. Among the unanswered questions in premenopausal women with hormone receptor-positive breast cancer is whether ovarian suppression/ablation (OS/OA) adds to the benefit of chemotherapy plus tamoxifen, or even tamoxifen alone. Is OS/OA with an aromatase inhibitor better still? The ongoing Suppression of Ovarian Function Trial (SOFT), Tamoxifen and Exemestane Trial (TEXT), Premenopausal Endocrine Responsive Chemotherapy (PERCHE), and Austrian Breast and Colorectal Cancer Study Group (ABCSG) trials should provide critical answers.

Many more questions exist and punctuate our discussions with patients in clinic. Which groups of premenopausal women with hormone receptor-positive breast cancer should be treated with chemotherapy vs endocrine therapy vs both? We know that, as a group, patients with hormone receptor-positive breast cancer benefit from the addition of chemotherapy to hormone therapy.[1] However, data from studies utilizing the multigene assay Oncotype DX suggest there is a subset of patients who receive little or no benefit from the addition of chemotherapy to tamoxifen.[2] It is likely that there are women who similarly receive little benefit from endocrine therapy. In general, we are willing to consider endocrine therapy in exchange for a very small benefit because it tends to be so well tolerated. Nevertheless, a 5-year (or longer) course of such therapy can be costly and may be associated with a constellation of side effects, including vasomotor symptoms, bone loss, and sexual difficulties. As we try to become more selective about our use of breast cancer treatments, it will be important to identify patient populations with hormone receptor-positive breast cancer who may not need or benefit from endocrine treatment.

Treatment Duration and Late Recurrence
The optimal duration of endocrine therapy remains a critical question. There is a growing appreciation of the risk of late recurrences in women with hormone receptor-positive disease. More than half of all recurrences are identified more than 5 years after diagnosis.[3] In addition, the results from the MA.17 trial unequivocally indicate that an active treatment can significantly lower the risk of late recurrence.[4] For some patients, however, the risks of therapy will outweigh the benefits. We will need to develop predictors of late recurrence, with the hope that we can be more selective in our treatment decisions in that setting as well. Finally, what is the role of extended therapy in premenopausal women? At the present time, a woman who remains premenopausal at the completion of a 5-year course of tamoxifen has no established treatment options, and clinical trials are not addressing this group of patients. Although it would take a multinational effort, a trial looking to reduce the risk of recurrence in this patient population is warranted.
Trials of New Targeted Agents
The development of a new generation of targeted agents has raised a number of questions about the role of endocrine therapy administered in conjunction with other treatments. The TAnDEM trial, a randomized, phase III trial evaluating anastrozole (Arimidex) plus trastuzumab (Herceptin) vs anastrozole alone in postmenopausal women with advanced, HER2-positive breast cancer demonstrated a doubling in progression-free survival from 2.4 to 4.8 months ($P = .0016$) and an increased response rate from 6.8% to 20.3% ($P = .018$). These results clearly indicate that there is a group of patients for whom endocrine therapy is not effective, though it is uncertain if the benefit of trastuzumab is additive or synergistic.

While these study results support the use of an aromatase inhibitor with trastuzumab, the modest improvement in response rate and time to progression in the absence of a survival benefit does not eliminate the option of endocrine therapy alone in these patients. The question partially hinges on whether resistance to hormonal therapy may be, at least in part, mediated through the HER2 pathway. Preclinical data support this notion, and would suggest that interfering with the EGFR pathways may be important to restoring or prolonging endocrine sensitivity.[5-7] This premise is being addressed in the recently opened phase III Cancer and Leukemia Group B (CALGB) clinical trial of fulvestrant (Faslodex) with or without lapatinib (Tykerb) in postmenopausal women with HER2-positive, hormone receptor-positive breast cancer.

The Southwest Oncology Group (SWOG) trial S0226, which compares anastrozole alone or in combination with fulvestrant in postmenopausal women with hormone receptor-positive breast cancer, is revisiting the question of combined hormonal therapy, based on preclinical evidence that a pure antiestrogen and an aromatase inhibitor may provide greater tumor suppression than either alone. If this study demonstrates positive results, it will likely lead to a large adjuvant effort. Finally, the CALGB will also be investigating the role of angiogenesis inhibition administered in combination with endocrine therapy. Preclinical data have suggested that estrogen may stimulate angiogenesis.[8,9] In this planned study, women with advanced breast cancer will be randomized to endocrine therapy alone vs endocrine therapy plus bevacizumab.

Conclusions Drs. Cianfrocca and Wolff have summarized the state of the art of endocrine therapy for women with breast cancer. Their review clearly demonstrates that we have a long way to go before we truly know how to optimize such therapy for our patients. Though we have made much progress, in the words of Robert Frost, we have "miles to go before (we) sleep."

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—Eric P. Winer, MD

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