

TRANSLATING ADVANCES IN HORMONAL THERAPIES FOR BREAST CANCER INTO CLINICAL PRACTICE

A continuing education monograph for oncology professionals

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TRANSLATING ADVANCES

IN HORMONAL THERAPIES FOR BREAST CANCER INTO CLINICAL PRACTICE

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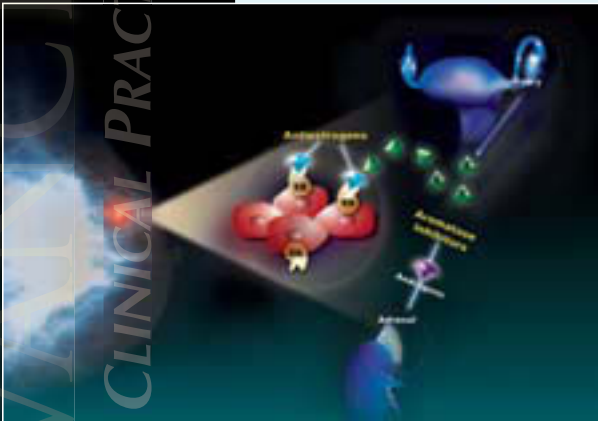
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TARGET AUDIENCE

The target audience for this educational activity includes oncology physicians who treat patients with breast cancer or who have an interest in learning about treatment options and considerations for this group of patients.

ACTIVITY RATIONALE AND PURPOSE

The American Cancer Society estimates that in 2006 there will be 214,640 new cases of invasive breast cancer among women in the United States and an estimated 41,430 women will die of this disease. Despite decreases in breast cancer death rates, primarily due to earlier detection and improved treatment, the 5-year survival rate for women with distant breast cancer metastasis is 26%. Five years of treatment with tamoxifen was considered the gold standard for adjuvant treatment of hormone-dependent breast cancer until recent trials indicated that aromatase inhibitor treatment further reduces the risk of disease recurrence and genetic profiling has begun to identify why some tumors are resistant to hormonal therapies. Because of these and other advances in the field, oncologists must critically process a very large body of new data to determine the most appropriate disease management strategy for each of their patients.

LEARNING OBJECTIVES

After completing this activity, physicians should be able to

- Describe current adjuvant treatment strategies for hormone-dependent operable breast cancer and discuss supporting evidence for treating premenopausal and postmenopausal patients
- Describe the current recommendations for management of advanced-stage hormone receptor-positive breast cancer
- Discuss the heterogeneity of estrogen receptors and endocrine therapy resistance in breast cancer and the implications that various subtypes may have on diagnosis, prognosis, and treatment
- Identify current and emerging methods for assessing molecular markers in breast cancer, and describe how they may be incorporated into clinical practice
- Describe the rationale for combining endocrine therapies with other targeted therapies in the management of breast cancer

When choosing among continuing education activities, clinicians should select those that are appropriate for their educational needs. Participants in educational activities have the implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional effectiveness. Clinicians should reflect on this activity and its applicability to their own patient population, and then identify and implement appropriate practice changes.

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PRODUCT DISCLOSURE

Clinical trials for the following drugs have been halted: BAY 12-9566, Marimastat, and U5416.

Generic Name	Trade Name	Investigational for Breast Cancer	FDA Approved for the Treatment of Breast Cancer	FDA Approved for Other Indications
Aminoglutethimide	Cytadren	√		√
Anastrozole	Arimidex		√	
Atamestane	–	√		
Cyclophosphamide	Cytosan, Neosar		√	√
Doxorubicin	Adriamycin		√	√
Exemestane	Aromasin		√	
Fluorouracil (5-FU)	Adrucil		√	√
Fluoxymesterone	Androxy		√	√
Fulvestrant	Faslodex		√	
Goserelin acetate	Zoladex		√	√
Letrozole	Femara		√	
Leuprolide (leuporelin) acetate	Eligard, Viadur	√		√
Megestrol acetate	Megace		√	√
Methotrexate	Various		√	√
RAD001		√		
Raloxifene	Evista	√		√
Tamoxifen citrate	Nolvadex		√	
Temsirolimus (CCI-779)		√		
Toremifene citrate	Fareston		√	
Trastuzumab	Herceptin		√	
Vorzole	Rivizor	√		

Agents may be approved for use in combination.

Adapted from *Drug Facts and Comparisons*. St Louis, Mo: Facts & Comparisons; 2006.

Editorial

Clifford Hudis, MD

For more than 100 years, endocrine manipulations have been known to produce therapeutic responses in a subset of women with advanced breast cancer. Since the initial observation that surgical removal of the ovaries produced a marked regression of breast cancer in a premenopausal woman, the identification of estradiol in the 1920s and the characterization of its endogenous receptor some 40 years later facilitated a series of advances that have defined current prevention and treatment strategies.¹⁻³ Among the most significant of these advances was the development and marketing of the first selective estrogen receptor modulator (SERM), tamoxifen, during the 1970s. Since that time, hundreds of clinical trials in all stages of breast cancer have identified a number of factors beyond the threshold concentration of tumor cell estrogen receptors that influence response to tamoxifen and other endocrine manipulations and have defined the optimal dosing, duration, and combinations of such therapies. Simultaneously, laboratory investigations defined the molecular basis of estrogen signaling through the estrogen receptors, the response of cancer cells to the modulation of estrogen receptor signaling, and the influence of gene expression profiles on the heterogeneity of ER expression. The convergence and impact of these advances is summarized in the articles within this monograph which describe the evidence supporting current treatment guidelines and the many questions that remain in defining the optimal management of hormone receptor-positive breast cancer.

Tamoxifen was included in all standard adjuvant regimens for estrogen receptor-positive (ER+) breast cancer in both pre- and postmenopausal women for many years. Although tamoxifen clearly reduces the risk of disease recurrence, there are risks such as endometrial cancer and thromboembolic complications associated with its use.⁴⁻⁶ In addition, the balance of potential benefits and risks of continuing therapy beyond the usual 5 years has also been the subject of much discussion. In the article by Drs Strasser-Weippl and Goss, the benefit of endocrine therapies such as tamoxifen appears to correlate with the concentration of hormone receptors; however, in most clinical trials, an arbitrary cutoff to determine ER positivity has been made. A more quantitative determination of the concentration of estrogen and progesterone receptors using immunohistochemistry will likely better define the subset of women who are most likely to benefit from hormonal therapies, especially in premenopausal women.⁷

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In recent years, the aromatase inhibitors (AIs) have been shown to be equivalent or superior to tamoxifen in terms of disease recurrence and safety in postmenopausal women^{8,9}; however, as described by Drs Strasser-Weippl and Goss, there are still many unanswered questions regarding the relative efficacy of the various AIs, the benefit of total estrogen blockade using AIs in combination with SERMs, the sequencing of agents, and the duration of therapy. Although the AIs would not be appropriate endocrine monotherapy for premenopausal women, their potential benefit in combination with ovarian function suppression or tamoxifen with or without chemotherapy is currently being evaluated in several important clinical trials.

In women with advanced breast cancer, the greatest challenge has been the development of resistance to tamoxifen or other endocrine therapies. More detailed understanding of modulation of the estrogen receptor growth factor signaling pathways and the expression of other markers such as HER2/*neu* are providing greater insight to defining prognosis and individualizing treatment. The availability of several antiestrogens (SERMs and SERDs) as well as both steroidal and nonsteroidal AIs raises many questions regarding optimal sequencing and combinations of endocrine therapies, and the impact on the development of endocrine resistance and patient safety. As described by Dr Pritchard, emerging information from clinical trials is beginning to answer some questions regarding cross-resistance and optimal sequencing; however, there is still much to be learned.

Recent evidence has demonstrated that multiple mutations in the estrogen receptor growth factor signaling pathways are likely to be responsible for heterogeneity of ER+ breast cancer and the development of clinical resistance to endocrine therapies. Drs Cynthia Ma and Matthew Ellis provide an intriguing discussion on the emerging importance of new tests to further define

these mutations. Correlation of specific somatic mutations with prognosis and treatment outcomes hopefully will guide the development of new treatment approaches, but the evidence assessing the overall value of these tests must be compiled using sound laboratory practices, well-designed clinical trials, and careful correlation of clinical outcomes.

Previous clinical trials and molecular research have paved the way for the current generation of clinical trials which are examining important questions that will help us integrate more patient- and tumor-specific information about breast cancer into the next generation of evidence-based guidelines and further improve the prognosis for women with hormone

receptor-positive breast cancer. It is as well possible that one size will never fit all and that patient- and tumor-specific information will in fact allow us to tailor therapy to the individual. The critical components of this progress will remain the creative investigators whose thoughts and insights are contained in these papers, and the patients who will enroll in these important clinical trials.

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Strategies for Adjuvant Therapy in Women With Hormone Receptor–Positive Breast Cancer

Kathrin Strasser-Weippl, MD
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INTRODUCTION

Approximately three quarters of all patients with invasive breast cancer have hormone receptor–positive disease, ie, the tumor cells express either estrogen receptors (ER) or progesterone receptors (PR) or both. ER-positive (ER+) and PR-positive (PR+) breast cancers offer the opportunity of treatment with endocrine agents that work by either blocking the hormone receptor itself or reducing circulating levels of the substrate binding to the receptor. In the following paper, the present status of adjuvant endocrine treatment in both premenopausal and postmenopausal women will be summarized.

PREMENOPAUSAL SETTING

Because adjuvant chemotherapy, which is administered to many premenopausal breast cancer patients, leads to ovarian dysfunction in a large proportion of women, the effect of endocrine interventions in this patient population has been difficult to interpret. In addition, many trials evaluating premenopausal breast cancer patients have included women with both hormone receptor–positive and –negative disease, and numerous studies have been small and statistically underpowered.

When summarizing the available data on adjuvant endocrine treatment in premenopausal women, several issues have to be considered. First, in women treated with both chemotherapy and endocrine therapy, the specific effects of each of these treatments alone are uncertain. Second, in women treated with ovarian function suppression (OFS), the best type and optimal duration of adjuvant therapy is still unclear, even more so when OFS is combined with other endocrine interventions, such as selective estrogen receptor modulators (SERMs), selective estrogen receptor downregulators (SERDs), or aromatase inhibitors (AIs). Third, in premenopausal women the effectiveness of endocrine therapies correlates with the concentration of steroid receptors on the tumor cells.^{1–3} However, in many studies, an arbitrary cutoff for ER and PR expression was used, which may have led to a dilution of the effect of endocrine treatments on highly hormone-sensitive disease. In the future, accurate discrimination of patients with strongly or weakly hormone-sensitive disease for endocrine treatment and for clinical trials will be important. It is

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recommended to use immunohistochemistry to determine ER and PR overexpression, and to report the results quantitatively instead of using a cutoff.^{4,5}

Ovarian Function Suppression

The use of ovarian ablation for the treatment of breast cancer goes back to the 19th century, when A. Schinzinger and G. Beatson produced remissions by performing bilateral oophorectomy in premenopausal patients with advanced breast cancer.^{6,7} In 1948, the first randomized trials of OFS in the adjuvant setting were started. Finally, in 1996, it was firmly established by the meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) that OFS leads to a significant improvement in relapse-free and overall survival in women under 50 years of age.³

METHODS OF OVARIAN FUNCTION

SUPPRESSION.—There are three known methods of OFS. The first form of OFS that was tested in clinical trials was surgical oophorectomy. This method has the advantage of additionally reducing the risk of ovarian cancer in predisposed women. However, as for every form of surgery, surgical oophorectomy is associated with certain perioperative morbidity and mortality. Radiation-induced OFS is safe, but it may be incomplete and OFS may be delayed in some women.⁸ Both surgical and radiation-induced OFS have the strong disadvantage of being irreversible and are associated with infrequent but significant comorbidities.

Suppressing ovarian hormone production by luteinizing hormone releasing hormone (LHRH) agonists has the great advantage of being safe and reversible.^{8,9} The response rates in metastatic disease are similar to surgical oophorectomy.⁹ There is no systematic comparison among the three forms of OFS. Because of its obvious advantages, the use of LHRH agonists is the preferred method of OFS used today. Due to its ability to suppress ovarian function in

some women, chemotherapy can also be seen as a form of ovarian ablation. In premenopausal women, the effects of chemotherapy on hormone-sensitive breast cancer are due to two different effects: direct cytotoxicity on tumor cells, and ovarian failure.¹⁰ However, the extent of the endocrine effect of chemotherapy is unknown as the risk of chemotherapy-induced ovarian failure is age-related and variable.¹¹ Overall, less than 50% of women under the age of 40 will become postmenopausal due to chemotherapy. On the other hand, most women aged 40 years or older will be rendered postmenopausal by chemotherapy. The rate of chemotherapy-induced amenorrhea is also dependent on the kind of chemotherapy used, ranging from approximately 40% after 4 cycles of doxorubicin and cyclophosphamide, to up to 70% after 6 cycles of oral cyclophosphamide, methotrexate, and 5-fluorouracil (CMF).¹²

EFFICACY OF OVARIAN FUNCTION

SUPPRESSION AS MONOTHERAPY.—It was shown by the EBCTCG meta-analysis of 1996 that OFS significantly improves recurrence-free and overall survival compared to controls in women less than 50 years of age.³ This meta-analysis included 12 of the 13 trials of OFS by irradiation or surgery, but no study on OFS by drugs. As menopausal status had not been consistently assessed in the trials and women over 50 years did not benefit from OFS, the main analysis was confined to women of less than 50 years of age. In the trials including chemotherapy, the net effect of OFS was smaller, most probably due to endocrine effects of chemotherapy. Less than 60% of all women included in the analysis had tumors known to be ER+.

In several studies, OFS was compared to chemotherapy in premenopausal women. In particular, the Zoladex

Early Breast Cancer Research Association (ZEBRA) and the International Breast Cancer Study Group (IBCSG) VIII studies compared goserelin with 6 cycles of CMF in node-positive and node-negative breast cancer patients, irrespective of ER status.¹³⁻¹⁵ Not surprisingly, CMF was superior to endocrine therapy in ER-negative patients, whereas in the ER+ cohort, goserelin and CMF were equal. The latter finding was confirmed by the Scandinavian trial and the Takeda Adjuvant Breast cancer study with Leuprorelin Acetate (TABLE).^{16,17} When patients were grouped according to the rate of ER expression in the Scottish Cancer Trials Breast Group ICRF Unit (SCTBG) trial, it was shown that patients with highly ER-expressing tumors benefited more from endocrine treatment, whereas those with weakly ER-expressing tumors did better on chemotherapy.¹⁸

SERMs and SERDs

In 1998, the efficacy of 5 years' therapy of the SERM tamoxifen in premenopausal and postmenopausal breast cancer patients was confirmed by the EBCTCG meta-analysis that included 37,000 women.² Adjuvant treatment with 5 years of tamoxifen resulted in a reduction

of 47% in disease recurrence, and a mortality reduction of 26%.² The effect of tamoxifen was confined to patients with ER+ tumors, but was independent of axillary lymph node involvement, age, tamoxifen dose, menopausal status, or use of chemotherapy. In premenopausal patients with hormone-responsive disease, tamoxifen given after chemotherapy led to a risk reduction of 40% for recurrence and of 39% for mortality.² Based on these data, the 2000 US National Institutes of Health Consensus Development Conference recommended the use of adjuvant tamoxifen therapy for women "regardless of age, menopausal status, involvement of axillary nodes, or tumor size."¹⁹ Apart from tamoxifen, no other SERM and no SERD has been tested in the adjuvant setting in premenopausal women.

Combined Endocrine Treatment

OFS PLUS TAMOXIFEN.—Several adjuvant studies have compared OFS plus tamoxifen with chemotherapy. In premenopausal patients with hormone-sensitive disease, the combination is safe and at least as effective as chemotherapy.¹² The question as to whether chemotherapy is at all necessary in premenopausal

Table.—The Adjuvant SOFT, TEXT, and PERCHE Trials

Trial Name	Main Inclusion Criteria	Treatment Arms
SOFT Suppression of Ovarian Function	Premenopausal after adjuvant chemotherapy	TAM for 5 y OFS + TAM for 5 y OFS + EXE for 5 y
TEXT Tamoxifen and Exemestane Trial	Premenopausal Receive GnRH agonist	OFS (+/- CT) + TAM for 5 y OFS (+/- CT) + EXE for 5 y
PERCHE Premenopausal Endocrine Responsive Chemotherapy Trial	Premenopausal Receive GnRH agonist	OFS + TAM/EXE for 5 y OFS + CT + TAM/EXE for 5 y

CT = chemotherapy; EXE = exemestane; OFS = ovarian function suppression; TAM = tamoxifen. Data from Strasser-Weippl and Goss.²⁰

patients with hormone-responsive disease is addressed in the ongoing Premenopausal Endocrine Responsive Chemotherapy (PERCHE) Trial (Table). In this study, OFS plus chemotherapy followed by tamoxifen or exemestane is compared to OFS plus tamoxifen or exemestane without chemotherapy. All patients in this trial must have hormone receptor-positive tumors, and they must have premenopausal hormone levels confirmed within 12 weeks of primary surgery.

OFS PLUS AROMATASE INHIBITORS.—AIs have brought about a significant change in the treatment of postmenopausal breast cancer patients. In premenopausal women, however, AIs given as monotherapy are ineffective in suppressing ovarian hormone production, and may cause ovarian hyperstimulation.²¹ Their use is thus currently restricted to being given in combination with OFS. The first evidence that AIs are effective in combination with LHRH agonists in premenopausal women came from a study using goserelin plus anastrozole after progression on goserelin plus tamoxifen in patients with advanced breast cancer.²² The use of AIs combined with OFS with or without chemotherapy or tamoxifen is now being investigated in 3 ongoing trials, Suppression of Ovarian Function Trial (SOFT), Tamoxifen and Exemestane Trial (TEXT), and PERCHE. The trial designs are shown in the Table. SOFT addresses the question of whether OFS should be initiated in patients who remain premenopausal after completion of adjuvant chemotherapy, and whether OFS plus exemestane is superior to OFS plus tamoxifen. TEXT will determine whether tamoxifen or exemestane is superior when combined with OFS prior to initiation of chemotherapy in premenopausal patients. Finally, PERCHE will help to tell whether the use of chemotherapy is necessary in

premenopausal patients with hormone-sensitive disease who receive OFS plus tamoxifen or exemestane.

Endocrine Treatment Plus Chemotherapy

Chemotherapy, tamoxifen, and OFS are all effective treatments in premenopausal patients, but little is known about their respective effects when combined. In the IBCSG trial VIII, pre- and perimenopausal breast cancer patients received goserelin for 2 years, or 6 cycles of CMF, or the chemotherapy followed by 18 months of goserelin.¹³ Patients with ER+ tumors had equivalent outcomes with goserelin and CMF. With the combined treatment, a nonsignificantly better outcome was achieved. As discussed above, the SOFT study is further investigating whether patients who remain premenopausal after the completion of adjuvant chemotherapy should receive OFS, or whether tamoxifen alone is sufficient.

POSTMENOPAUSAL SETTING

Tamoxifen

The available data on the use of tamoxifen in the adjuvant setting have been extensively reviewed by the EBCTCG,^{2,23} and the recommendations by the National Institutes of Health and the St Gallen 2001 Seventh International Conference on Adjuvant Therapy of Primary Breast Cancer held in St Gallen, Switzerland, to use tamoxifen in the adjuvant setting of patients with ER+ breast cancer apply to postmenopausal patients as well. However, in the postmenopausal setting, AIs are increasingly challenging the role of tamoxifen and becoming an important part in the endocrine treatment of postmenopausal patients with ER+ tumors.

Aromatase Inhibitors

AIs work by blocking the enzyme complex responsible for the final step

in estrogen synthesis, aromatase, thus preventing the production of the ligand of the ER. The AIs are generally divided into nonsteroidal and steroidal types. The major nonsteroidal types available are anastrozole and letrozole. The available steroidal AI is exemestane. The nonsteroidal AIs bind to the heme part of the enzyme and this binding is reversible. The steroidal AIs, on the other hand, bind to the substrate binding site of the enzyme. This binding is irreversible; thus, these drugs are often referred to as aromatase inactivators. This irreversible binding could, in theory, provide some additional benefit, but that benefit remains to be proven in clinical trials.

In contrast to the premenopausal situation, all of the third generation AIs suppress circulating estrogen levels by approximately 98% in postmenopausal women.²⁴⁻²⁶ At least 10 adjuvant trials with AIs, including over 40,000 women, are currently ongoing or have been completed. The results of 4 of them have shown that the outcome of postmenopausal breast cancer patients with hormone-sensitive tumors can be improved if AIs are included in the adjuvant treatment strategy. However, it is still unclear which patients should be given AIs within the first 5 postoperative years, and in whom it is more beneficial to give AIs following 5 years of tamoxifen, thus extending the overall treatment duration.

Several large trials have evaluated the use of AIs within the first 5 postoperative years. Results from the first of these studies, the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial (anastrozole, tamoxifen, and combined, n = 9,366), were published in 2002 and last updated in 2005.^{27,28} The intent-to-treat analysis showed that when anastrozole was compared to tamoxifen for 5 years, the AI led to improved disease-free survival (DFS) (hazard

ratio [HR] 0.87, $P = .01$) and time to recurrence (HR 0.79, $P = .0005$) after a median follow-up of 68 months.^{29,30} To date, there is no difference in the rates of death from any cause or of breast cancer-related deaths.

In the Intergroup Exemestane Study (IES) trial, 4,742 women completing 2 to 3 years of adjuvant tamoxifen were assigned to either tamoxifen or exemestane for the remainder of the 5 years.^{31,32} After a median follow-up of 37.4 months, the HR for DFS was 0.68 ($P = .00005$) in favor of exemestane. No difference in survival has been noted yet.

Data on the comparison of tamoxifen versus letrozole for 5 years have been published from the adjuvant Breast International Group Femara-Tamoxifen (BIG FEMTA) trial.³³ BIG FEMTA is a 4-arm trial, also including 2 additional arms with a crossover design from tamoxifen to letrozole and vice versa, that is ongoing. This initial analysis compared the two groups receiving letrozole initially to those receiving tamoxifen initially. After a median follow-up of 25.8 months, the HR for event-free survival was 0.81 ($P < .003$) in favor of letrozole, translating into an absolute difference of 2.6%. The risk of distant recurrence was also reduced ($P = .001$). Regarding breast cancer-free survival, the absolute difference was 3.4% in favor of letrozole ($P < .001$). Unfortunately, the crucial question whether tamoxifen followed by letrozole is superior to letrozole alone is an exploratory analysis of the trial and the trial is not powered to answer this question specifically. It will also be some time before data from this analysis will be available.³⁴

Among the other ongoing adjuvant AI studies evaluating a total of 5 years of adjuvant therapy, the ARNO (Arimidex-Nolvadex) trial is of similar design to

the study presented above. After 2 years of adjuvant tamoxifen, patients were randomized to either tamoxifen or anastrozole for the following 3 years. The ongoing FACE trial is comparing 5 years of anastrozole to letrozole in node-positive, early-stage breast cancer. Two other ongoing exemestane studies are the Tamoxifen and Exemestane Adjuvant Multicenter (TEAM) International study, comparing exemestane to tamoxifen for 5 years, and the exemestane (EXEM 027) trial, in which exemestane or placebo were given for 2 years in very low-risk patients with ER+ disease.

Based on the published data, the American Society of Clinical Oncology Technology Assessment Panel in 2005 recommends that adjuvant hormonal therapy for postmenopausal women with hormone receptor-positive breast cancer should “include an aromatase inhibitor as initial therapy or after treatment with tamoxifen. Treatment options include 5 years of aromatase inhibitor treatment or sequential therapy consisting of tamoxifen (for either 2 to 3 years or 5 years) followed by aromatase inhibitors for 2 to 3 years or 5 years.”³⁵

Results from the first large study employing an AI after 5 years of tamoxifen, National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) MA-17, have also been published.^{36,37} The rationale for extending adjuvant therapy beyond 5 years is that approximately half of all breast cancer recurrences in women with ER+ tumors taking 5 years of tamoxifen occur between 5 to 15 years after surgery, and that the risk of recurrence appears to continue indefinitely.²² In MA-17, after having completed 4.5 to 6 years of prior adjuvant tamoxifen, a total of 5,187 women were randomized to 5 further years of letrozole 2.5

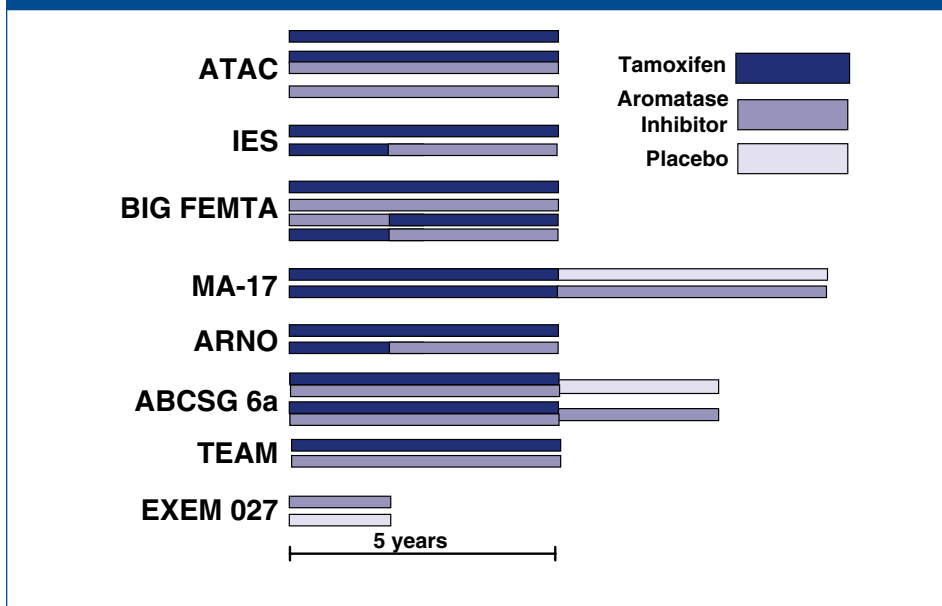
mg daily or placebo. After a median follow-up of 2.5 years, women on letrozole had a significantly superior DFS (HR 0.57, $P = .00008$) and there was a trend towards improved overall survival. Based on the first interim analysis, the trial was terminated by the independent data and safety monitoring committee in order to offer women taking placebo an opportunity to take letrozole.

In the Austrian Breast Cancer Study Group trial (ABCSCG 6a), patients completing 5 years of adjuvant tamoxifen, either as monotherapy or combined with aminoglutethimide, were randomized to a further 3 years of anastrozole or no treatment. After a median follow-up of 60 months, significantly fewer patients in the anastrozole group experienced disease recurrence compared with placebo (HR 0.64; $P = .047$).³⁸

The data from MA-17 and ABCSCG 6a show that extending adjuvant endocrine therapy beyond 5 years with an AI offers significant benefit in DFS for patients who are relapse-free after 5 years of adjuvant treatment. MA-17 patients completing 5 years of letrozole are now being re-randomized to a further 5 years versus placebo. This will allow duration of efficacy and toxicity to be further evaluated. Another trial testing an AI after tamoxifen in the adjuvant setting, the National Surgical Adjuvant Breast Project (NSABP) B-33 study, was discontinued based on the results of MA-17.

The trial designs of ongoing and completed adjuvant AI studies are shown in the Figure. In summary, a direct comparison of each of the 3 AIs for 5 years versus tamoxifen for 5 years is now available. In all three large trials, the AI was superior to tamoxifen. However, giving both an AI and

Figure.—Ongoing and completed breast cancer trials including aromatase inhibitors. (From Strasser-Weippl and Goss,³⁹ with permission.)



tamoxifen sequentially might be even more superior. This strategy is being tested with all 3 inhibitors following 2 to 3 years of tamoxifen, and data coming from the IES look promising. The inverse sequence, tamoxifen given after 2 to 3 years of an AI, will only be evaluated in the BIG FEMTA trial with letrozole.

In the future, it has to be clarified whether 5 or more years of an AI as an initial treatment are better than sequential treatment with tamoxifen followed by an AI for 5 or more years. Important data pertaining to this issue will come from the ongoing arms of BIG FEMTA. Cuzick et al published a model calculating recurrence rates up to 10 years for a range of efficacy parameters.⁴⁰ It showed that initial or early treatment with an AI is a better option than a strategy of using tamoxifen for 5 years initially for a wide range of parameters. It was concluded that using an AI as initial adjuvant treatment is thus a better option than switching patients to an inhibitor after 2 or more years of tamoxifen. However, in another mathematical model developed to predict the best

adjuvant strategy, the opposite was concluded.⁴¹ When patients were analyzed by receptor status of the primary tumor, sequential tamoxifen followed by an AI after 2 years appeared superior for ER+ and PR+ tumors, whereas upfront treatment with an AI yielded superior outcomes for ER+ and PR-negative tumors.

Combined Endocrine Treatment

The combination of tamoxifen and an AI in postmenopausal women has been evaluated in the adjuvant ATAC trial.²⁷ This arm was suspended when the combination was shown to be equivalent to or worse than tamoxifen alone, and significantly worse than anastrozole. The reason for this finding might be that tamoxifen is more of an estrogen agonist in an estrogen depleted environment. Thus, the use of a less agonistic SERM such as toremifene or the SERD fulvestrant plus an AI may achieve the intended “total estrogen blockade.” Toremifene plus an investigational steroidal inhibitor, atamestane, is being compared to letrozole in women with locally advanced or metastatic breast cancer. In addition,

anastrozole plus fulvestrant is being compared to anastrozole alone by the Southwest Oncology Group (SWOG) and the Fulvestrant and Anastrozole Combination Trial (FACT) in women with metastatic disease.

UNANSWERED QUESTIONS

Duration of Endocrine Therapy

Currently, tamoxifen is given for 5 years in the adjuvant setting. This strategy is based on the data from the EBCTCG overview from 1998 which showed that 5 years of tamoxifen therapy are better than 1 or 2 years of treatment. The question whether even longer tamoxifen treatment would be more beneficial was answered in part by the NSABP B-14 and the Scottish trials.⁴²⁻⁴⁴ Neither trial was able to demonstrate a benefit from continuing tamoxifen beyond 5 years. Another study published in 1996 suggested that tamoxifen for more than 5 years might be beneficial for women with lymph node-positive, ER+ tumors.⁴⁵ The ongoing Adjuvant Tamoxifen Longer Against Shorter (ATLAS) and Adjuvant Tamoxifen Treatment, Offer More? (ATTom) studies, randomizing patients to 5 versus more than 5 years of adjuvant tamoxifen, will help to clarify this issue but are not due to report for some time.

As the studies evaluating OFS used treatment durations ranging from 2 to 5 years, the optimal duration of OFS still remains unclear. Until better data regarding duration is available it is reasonable to use 5 years of OFS in view of that duration being selected by the international community for the SOFT and TEXT trials. In individual patients, however, the decision about treatment duration should be based on tolerability and other factors such as family planning.

Inclusion of Novel Agents

In future trials of endocrine therapy, the question whether to combine

endocrine treatments with one of the novel anticancer agents, in particular antibodies targeting the epidermal growth factor or insulin-like growth factor receptor family or vascular endothelial growth factor or small molecule inhibitors, must be addressed. Studies including these novel agents should be tailored to groups with hormone responsive, weakly hormone responsive, and nonresponsive disease. Furthermore, the type of endocrine therapy must be considered. For example, there are concerns that the effectiveness of tamoxifen is diminished by HER2 overexpression.⁴⁶ However, when tamoxifen is combined with OFS, it seems that the magnitude of the beneficial effect is greater in women with HER2-overexpressing tumors.⁴⁷ In the large adjuvant trials employing trastuzumab, the positive effect of the antibody on recurrence-free and overall survival was independent of menopausal status and of hormone receptor expression.^{48,49}

Comparison Between AIs

Data comparing different AIs are quite limited and as yet there are no data at all in the adjuvant setting. Letrozole was associated with a more profound suppression of aromatase than anastrozole in a small crossover study.⁵⁰ In a clinical trial in advanced disease after tamoxifen, letrozole was associated with a significantly better overall response rate (19.1% vs 12.3%, $P = .014$), but was similar to anastrozole regarding the primary end point of time to progression and several other response parameters.⁵¹ Data comparing exemestane to any of the other inhibitors are not available. A pivotal trial that will compare a nonsteroidal AI with a steroidal inhibitor is the large international adjuvant trial currently under way comparing anastrozole to exemestane (MA-27). This trial will also compare the toxicities of these two classes of AIs and a bone substudy will specifically evaluate

differences in bone metabolism. The Femara vs Anastrozole Clinical Evaluation (FACE) trial is comparing anastrozole and letrozole in node-positive patients.

Sequential Use of AIs

As discussed previously, several important trials have demonstrated that AIs used sequentially following tamoxifen are beneficial in reducing recurrence of breast cancer. In addition, as discussed in the next article in this monograph, the use of exemestane following disease progression during treatment with a nonsteroidal AI has also shown clinical benefit.⁵² Although these data raise the question of the potential benefit of using AIs in sequence, there are no adjuvant studies exploring this strategy.

TOLERABILITY AND RISK OF ADJUVANT ENDOCRINE THERAPY

As with any adjuvant therapy, the risks or potential adverse consequences associated with endocrine therapies must be carefully balanced against the potential benefits. For individuals who have been rendered disease-free following primary surgery and who have varied risk of disease recurrence, concern is legitimately raised regarding both acute and long-term toxicities that may range from discomforting menopausal symptoms to secondary cancers. Over the past several decades, numerous adjuvant and prevention trials have provided a great deal of insight regarding the risks and benefits associated with tamoxifen therapy.^{2,53} Likewise, the long-term risks of OFS are also well characterized. In general, the third generation AIs are considered well tolerated. Toxicity information from studies comparing AIs to megestrol acetate therapy for metastatic disease indicates that the short-term adverse effects that included low-grade hot flashes, headache, nausea, and fatigue were equivalent to or less severe than the megestrol acetate adverse effects.⁵⁴⁻⁵⁷

Data from the now mature adjuvant studies using AIs, however, provide greater insight regarding the relative long-term risks.^{33,36-38} The specific adverse effects and general tolerability of the various endocrine therapies are discussed in the next sections.

Menopausal Symptoms and General Tolerability

As ovarian ablation renders premenopausal patients postmenopausal, the side effects of this intervention include risks and symptoms of menopause. One of the adjuvant trials which carefully evaluated the side effects of ovarian ablation and compared them to chemotherapy was the ZEBRA study.¹⁵ In this adjuvant breast cancer study, 1,640 pre- or perimenopausal patients were randomized to receive CMF chemotherapy for 6 cycles or the LHRH agonist goserelin for 2 years. As expected, the side effects of the LHRH included menopausal symptoms such as hot flashes (60.4%), vaginal dryness (25.9%), and amenorrhea (> 95%). After cessation of treatment, more than 90% of patients below 40 years of age had a return of menstruation.

More than 28,000 women with normal or increased risk of breast cancer participated in the 4 major chemoprevention trials that compared tamoxifen to placebo.⁵⁸⁻⁶² As anticipated based on the antiestrogenic effects, women receiving tamoxifen experienced a higher incidence of hot flashes, vaginal discharge, and abnormal vaginal bleeding. The NSABP P-1 study also included tools for self-assessment of depression, medical outcomes, and sexual functioning, and no differences were observed between the 2 groups relative to any of these tools.⁵⁸

In trials that compared either letrozole or anastrozole to tamoxifen as initial adjuvant therapy for early-stage

breast cancer, the AIs appeared to be associated with a lower incidence of hot flashes, vaginal discharge, and abnormal vaginal bleeding.^{27,33} In the ATAC trial, patients receiving anastrozole alone experienced significantly less of these adverse effects than patients receiving tamoxifen alone; however, a parallel QOL assessment did not show any difference between the 3 treatment groups.⁶³ The decreased incidence of abnormal vaginal bleeding reflects the nonstimulatory or negative effect of the AIs on the endometrium. Other bothersome side effects such as nausea, headache, fatigue, mood disturbances, and dizziness were equivalent in the ATAC trial. In trials that initiated an AI after several years of adjuvant tamoxifen, these symptoms were also evaluated. The IES trial randomized women who had received 2 to 3 years of adjuvant tamoxifen to either exemestane or continuation of tamoxifen. Gynecologic symptoms, vaginal bleeding, and muscle cramps were more frequent in patients continuing tamoxifen, but arthralgias and diarrhea were more commonly associated with exemestane.³²

The MA-17 study randomized women who had completed 5 years of adjuvant tamoxifen to either letrozole or placebo. Hot flashes were more frequent in the letrozole arm (47.2% vs 40.5%). Arthralgia, myalgia, and arthritis were also more common in the letrozole arm. Most symptoms were mild to moderate or National Cancer Institute Common Toxicity Criteria (NCI CTC) grade 1 or 2. Other symptoms such as fatigue, sweating, constipation, headache, and dizziness were equivalent between the 2 arms.³⁶

Lipid Metabolism

Over the past several decades, there has been much discussion regarding the effect of estrogen on lipid

metabolism and cardiovascular disease. Although the addition of exogenous estrogen following menopause was believed to have a cardioprotective benefit, the results of the Women's Health Initiative Study suggest that estrogen plus progestin does not confer a cardiovascular benefit.⁶⁴ The effect of both hormonal and cytotoxic chemotherapy on cardiovascular risk has also been widely studied due to the effect that these interventions have on lipid metabolism. It is particularly important in women receiving adjuvant therapy because the long-term risks associated with any therapeutic intervention will have more impact long-term, and because cardiovascular disease is so prevalent and is the leading cause of death in women with early-stage breast cancer.⁶⁵

The antiestrogenic effect of tamoxifen has been shown to produce changes in plasma lipids that may be associated with reductions in cardiovascular disease. Several studies have reported small decreases in total and low-density lipoproteins (LDL) and small increases in high-density lipoproteins (HDL).^{66,67} Retrospective analysis of three large randomized trials comparing tamoxifen to either placebo or no therapy demonstrated a reduction in coronary heart disease (CHD),⁶⁸⁻⁷⁰ but the NSABP P-1 tamoxifen prevention trial did not report such a benefit.⁵⁸ In the NSABP study, there were 2.73 ischemic events per 1,000 women in those receiving tamoxifen compared to 2.37 per 1,000 women receiving placebo (RR = 1.15; 95% CI, 0.81–1.64).

Conflicting results have been reported regarding the effects of the AIs on lipid metabolism.⁷¹ While a number of studies have reported an increase in total cholesterol among women receiving letrozole,⁷² others have not observed this effect.^{33,73,74} Many

of the AI studies have also reported conflicting evidence in the incidence of cardiovascular events. In the updated analysis of the adjuvant MA-17 study, there was no trend towards a higher rate of cardiovascular events in the letrozole group compared to placebo.^{36,74} The lipid substudy of MA-17 showed that letrozole does not significantly alter serum cholesterol or triglycerides in nonhyperlipidemic postmenopausal women with primary breast cancer treated up to 36 months following at least 5 years of adjuvant tamoxifen therapy.⁷⁵ Importantly, the Breast International Group (BIG) 1-98 trial showed a similar incidence of cardiovascular events in women on the letrozole arm of the trial compared to those on tamoxifen but slightly more women in the letrozole group had serious cardiac events ($P < .001$). It is unclear whether this is due to protective effects of tamoxifen or adverse effects of letrozole.³³ An adjudication by external experts of all cardiovascular events in the BIG 1-98 trial as well as MA-17 is currently under way.

The effect of anastrozole, tamoxifen, or the combination on serum lipids was not systematically collected from the ATAC trial; however, anastrozole was associated with a slightly higher, but insignificant, rate of ischemic cardiovascular disease.^{27,28} The Italian Arimidex Trial and a small study by Hozumi and colleagues reported increased cholesterol in patients receiving anastrozole.^{76,77} Several other studies with anastrozole showed no effect on serum lipids.^{78,79}

A preclinical trial in ovariectomized rats reported that exemestane improved the serum lipid profile in treated rats compared with either oophorectomy or letrozole.⁸⁰ In a number of reports, exemestane has had different effects on lipid metabolism than the nonsteroidal

Als. When compared to tamoxifen as first-line therapy for metastatic breast cancer, no adverse effect on total cholesterol or HDL cholesterol was associated with either drug and exemestane had a beneficial effect on triglyceride levels.^{81,82} In postmenopausal women receiving adjuvant exemestane versus placebo, decreased levels of cholesterol, LDL cholesterol, and triglycerides were seen in both groups.⁸³ Although cholesterol levels were not routinely assessed in the IES trial, there was no difference in the incidence of myocardial infarctions between the exemestane and tamoxifen groups.³¹

Musculoskeletal Effects

One important adverse event occurring after ovarian ablation of any kind is loss of bone mineral density (BMD). In the ZEBRA study, the mean percentage of loss in BMD for goserelin after 2 years was 10.5% for lumbar spine and 6.4% for femoral neck. The loss in BMD while on the LHRH agonist was significantly greater than in patients receiving chemotherapy. After cessation of goserelin, a partial recovery of BMD was seen at the 3-year assessment.⁸⁴

Several trials have reported that tamoxifen appears to preserve BMD in postmenopausal women with breast cancer, presumably due to its estrogenic agonistic effect.⁸⁵⁻⁸⁷ The International Breast Cancer Intervention Study (IBIS) of patients in a tamoxifen prevention trial reported no significant difference in osteoporotic fractures of the hip, spine, wrist, or forearm between the tamoxifen and placebo groups ($P = .66$), and the NSABP P-1 prevention study showed a 19% (RR = .81; 95% CI, 0.63–1.05) reduction in fractures of hip, spine, and lower radius.^{58,62}

The nonsteroidal Als anastrozole and letrozole have been shown to increase bone resorption^{73,88} and have

been associated with an increased incidence of musculoskeletal disorders including fractures.^{28,33,36} According to the most recent update from the ATAC trial, arthralgia (35.6% vs 29.4%, $P < .0001$) and fractures (11% vs 7.7%, $P = < .0001$) occurred more frequently in patients in the anastrozole group than in the tamoxifen group.²⁸ Likewise, the BIG trial reported arthralgia (20.3% vs 12.3%, $P < .001$) and fractures (5.7% vs 4.0%, $P < .0001$) more frequently in those receiving letrozole than tamoxifen.³³ In the MA-17 trial, in women who had previously completed 5 years of adjuvant tamoxifen, arthritis (5.6% vs 3.5%, $P < .001$), arthralgia (21.3% vs 16.6%, $P < .001$), and myalgia (11.8% vs 9.5%, $P = .02$) were reported more often by women receiving letrozole than those receiving placebo.³⁶ There was no significant difference in the incidence of fractures in the MA-17 trial.

In the preclinical model of ovariectomized rats, exemestane protected against bone loss.⁸⁰ When compared to placebo and letrozole in healthy postmenopausal women, 12 weeks of exemestane appeared to cause a similar increase in bone resorption as letrozole but also increased the serum level of P1NP, a marker of bone formation which was not observed with letrozole.⁸⁸ In women who participated in the IES trial which randomized them to exemestane or continued tamoxifen after 2 to 3 years of adjuvant tamoxifen, there was a higher incidence of arthralgia (5.4% vs 3.6%, $P = .01$) and osteoporosis (7.4% vs 5.7%, $P = .05$) in those receiving exemestane; however, data reported fewer fractures in the tamoxifen group.⁸⁹ Given the known protective effect of tamoxifen on BMD, it is difficult to assess whether the reduced incidence of skeletal effects attributed to tamoxifen in this trial and the ATAC trial described above is due to a negative effect of the AI or the protective effect of tamoxifen.

Thromboembolic Events and Endometrial Cancers

Tamoxifen has been associated with an increased risk of thromboembolism and stroke when compared to placebo.^{58,60,62,90} The incidence of venous thromboembolic events was increased in each of the major tamoxifen breast cancer prevention trials, with an RR of 1.9 in those receiving tamoxifen versus the placebo groups ($P < .0001$).⁵³ Pulmonary emboli were reported in almost three times as many women receiving tamoxifen than placebo in the NSABP P-1 trial (RR = 3.01; 95% CI, 1.15–9.27), with the greatest risk in women over age 50.⁵⁸ Strokes were also more common in the tamoxifen group, especially in those over age 50 (RR = 1.75; 95% CI, 0.98–3.20). A recent meta-analysis also reported an increased risk of stroke for women receiving tamoxifen in breast cancer trials versus those receiving placebo.⁹⁰

Overall, in the trials which compared any of the third generation Als to tamoxifen, the adverse effects typically associated with estrogenic properties of tamoxifen were significantly less common in the AI groups.^{31,91,92} When compared to tamoxifen, anastrozole, letrozole, and exemestane were associated with fewer thromboembolic events in the ATAC (2.8% vs 4.5%, $P = .0004$), BIG 1-98 (1.5% vs 3.5%, $P < .001$), and IES (1.0% vs 1.9%, $P = .003$) trials, respectively. As alluded to above, these results are consistent with the estrogenic effects of tamoxifen and make the Als preferable to tamoxifen in women with a history of thrombosis or stroke.

Endometrial Cancer

Women who received tamoxifen in the breast cancer prevention trials had a 2.4 times greater risk of developing invasive endometrial cancer than those who received placebo ($P = .0005$)

and an even greater risk (3.4 times; $P = .0002$) was reported from the EBCTCG analysis of 55 adjuvant tamoxifen trials.^{23,58} A follow-up report at a median of 25.8 months after the BIG 1-98 trial reported invasive endometrial cancer in 0.1% of patients receiving letrozole and 0.3% of those receiving tamoxifen ($P = .18$) and at a median follow-up of 68 months the ATAC trial reported that endometrial cancer had developed in 0.2% of those receiving anastrozole and 0.8% of those who received tamoxifen ($P = .2$).^{28,33}

CONCLUSION

Hormone-responsive breast cancer is the most common form of the disease, accounting for around three quarters of all cases. Unlike receptor-negative disease, it results in a long-term chronic risk of recurrence. While tamoxifen reduces the risk during treatment and has a carryover benefit for many years, there is nevertheless an unmet medical need to further reduce recurrence. This need has in part now been addressed by the AIs and they have added benefit whether given as alternative up-front therapy, as a switch in the midpart of a 5-year treatment, or as extended therapy after 5 years of tamoxifen. However, many questions remain unanswered: whether to give the AIs up front or in sequence with tamoxifen; the optimal duration of treatment; whether there is a superior class of AI; the role of sequencing AIs; if total estrogen blockade can be achieved and if it will be superior to AI treatment alone; the role of AIs in premenopausal disease; if de novo resistance to AIs can be overcome by combinations with other endocrine agents, cell surface receptor inhibitors, or small molecules of intracellular signalling pathways; how to know the correct schedule for administering endocrine therapy. Finally, despite the advances shown by

the recent trials, the toxicity and cost of the inhibitors mandate that we try to reduce the numbers needed to treat to benefit one patient. For example, in the MA-17 trial the number needed to treat for node-negative women was 37 and for node-positive patients it was 13. As an example of addressing this issue we are currently undertaking a tumor profile project wherein we are comparing standard semiquantitative immunohistochemistry with quantitative immunofluorescence and 2 gene signatures, the MGH 2-gene signature, and the Genomic Health 21-gene signature for prognostic and predictive power. In this way we hope to identify women in whom tamoxifen is sufficient, those who need sequential AI, and those who relapse despite these two treatments and need additional investigational therapy. In summary, endocrine therapy continues to evolve and to contribute substantially to improving the outcome of women with hormone-sensitive breast cancer.

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Management of Hormone Receptor–Positive Advanced Breast Cancer

Kathleen Pritchard, MD, FRCP(C)

INTRODUCTION

Endocrine therapy remains an important approach to the treatment of advanced breast cancer. It is particularly useful because it is not only efficacious but, in comparison to combination cytotoxic chemotherapy, it is associated with minimal serious toxicity and excellent quality of life for most women. Although endocrine therapy has been widely used in the treatment of metastatic breast cancer for over 3 decades, advances in recent years have further improved patient outcomes.

PREMENOPAUSAL WOMEN

Tamoxifen Versus Ovarian Ablation

There are considerable data showing that in the premenopausal setting, estrogen stimulates breast cancer growth. Approximately 30% of unselected premenopausal women with metastatic breast cancer will demonstrate disease regression following reduction of estrogen levels by ovarian removal, ovarian irradiation, or the use of a luteinizing hormone-releasing hormone (LHRH) agonist. Women whose tumors are either estrogen receptor–positive (ER+) or progesterone receptor–positive (PR+) have response rates of 30% or 40%, respectively, to hormonal manipulation, whereas those whose tumors are both ER+ and PR+ have response rates as high as 70%. Women whose tumors are both ER-negative and PR-negative have response rates to endocrine therapy of less than 5%.^{1,2}

Although ovarian ablation by surgery or radiation was historically the first line of endocrine manipulation in premenopausal women with metastatic disease,³ more than 25 years ago tamoxifen was also found to be active.⁴ Since that time, several small randomized studies^{5–7} and one small meta-analysis⁸ have demonstrated that tamoxifen is approximately equivalent to ovarian ablation in terms of both disease response and overall survival (OS) as a treatment for metastatic breast cancer in the premenopausal setting. In addition, the meta-analysis indicated that initial response to one hormonal therapy (either tamoxifen or ovarian ablation) was predictive of a subsequent response to the other at the time of disease progression.⁸ Until the 1990s, most clinicians included tamoxifen in the initial management of premenopausal women with metastatic disease and after disease progression,

then proceeded to ovarian ablation by surgery or radiation.

Chronic administration of synthetic LHRH agonists such as goserelin results in downregulation of the number of LHRH receptors and subsequent castrate levels of estrogen within 21 to 28 days in more than 90% of premenopausal women.⁹ Phase II trials of LHRH agonists in premenopausal women with metastatic breast cancer showed response rates from 11% to 45%. As expected, women with ER+ and PR+ tumors were more likely to respond and soft tissue disease sites were more likely to regress.^{10–13} A randomized phase III study in premenopausal women with ER+ and/or PR+ metastatic breast cancer compared goserelin 3.6 mg sc every 4 weeks to surgical ovariectomy and showed that failure-free survival and OS were similar in the 2 groups.¹⁴ These data motivated some physicians to move toward the use of LHRH agonists as first-line endocrine therapy in premenopausal women, followed by tamoxifen.

LHRH Agonists Plus Tamoxifen

The combination of an LHRH agonist with tamoxifen has been shown to completely suppress the stimulatory effects of tamoxifen on pituitary-ovarian function and reduce circulating estrogen to postmenopausal levels in premenopausal women with breast cancer.¹⁵ A meta-analysis of 4 randomized trials with a total of 506 patients^{16–19} compared an LHRH agonist (goserelin or buserelin) plus tamoxifen to an LHRH agonist alone in the treatment of premenopausal women with metastatic disease.²⁰ At a median follow-up of 6.8 years, this analysis demonstrated a modest but significant improvement in overall response rate (ORR) (hazard ratio [HR] = 0.67, $P = .03$), progression-free survival (PFS) (HR = 0.70, $P = .0003$), and OS (HR = 0.78, $P = .02$) in women who received the combination in comparison to the LHRH agonist alone.²⁰ Although these results suggest that the combined endocrine therapy is more beneficial than an LHRH agonist alone, there

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are some questions to be considered in the interpretation of these data. In particular, what is the potential benefit of receiving the LHRH agonist alone with tamoxifen as second-line therapy? In fact, what one would like to compare would be the 2 drugs used concurrently, versus their use sequentially. In addition, the toxicity data were not collected in any detail, and no quality of life data exist that compare the combination to the use of an LHRH agonist alone. Nonetheless, the available data suggest that the use of an LHRH agonist plus tamoxifen could result in an improved clinical outcome, in comparison to the use of an LHRH agonist alone followed by tamoxifen, in the premenopausal metastatic setting. The current options for the premenopausal metastatic cascade are shown in Figures 1A and 1B.

Aromatase Inhibitors

Currently, there are no data to support the use of aromatase inhibitors (AIs) in women with advanced breast cancer who are still premenopausal. AIs are unable to overcome the action of ovarian aromatase, and

their use may result in a surge of ovarian aromatase activity, producing even higher estrogen levels in the premenopausal woman. Thus, clinicians are strongly advised against the use of an AI unless they are certain that the patient is postmenopausal. It is also interesting to note that about 20% of women may still have premenopausal hormone levels even though they become amenorrheic following chemotherapy.²² Thus, it may be worthwhile to test the hormone levels in perimenopausal patients, and in women who have seemingly become postmenopausal following chemotherapy, before considering the use of an AI.

POSTMENOPAUSAL WOMEN

Even though estrogen levels in postmenopausal women are only approximately 5% of those in premenopausal women, they are sufficient to stimulate breast cancer cell growth.^{23,24} Postmenopausal estrogens are derived from the conversion of adrenal androgens by the enzyme aromatase, which

exists in fat, muscle, brain, and many other tissues. AIs reduce the levels of estrogen produced through androgen conversion by blocking the aromatase enzyme. As discussed in the previous article in this monograph, both steroidal (exemestane) and nonsteroidal (anastrozole and letrozole) AIs are available.

Second-Line Therapy Following Antiestrogen Failure

Prior to the availability of the newer AIs, megestrol acetate was most commonly used as second-line endocrine therapy following progression after tamoxifen. Initial studies with the new generation of AIs compared them to either megestrol acetate or aminoglutethimide in women whose breast cancer had progressed following therapy with tamoxifen. As shown in Table 1, several large randomized trials have compared anastrozole, exemestane, and letrozole to megestrol acetate.²⁵⁻²⁸ Overall, these trials demonstrated superiority or equivalency in OS, time to progression (TTP), time to treatment failure (TTF), and ORR of the AIs when compared to megestrol in this setting, with fewer serious side effects attributed to the AIs. When compared to aminoglutethimide in postmenopausal women who had disease progression while receiving an antiestrogen or who had disease recurrence within 6 months of adjuvant antiestrogen therapy, letrozole was found to be superior in TTP, TTF, and OS.²⁹

First-Line AI Therapy Compared With Tamoxifen

Documentation of the benefit of AIs following progression on tamoxifen prompted randomized clinical trials to assess the AIs as first-line therapy. Each of these trials compared AIs (anastrozole, letrozole, or exemestane) to tamoxifen in women with locally advanced or

Figure 1.—Current options for the premenopausal metastatic cascade. (From Pritchard,²¹ with permission.)

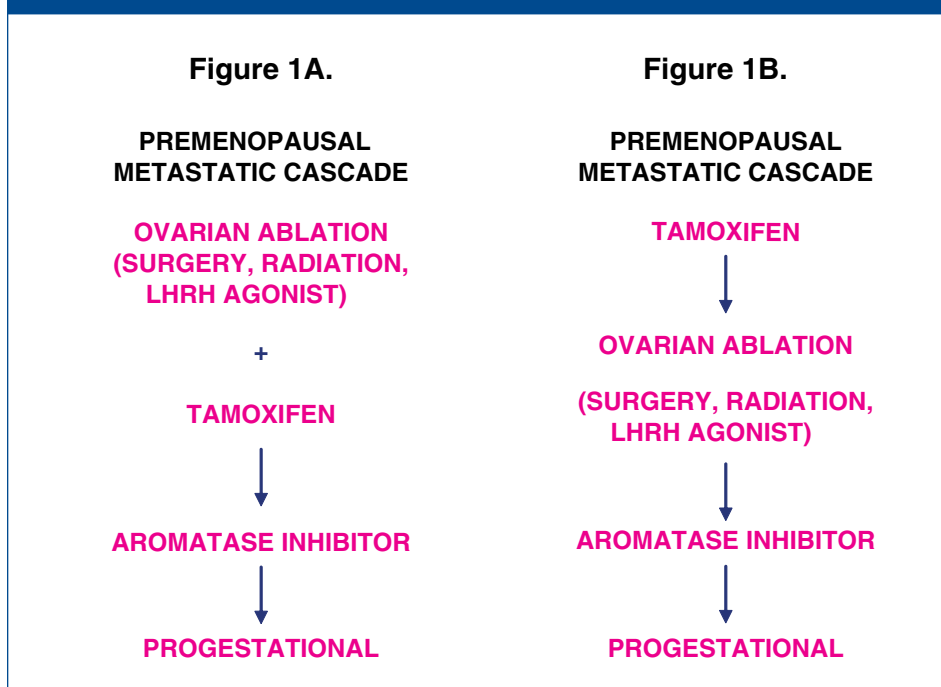


Table 1.—Outcome for Aromatase Inhibitors as Therapy for Metastatic Breast Cancer in Postmenopausal Women

		Number of Trials Showing Benefit for AI			
	3 trials of new AI challenging megestrol N = 2250	OS 2 (A/E)	TTF 3 (L/E)	TTP 2 (E)	RR 1 (L)
Tamoxifen Failures					
	2 trials of new AI challenging aminoglutethimide N = 919	1 (L)	2 (L/V)	1 (L)	0

A = anastrozole; E = exemestane; L = letrozole; OS = overall survival; RR = response rate; TTF = time to treatment failure; TTP = time to progression; V = vorozole. Data from Pritchard,²¹ with permission.

metastatic breast cancer who had either not received adjuvant hormonal therapy or who had completed adjuvant hormonal therapy more than 12 months previously. Eligibility requirements included either ER+ and/or PR+ tumors or unknown receptor status.

Two large trials that compared anastrozole to tamoxifen as first-line hormonal therapy were identical in design and randomized 353 US and Canadian³⁰ women and 688 European women.³¹ The planned primary end points were TTP, ORR defined as complete response (CR) plus partial response (PR), and tolerability. The secondary objectives were to compare the 2 treatment groups with regards to TTF, response duration, and clinical benefit (CB) duration. The trial was designed for a pooled analysis of all 1,021 patients.³²

The results of these 2 trials and the pooled analysis are shown in Table 2. In the US/Canadian trial, 21% of the patients receiving anastrozole and 17% of those in the tamoxifen group had either a CR or PR. When the end point of CB was compared (CR + PR + stable disease for 24 weeks or longer) there was a statistically significant difference in favor of anastrozole (59% vs 46%, $P = .009$). Median TTP was also significantly longer for anastrozole (11 vs 5.6 months, $P = .005$) in the North

American trial.³⁰ In the European trial, anastrozole was also equivalent to tamoxifen in ORR, median TTP, and CB.³¹

When the results were pooled as planned, anastrozole was at least equivalent to tamoxifen in terms of TTP (8.5 vs 7 months, $P = .103$, 2-sided), ORR (29% vs 27.1%), and CB rate (57.1% vs 52%, $P = .1129$). However, when only those patients with tumors confirmed to be ER+ and/or PR+ (59.8% of the total study population) were included in the analysis, the median TTP was significantly longer in those receiving anastrozole (10.7 vs 6.4 months, $P = .022$).³¹ The incidence

of venous thromboembolic disease was somewhat lower in both subtrials and in the pooled data (3.6% vs 6.5%, $P = .0434$) in favor of anastrozole, while hot flushes were similar in one substudy, greater in the anastrozole arm in the other, and equivalent in the pooled analysis.

Letrozole 2.5 mg/day was also compared to tamoxifen as first-line hormonal therapy in women with locally advanced or metastatic breast cancer. The women included in this study also had tumors which were ER+ and/or PR+ or unknown receptor status. Eligibility did include one prior

Table 2.—Anastrozole (A) Versus Tamoxifen (T) as First-Line Hormonal Therapy in Metastatic Breast Cancer

	Anastrozole	Tamoxifen
Europe		
PR + CR, %	33	33
PR + CR + NC, %	56	55
TTP, mo	8	8
US/Canada		
PR + CR, %	21	17
PR + CR + NC, %	59 ($P = .009$)	46
TTP, mo	11	5.6 ($P = .005$)
Pooled		
PR + CR, %	29	27
PR + CR + NC, %	57	52
TTP, mo	8.5	7 ($P = .103$)

CR = complete response; NC = no change; PR = partial response; TTP = time to progression. Data from Bonnetterre et al,³² Mouridsen et al,³³ Paridaens et al,³⁵ and Pritchard,²¹ with permission.

Table 3.—Letrozole Versus Tamoxifen as First-Line Therapy

	TTP, median	TTF, median	ORR, %	Clinical Benefit, % (CR + PR + NC ≥ 6 mo)
Letrozole, n = 453	9.4 mo	9.0 mo	32	50
Tamoxifen, n = 454	6.0 mo	5.7 mo	21	38
<i>P</i> Value	< .0001	< .0001	.0002	.0004

CR = complete response; NC = no change; ORR = overall response; PR = partial response; TTF = time to failure; TTP = time to progression.
Data from Mouridsen et al,³⁴ with permission.

cytotoxic chemotherapy regimen (but no hormonal therapy) for advanced breast cancer as long as the disease had progressed during that therapy. Prior adjuvant endocrine therapy was permitted but must have been completed at least 12 months prior to study entry.³³ At a median follow-up of 32 months, the TTP, TTF, ORR, and CB were all significantly better in favor of letrozole (Table 3).³⁴

In a variety of prospectively defined subgroups, which included the intent-to-treat group, patients previously treated and previously not treated with adjuvant tamoxifen, receptor-positive women, receptor-unknown women, women with soft tissue disease, and women with bone metastases, as well as those with visceral metastases, letrozole was also superior (Figure 2).³³ The overall tolerability of the 2 regimens was similar; however, it is of interest that the rate of thromboembolic events for tamoxifen reported in this trial is less than half of that collected in a similar group of patients in the anastrozole versus tamoxifen trials.

OS rates comparing letrozole to tamoxifen in first-line hormonal therapy are shown in Figure 3. Although there was a significant OS advantage for the letrozole group between 6 and 20 months (*P* = .003), at the median follow-up of 32 months there was no significant difference in OS (34 months for letrozole vs 30 months for tamoxifen (*P* = .53). The early survival

advantage for letrozole is consistent with the prolonged TTP noted for letrozole in this study.³⁴ Two hundred thirty-three of the 458 patients initially randomized to letrozole crossed over to tamoxifen at the time of progression and 226 of the 458 first-line tamoxifen patients crossed over to letrozole. The duration of survival with second-line letrozole (31 months; 95% CI, 22–40 months) was longer than with second-line tamoxifen (19 months; 95% CI, 17–24 months) and an analysis of patients whose time to death was censored at crossover suggested that there might be a survival advantage for letrozole beyond the 20 months; however, this could not be confirmed due to the design of this study.³⁴

The European Organization for the Research and Treatment of Cancer (EORTC) compared first-line exemestane (25 mg/day) to tamoxifen (20 mg/day) in a randomized phase III study of postmenopausal women with metastatic breast cancer. As in the other trials, women had either ER+ and/or PR+ tumors or unknown receptor status; could have received one prior cytotoxic chemotherapy regimen; and, in this study, must have completed adjuvant tamoxifen at least 6 months prior to randomization. The results were presented at the 2004 Annual Meeting of the American Society of Clinical Oncology.³⁵ This trial was somewhat smaller than the first-line anastrozole and letrozole trials, with only 382

Figure 2.—Letrozole superior TTP independent of baseline covariates. (From Pritchard,²¹ with permission.)

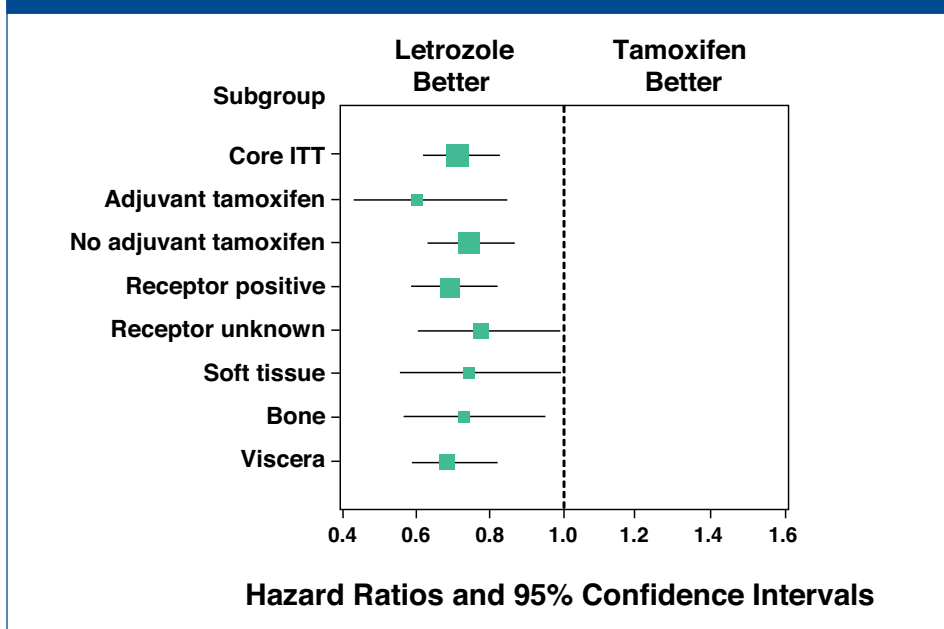
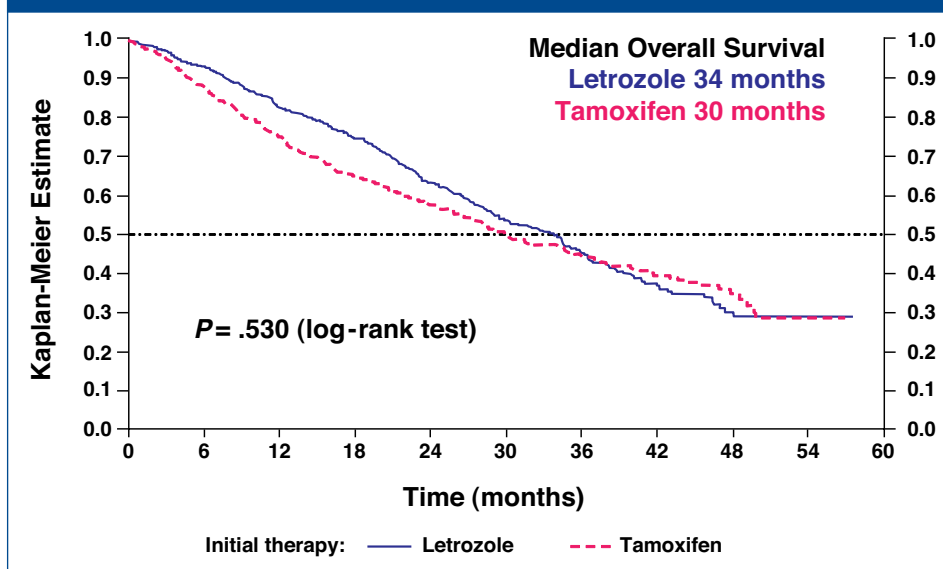


Figure 3.—Overall survival was not significantly different at 32 months; however, there was a significant difference in favor of letrozole between 6 and 20 months ($P = .003$). (From Pritchard,²¹ with permission.)



patients randomized (190 exemestane and 192 tamoxifen). The primary end point was PFS and the secondary end points were safety and OS. The median PFS was longer with exemestane (9.9 months; 95% CI, 8.7–11.8 months) than with tamoxifen (5.8 months; 95% CI, 5.3–8.1 months). The ORR (46% vs 31%) was also significantly better for the exemestane group, with a favorable tolerability profile.

Table 4 compares the results from all of these randomized phase III trials of tamoxifen versus an AI. The asterisks indicate a significantly better response for the AI than for tamoxifen. These

large randomized trials support at least the equivalency of the AIs to tamoxifen as first-line therapy in metastatic disease which is reflected in the current NCCN guidelines.³⁶

COMPARISON OF AROMATASE INHIBITORS AS SECOND-LINE THERAPY FOLLOWING PROGRESSION ON TAMOXIFEN

In 2004, Rose and colleagues reported the results of a phase III trial comparing anastrozole (1 mg daily) to letrozole (2.5 mg daily) as second-line therapy in postmenopausal women with advanced breast cancer who had failed tamoxifen or relapsed during

or within 12 months of completing adjuvant tamoxifen.³⁷ This multicenter, open-label study randomized 713 women with measurable or assessable lesions and either ER+ and/or PR+ or unknown receptor status tumors. The primary end point was TTP and secondary end points included ORR (CR + PR), TTF, and OS. The TTP was 5.7 months for both the letrozole and anastrozole groups. As shown in Table 5, the ORR was slightly better for letrozole than anastrozole (adjusted odds ratio = 1.70, $P = .013$) and the CB rate was similar (27% vs 23%, odds ratio 1.24, $P = .216$). There was also no difference in TTF, duration of response, or OS (22 months for letrozole and 20.3 months for anastrozole ($P = .624$). When only women with ER+ and/or PR+ tumors were analyzed, the ORR was significantly better than with anastrozole ($P = .014$); however, there was no difference in any other end point between the 2 treatment arms with this subgroup analysis.

Activity of AIs After Failure of Another AI

In an open-label, uncontrolled, phase II trial, Lonning and other investigators at 75 clinical centers administered exemestane to 241 postmenopausal women who had progressive disease while receiving a therapeutic dose of a nonsteroidal aromatase inhibitor (aminoglutethimide, anastrozole,

Table 4.—Randomized Phase III Trials of Tamoxifen Versus Aromatase Inhibitors as First-Line Therapy in Metastatic Breast Cancer

Efficacy Results, AI/Tamoxifen	ORR, %	Clinical Benefit, %	TTP, mo
Anastrozole, N = 1021 (pooling)	29 / 27	57 / 52	8.5 / 7.0
Letrozole, N = 907 (1 trial)	30 / 20*	49 / 38*	9.4 / 6.0*
Exemestane, N = 382 (randomized phase II/III trial)	44 / 29*	72 / 66	10.9 / 6.7*

*Statistically significant.

CB = clinical benefit rate; ORR = overall response; TTP = time to progression.

Data from Bonneterre et al,³² Mouridsen et al,³³ Paridaens et al,³⁵ and Pritchard,²¹ with permission.

Table 5.—Letrozole Versus Anastrozole in Metastatic Breast Cancer

	ORR	CB
Letrozole	19.1%	27.0%
Anastrozole	12.3%	23.0%
ORR	1.70	1.24
P Value	0.013	0.216

No difference in TTP, TTF, duration of response, duration of CB.

CB = clinical benefit; ORR = overall response rate.

Data from Rose et al,³⁷ and Pritchard,²¹ with permission

letrozole, or vorozole).³⁸ They reported an ORR of 6.6% (95% CI, 3.8%–10.6%) and a CB rate of 24.3% (95% CI, 19%–30.2%) with median duration of ORR and CB of 58.4 weeks (95% CI, 49–71.1 weeks) and 37 weeks (95% CI, 35–39.4 weeks), respectively. The majority of women in this study were receiving third- or fourth-line therapy for metastatic breast cancer and had received either prior aminoglutethimide or another nonsteroidal aromatase inhibitor, suggesting that there is incomplete cross-resistance between the nonsteroidal AIs and the steroidal AI, exemestane.³⁸

Selective Estrogen Receptor Downregulator

Fulvestrant, a so-called “pure” antiestrogen, is better known as a selective estrogen receptor downregulator (SERD) or an antiestrogen without known agonist effects and is now widely available in North America and Europe.³⁹ Fulvestrant has been in clinical development for a number of years, but was not actively pursued because there is no oral formulation and it must be administered as an intramuscular injection. There has been concern that the recommended dose of 250 mg monthly may not be adequate. According to V. Sandor, MD (January 2006), loading with 250 mg every 2 weeks for 3 to 4 injections, followed

by dosing at 250 mg monthly, results in steady-state kinetics much more quickly than does monthly dosing.

Early evidence of clinical activity of fulvestrant was demonstrated in 7 of 19 women who had previously relapsed following tamoxifen therapy for either metastatic or early (adjuvant therapy) disease.⁴⁰ Six of these women had stable disease for a significant duration with a CB rate of 69%. This apparent lack of cross-resistance to tamoxifen prompted further investigation.

Two large phase III clinical trials of fulvestrant compared to anastrozole were opened in North America and in the rest of the world (ROW).^{41,42} The North American trial (Faslodex Trial 0021) was a double-blinded study,

while that for the ROW (Faslodex Trial 0020) was open-label. These trials, however, were designed to be analyzed together. A total of 851 postmenopausal patients with advanced breast cancer who had relapsed or progressed following endocrine therapy were studied in these trials. The initial pooled analysis at a median follow-up of 15.1 months showed no difference in TTP (5.5 months for fulvestrant vs 4.1 months for anastrozole) and no significant difference in TTF (4.6 months for fulvestrant vs 3.6 months for anastrozole). A subsequent analysis at a median follow-up of 27 months showed a similar OS between treatments (27.4 months for fulvestrant and 27.7 months for anastrozole; HR 0.98; 95% CI, 0.84–1.15; *P* = .809).^{43,44} The trend of benefit for fulvestrant in terms of TTP and TTF was greater in the North American⁴² than in the ROW subtrial.⁴² Adverse effects, including vasodilation, injection site pain, and nausea, were virtually identical in the 2 treatment arms. Withdrawals due to drug-related adverse events were 0.5% in the fulvestrant arm and 1% in the anastrozole arm. The incidence of thromboembolic events, weight gain, and vaginitis were low for both treatments.⁴³

Subsequently, a large randomized trial (Faslodex Trial 0025) of

Table 6.—Fulvestrant Versus Tamoxifen for Metastatic Breast Cancer (All Patients)

	ORR	CB	Med Resp Duration, mo	TTF, mo	Med Surv Duration, mo
Fulvestrant, (N = 313)	31.6	54.3	17.3	5.9	36.9
Tamoxifen, (N = 274)	33.9	62.0	19.8	7.8	38.7
P Value	NS	.026	NS	.026*	.04*

*Adjusted for baseline covariates.

CB = clinical benefit; NS = not significant; ORR = overall response; TTF = time to failure.

Data from Howell et al.⁴⁵

fulvestrant versus tamoxifen in first-line therapy was carried out. The primary end point for this study was TTP with secondary end points including response rate, duration of response, TTF, time to death, tolerability, and quality of life. This study, like that comparing fulvestrant and anastrozole in patients who had previously failed endocrine therapy, was reported as a combined analysis of 2 phase III trials, one done in Europe and one in North America. Although it was expected by many that fulvestrant would be superior to tamoxifen, the primary outcome of TTP was not different for either the entire group of patients (N = 587) or the subset of patients with ER+ and/or PR+ disease (n = 459). Similarly, as shown on Table 6 for the intent to treat group, ORR, CB, and median response duration were not different while TTF and median survival duration favored tamoxifen very slightly. When the subset of patients with ER+ and/or PR+ were studied there was no significant difference between TTP, ORR, CB, median response duration, TTF, or median survival duration (see Table 7).⁴⁵

Subsequent to these 2 large randomized trials, due to its intramuscular route of administration and because it appeared to be at least as effective as an AI in women who had previously received tamoxifen, and of similar efficacy but not clearly superior to tamoxifen in first-line therapy, fulvestrant has moved to a third-line position in the treatment of women with metastatic breast cancer.³⁶ In that setting there has now been considerable data generated defining its role.

A review of the European Compassionate Use Program by Steger and colleagues⁴⁶ reported the results of 339 patients treated with fulvestrant in 8 European centers. In this program,

patients received fulvestrant as first- (n = 22), second- (n = 125), third- (n = 105), fourth- (n = 58), fifth- (n = 22), or sixth- (n = 5) line hormonal treatment for advanced breast cancer. A partial response was achieved by 40 patients, and stable disease lasting 6 months or more by 92 patients, giving an overall CB in 132/339 (39%). CB decreased as fulvestrant was used later in the sequence of treatments from 10/22 (46%) with first-line fulvestrant, to 6/22 (27%) with fifth-line fulvestrant. Further details are shown in Figure 4. In this report, fulvestrant was well tolerated with adverse events noted in 18/339 patients (5%). A report of

a US single-center experience by Franco and colleagues⁴⁷ described 42 patients heavily pretreated with multiple endocrine therapies and chemotherapy, who were then treated with fulvestrant leading to stable disease for ≥ 24 weeks in 8 patients (19%).

A US postmarketing registration study enrolled 213 women treated with fulvestrant following previous endocrine therapy that included tamoxifen, anastrozole, exemestane, letrozole, toremifene, or megestrol (200/213). One hundred and sixty-four patients (77%) had prior exposure to tamoxifen and of these, 51 (24%) had metastatic disease

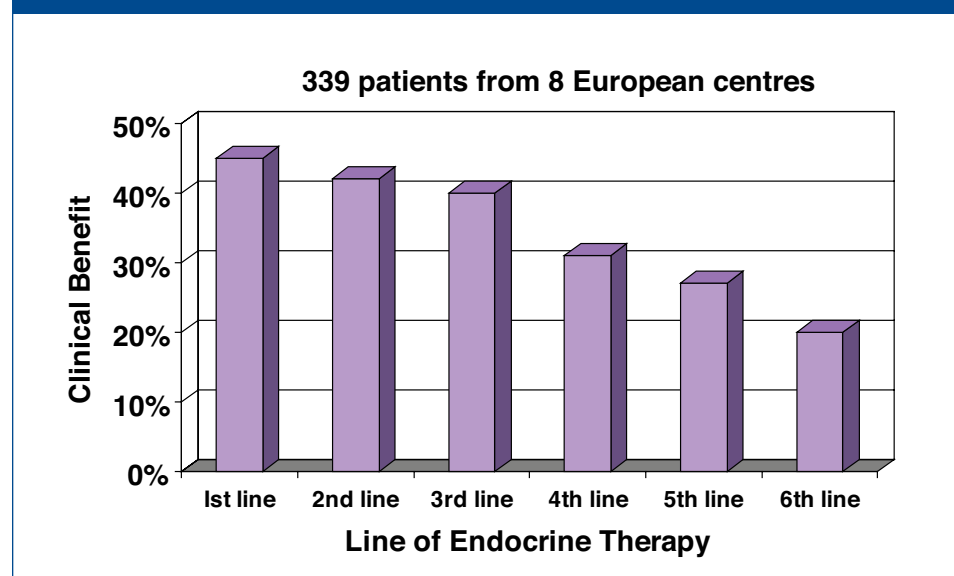
Table 7.—Fulvestrant (F) Versus Tamoxifen (T) for Metastatic Breast Cancer (ER+ and/or PR+ Tumors Only)

F vs T	ORR	CB	TTP, mo	TTF, mo	Med Surv Dur'n, mo
F (n = 247)	33.2	57.1	8.2	7.5	39.3
T (n = 212)	31.1	62.7	8.3	8.0	40.7
P Value	NS	NS	NS	NS	NS

CB = clinical benefit rate; NS = not significant; ORR = overall response; TTF = time to failure; TTP = time to progression.

Data from Howell et al.⁴⁵

Figure 4.—Clinical benefit achieved with fulvestrant by number of prior endocrine treatments for advanced breast cancer. (From Steger et al,⁴⁶ with permission.)



which had progressed on tamoxifen before receiving fulvestrant. Of the 213 enrolled patients, 102 (47.9%) demonstrated CB as defined by CR, PR, and stable disease \geq 24 weeks.⁴⁸

Fulvestrant represents the first in a new class of drugs that bind, block, and downregulate the ER. It is at least as effective as the third generation AIs in women who have previously received tamoxifen, and similar in efficacy to tamoxifen at least for those women with ER+ and/or PR+ disease, the subset in whom these agents are most appropriately used. It is generally well tolerated in spite of its intramuscular route of administration.

Sequencing of Endocrine Therapies

There are also considerable data regarding the use of one class of AI followed by the other class, particularly for the role of exemestane used after a nonsteroidal AI.³⁸ Because both fulvestrant and exemestane might be considered for third-line therapy, a large trial comparing these 2 agents following disease progression on a nonsteroidal AI has now completed accrual. Results of this trial, The Faslodex versus Exemestane in Postmenopausal Women with Hormone Receptor Positive Advanced Breast Cancer with Disease Progression after prior nonsteroidal AI therapy (EFECT), are expected in late 2006.

The effect of the sequence of tamoxifen and anastrozole as first- and second-line therapy for advanced breast cancer in postmenopausal women has also been evaluated. Thurlimann and colleagues reported the retrospective combined analysis of 2 international, randomized, double-blind trials of 1,021 evaluable women with hormone receptor-positive tumors.⁴⁹ Specifically, they analyzed the crossover from anastrozole to tamoxifen and vice versa from 2 other large trials that had compared the 2 as first-line therapy with a crossover at the time of

progression. Forty-three of 85 patients (50.6%) who crossed directly over to tamoxifen subsequent to anastrozole had a CB of more than 24 weeks. Of the patients who received anastrozole as second-line therapy directly following tamoxifen, 45 of 74 patients (60.8%) showed a CB for a similar duration of time.⁴⁹ A retrospective analysis has also shown that women with advanced breast cancer whose tumors progress while on fulvestrant remain sensitive to subsequent treatment with anastrozole and letrozole.⁵⁰ Currently, agents such as megestrol acetate have been relegated to fourth- and fifth-line therapies, and agents such as fluoxymesterone and estrogen (DES) are only occasionally used because of their relatively greater toxicity. Considering that AIs produce a very low estrogen environment, it will be important to explore the role of fulvestrant, an estrogen downregulator, and whether this may be more or less useful in this setting than in other approaches. Perhaps drugs such as DES should be re-examined in this environment.

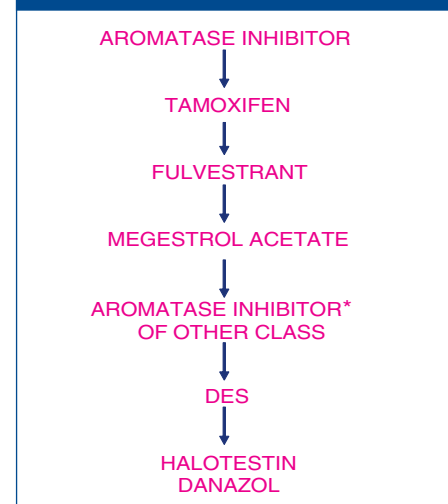
In summary, while the optimal sequence of endocrine therapies in postmenopausal women remains somewhat undetermined, it is probably reasonable to start with an AI followed by tamoxifen followed by fulvestrant as a third-line therapy. Megestrol acetate and high-dose estrogen may remain fourth- and fifth-line options (Figure 5).

SELECTION OF ENDOCRINE AGENTS BASED ON HER2/NEU/ERB-B2 RESULTS

In women with breast cancer, overexpression of the *c-erb-b2* (HER2/*neu*) proto-oncogene has been associated with a worse prognosis compared to those whose tumors do not overexpress this protein,⁵¹ and

results of some clinical studies have suggested that this worse prognosis may be attributed to a poorer response to either hormonal or cytotoxic chemotherapy.^{52,53} Over the past decade, there have been a number of reports suggesting that women whose breast cancers are ER+ and/or PR+ and overexpress HER2/*neu* are less responsive to endocrine therapy, particularly tamoxifen, in the advanced or adjuvant setting⁵⁴⁻⁵⁹; however, some reports have provided conflicting results.^{59,60} Interestingly, data from a randomized study comparing neoadjuvant letrozole to tamoxifen reported that women whose tumors are ER+ and/or PR+, but also HER2/*neu/erb-b1* and/or HER2/*neu/erb-b2* overexpressing, are much more likely to respond to the AI letrozole than to tamoxifen (60% vs 41%, $P = .004$) and subsequently more likely to undergo successful breast-conserving surgery.⁶¹ Once again, there have been conflicting reports. Data have been published from Love and colleagues⁶² regarding premenopausal Vietnamese and Chinese women randomized to receive ovarian ablation and tamoxifen in the adjuvant setting versus the same

Figure 5.—Current options for the postmenopausal metastatic cascade. Asterisk = may be useful earlier ahead of fulvestrant or megestrol acetate.



endocrine therapy delayed to the time of recurrence. In this trial, the women whose tumors were ER+ and PR+ benefited highly from adjuvant therapy as opposed to delayed ovarian ablation and tamoxifen,⁶² and those whose tumors also overexpressed *neu/erb-b2* showed even more benefit in comparison to those who received delayed therapy.⁶² Thus, the response in relation to *neu/erb-b2* in premenopausal women to ovarian ablation and tamoxifen is the opposite of what has been reported with tamoxifen alone in many other settings. That is, women who overexpressed *neu/erb-b2* are more likely to respond to endocrine therapy in this study, whereas other studies have suggested they are less likely to respond.⁶⁴ It seems that this matter requires further clarification.⁶⁵ First, the inconsistent findings may relate to incorrect measurements of ER, PR, and *neu/erb-b2*. When careful measurements of ER/PR are done, there is actually quite a small proportion of women with ER+ and/or PR+ disease whose tumors also overexpress *neu/erb-b2*. More careful work in a variety of clinical trial settings will hopefully clarify this issue.

SUMMARY

Endocrine therapy for women with metastatic breast cancer has become more complex but even more rewarding than previously. In the last 30 years we have developed a large number of agents including the antiestrogen tamoxifen, the LHRH agonists, the AIs, and the SERD, fulvestrant. We must continue to explore the optimal usage of these compounds over future years in order to provide the best benefit for patients in this setting. Further exploration in the role of other predictive measures, such as *neu/erb-b2* overexpression, in the selection of optimal endocrine therapy will constitute an important part of these future studies.

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Endocrine Therapy Resistance: Molecular Predictive Models and Mechanism-Based Solutions

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INTRODUCTION

Endocrine therapy has been the treatment of choice for estrogen receptor-positive (ER+) breast cancer since the historic observation of tumor regression following ovariectomy by Beatson in 1896.¹ Over the years, multiple agents have been developed to target the ER signaling pathway. These include the selective estrogen receptor modulators (SERMs, tamoxifen, raloxifene, and toremifene), pure anti-estrogens (fulvestrant), luteinizing hormone-releasing hormone (LHRH) agonists (leuprolide, goserelin), selective aromatase inhibitors (anastrozole, letrozole, exemestane), and steroid hormones (progestins, androgens, and high-dose estrogens). While effective in many women, endocrine therapy has been limited by either inherent (de novo) or acquired resistance, and resistance patterns in both settings may be agent-specific or agent-independent (panendocrine therapy resistance).

Recent advances in genomic technologies are beginning to improve our understanding of the molecular heterogeneity of ER+ breast cancer. These studies fuel the hope that we will soon be able to accurately delineate the underlying genetic abnormalities that are associated with endocrine-resistant disease. From this new knowledge base we should be able to develop a mechanism-based therapeutic approach to this critical clinical problem.

THE DEVELOPMENT OF ER+ BREAST CANCER FROM THE PERSPECTIVE OF NORMAL BREAST PHYSIOLOGY

Normal breast physiology is regulated by the ovarian-pituitary axis during the reproductive phase of life. After menopause the glandular component of the breast gradually atrophies and the breast becomes largely replaced by adipose tissue. The development of postmenopausal breast cancer can be seen as an aberration of this process of involution, whereby breast duct epithelial cells develop deregulated growth and survival capabilities and subsequently the lethal triad of neo-angiogenesis, invasion, and metastasis. The acquisition of these properties is a consequence of the accumulation of somatic mutations, chromosomal instabilities, and epigenetic changes. During this process, the

cancer cell of ER+ tumors often maintains some dependence on female reproductive hormones, particularly estrogens. This is an example of “cell lineage dependence” where tumor stem cells maintain an important remnant of the normal physiology of the progenitor cell. Remarkably, data from adjuvant endocrine studies suggest that in some instances all the components of the malignant phenotype are supported by estrogen-dependent signals since some patients who receive an adjuvant endocrine intervention can be cured of their systemic disease. Recent studies have indicated that estrogen dependence is reduced by genetic events that corrupt the regulatory feedback loops that control growth factor pathways and these mutations underlie the molecular mechanism of ER+ breast cancer heterogeneity and endocrine resistance. In this model tumor heterogeneity is caused by the stochastic accumulation of different classes of mutations, in multiple combinations, with varying phenotypic consequences.

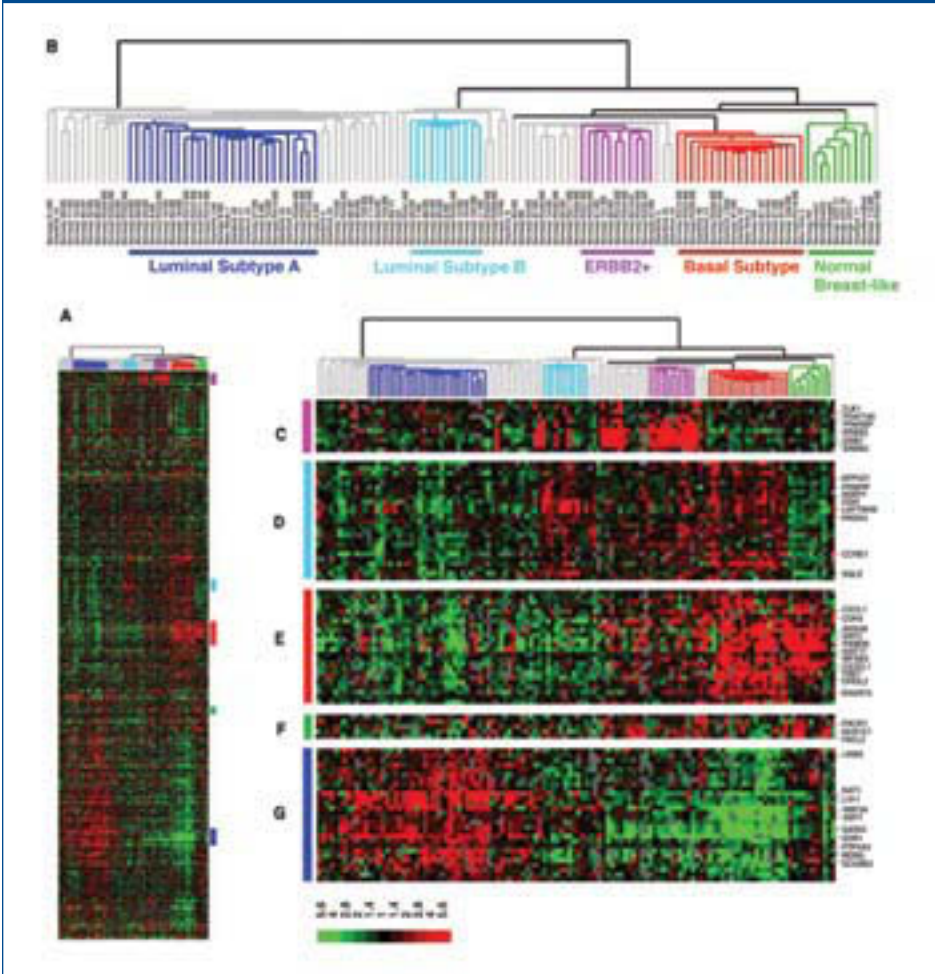
GENE EXPRESSION PROFILING REVEALS INSIGHTS INTO THE MOLECULAR HETEROGENEITY OF ER+ BREAST CANCER

One approach to unraveling the clinical consequences of tumor heterogeneity has been the development of transcriptional profiling with DNA microarrays. High-density DNA microarrays prepared by high-speed robotic printing of complementary DNA on glass microscope slides made it possible for quantitative measurement of expression levels for thousands of genes in parallel.² Later methodologies use on-chip oligonucleotide synthesis or, alternatively, oligonucleotide printing. A landmark study using an unsupervised clustering method subclassified breast cancers into “ER+/luminal-like,” “basal-like,” “HER2+/ER-negative,” and “normal breast” based on the gene expression patterns.³ ER+ tumors manifested gene expression patterns reminiscent of normal mammary luminal epithelium while basal-like tumors were

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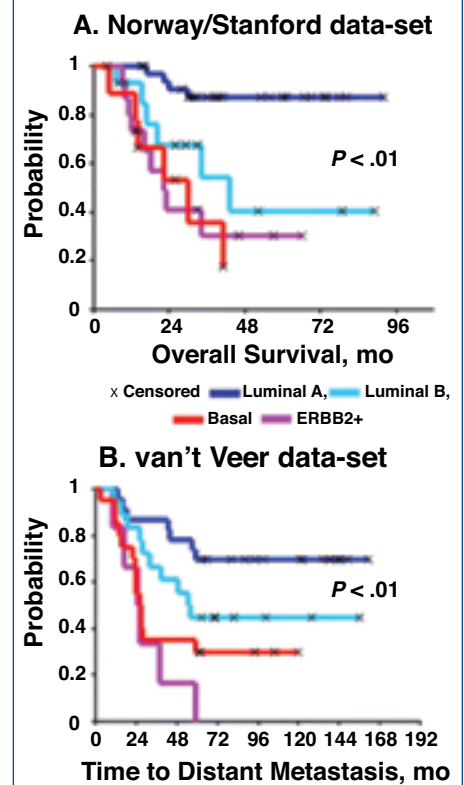
Figure 1.—Gene expression profiling of 115 breast tumor tissues and 7 nonmalignant breast tissues. A, hierarchical clustering using the 540 “intrinsic” gene set; B, experimental dendrogram showing tumors subdividing into 5 subtypes based on similarities in gene expression; C, HER2+ gene cluster; D, luminal subtype B gene cluster; E, basal subtype gene cluster; F, normal breast-like subtype gene clusters; G, luminal subtype A gene cluster. (From Sorlie et al,⁵ with permission.)



mainly ER-negative tumors with gene expression patterns reminiscent of mammary basal epithelium. The ER+/luminal tumors were further subclassified into at least two subgroups with distinctive expression profiles (Figure 1A and B).^{3,4} The luminal subtype A tumors demonstrated the highest expression of the ER- α gene, GATA binding protein 3 (GATA-3), X-box binding protein 1 (XBP1), trefoil factor 3, hepatocyte nuclear factor 3- α , and estrogen-regulated LIV-1. The luminal subtype B tumors had low-to-moderate expression of luminal-specific genes but with expression of

some of the genes characteristic of ER-negative tumors. An analysis of TP53 suggests that luminal subtype B tumors have accumulated more mutations than luminal subtype A tumors because only 16% of luminal subtype A tumors were TP53 mutation-positive while 71% of luminal subtype B tumors harbored this gene abnormality. A significantly worse overall survival and relapse-free survival were observed for patients with luminal subtype B ER+ tumors compared to those with luminal subtype A ER+ tumors (Figure 2).^{3,5} These data suggest that prognosis of ER+ breast cancer is determined by the presence of not

Figure 2.—Analyses of disease outcomes in two independent patient cohorts. A, overall survival (Norway/Stanford data set); B, time to distant metastasis (van’t Veer data set). (From Sorlie et al,⁵ with permission.)



only ER but several other transcription factors (GATA-3 and XBP1) that work in concert with ER to regulate transcriptional responses to estrogen. Low expression of any of these factors or the presence of critical mutations, such as TP53 loss-of-function or HER2 gene amplification, will be associated with poor outcomes.

TRANSITIONING MOLECULAR TESTS FROM EXPLORATION TO PROSPECTIVE CLINICAL TESTING

To use new information on molecular heterogeneity in ER+ breast cancer, good laboratory practice (GLP) tests need to be developed so that prospective trials can be conducted. This critical step is reflected in our

Table 1.—Levels of Evidence for Molecular Tests in Cancer

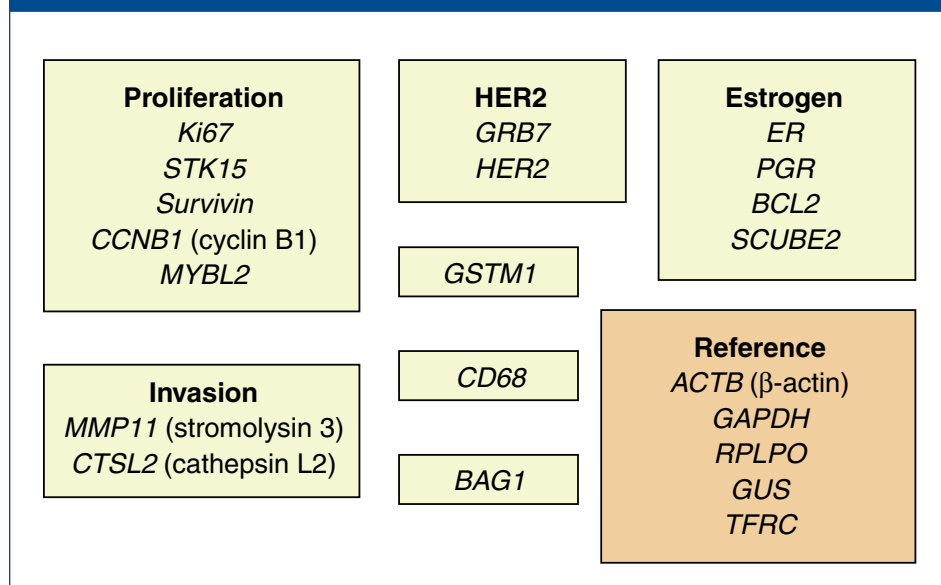
Level 1 – Prospective randomized trial using a validated and reproducible GLP assay as a means to select patients versus a standard selection approach, showing clinical benefit
Level 2 - Prospective cohort study using a validated and reproducible GLP assay as a means to identify patients with certain outcomes more effectively than with a standard clinical algorithm
Level 3 – Retrospective analysis of samples from a randomized trial using a GLP assay as a means to identify patients who benefited from an intervention versus those who did not
Level 4 – Retrospective cohort study with a validated and reproducible GLP assay
Level 5 – Retrospective cohort study on a non-GLP assay that shows statistically significant and independent effects on outcomes in adequately powered test and validation sets
Level 6 - Retrospective cohort study without validation

proposed modification of the evidence level approach for molecular testing in the cancer arena (Table 1). Level 1 evidence requires a prospective test of a GLP assay. The Oncotype DX assay is therefore of great interest as a GLP test that is ready for prospective studies. This test has been shown to distinguish between good and poor prognosis ER+ disease in the setting of a retrospective analysis of randomized clinical trials that examined both tamoxifen versus placebo with or without chemotherapy (Level 3 evidence). The Oncotype DX assay was developed to predict the recurrence rate of lymph node–negative and ER+ early-stage breast cancer (Figure 3).⁶ It consists of a panel of 16 cancer-related genes and 5 reference genes measured by quantitative reverse transcriptase polymerase chain reaction using RNA obtained from formalin-fixed paraffin-embedded tissue block with subsequent calculation of a recurrence score (RS). The 21-gene list and the RS were derived from the analysis of an initial 250 candidate genes, selected based on DNA microarray data in 3 genomic databases where gene expression patterns had been linked to patient outcome data.

Eight of the 16 cancer-related genes selected for the Oncotype DX assay were reported to distinguish between luminal A and luminal B subtypes, reflecting the fact that the genes used in the Oncotype DX assay were drawn from the published breast cancer gene lists. The utility of Oncotype DX assay was examined retrospectively in the large, multicenter NSABP trials B-14 (Tamoxifen versus Placebo in

Patients with Primary Breast Cancer and Negative Axillary Nodes Whose Tumors Are Positive for Estrogen Receptors) and B-20 (Tamoxifen versus Tamoxifen plus Either CMF or Methotrexate plus 5-fluorouracil in Premenopausal or Postmenopausal Women with ER-positive, Node-negative Breast Cancer). In patients on the tamoxifen arm of the NSABP B-14 trial, the 10-year distant recurrence rates for those at low (RS < 18), intermediate (RS 18 to 30), and high risk (RS ≥ 31) as predicted by the RS, were 6.8%, 14.3%, and 30.5%, respectively, independent of age and tumor size (Figure 4).⁶ A subset of individual genes (Cyclin B1, Survivin, MYBL2, STK15, Ki-67 PR, and GSTM1), the proliferation gene group score, and the RS were significantly associated with distant relapse-free survival in patients on the placebo arm of the NSABP B14 trial. Importantly, the RS appears to predict clinical benefits from tamoxifen and chemotherapy. Patients with high quantitative ER and low RS were found to benefit most from treatment with adjuvant tamoxifen (NSABP B-14 trial),

Figure 3.—Oncotype DX assay. The 21-gene panel including 16 cancer-related genes and 5 reference genes. (From Paik et al,⁶ with permission.)



and those with high RS were found to benefit most from chemotherapy (NSABP B-20 trial).⁷ Based on these data, the Oncotype DX assay is being used to change the management plan for a significant number of patients in clinical practice.⁸ However, because of the lack of Level 1 evidence, its routine use in the clinic remains controversial. A prospective study (US Intergroup Program for the Assessment of Clinical Cancer Tests [PACCT]) has recently been launched to further validate the utility of Oncotype DX assay (Figure 5).

ADDITIONAL MOLECULAR PROFILING APPROACHES IN DEVELOPMENT

The molecular features of luminal subtype A tumors (ER-rich, ER-regulated gene overexpression, low expression of “proliferation genes,” and absence of HER2 gene amplification signature) provide a rationale for these tumors’ sensitivity to endocrine therapy. However, with the exception of

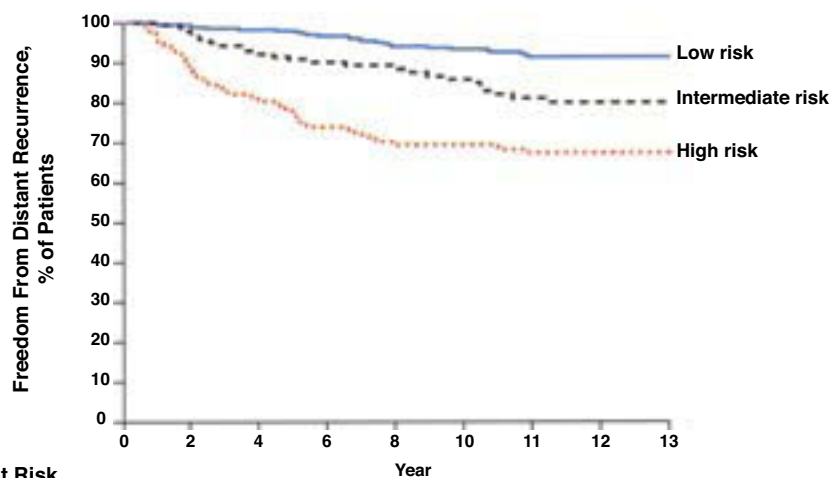
HER2 and Grb7, the genes utilized in the Oncotype DX panel and the categorization of luminal subtype A versus luminal subtype B do not provide a clear mechanistic insight into the nature of endocrine therapy resistance. One of the more recent applications for transcriptional profiling studies addresses this issue by exploring gene expression studies as a “pathway signature” identification tool that could be used to guide targeted therapy. Bild et al reported the feasibility of using recombinant adenovirus to express various oncogenic activities in human primary mammary epithelial cell cultures (HMECs) to develop gene expression signatures reflecting the activation status of a series of oncogenic pathways.⁹ Importantly, patterns of pathway deregulation that correlated with disease outcome were identified in several large collections of tumors that included lung cancers and breast cancers. Of particular interest is how pathway signatures predict sensitivity to therapeutic agents that target components of the

deregulated oncogenic pathways in breast cancer cell lines.⁹ This offers an opportunity to identify pathway-specific drugs that would also target ER+ tumors which are resistant to endocrine therapy.

Despite the potential utility of DNA microarray profiling, multiple pitfalls have slowed the clinical application of this technology. DNA microarray requires the use of high quality RNA obtained from fresh frozen samples, creating difficulties in tissue acquisition in day to day clinical practice. The use of different platforms and analytical tools affect the reproducibility of these tests. In addition, the immense amount of gene expression data presents a significant challenge for data management and analysis, as well as statistical validity. Potentially misleading information and false discovery can be a result of ignorance of important biological principles. Gene expression profiling provides only limited information on the underlying genetic abnormalities triggering the particular gene expression pattern, which is especially important in understanding the process of tumorigenesis, endocrine resistance, and identification of novel therapeutic targets.

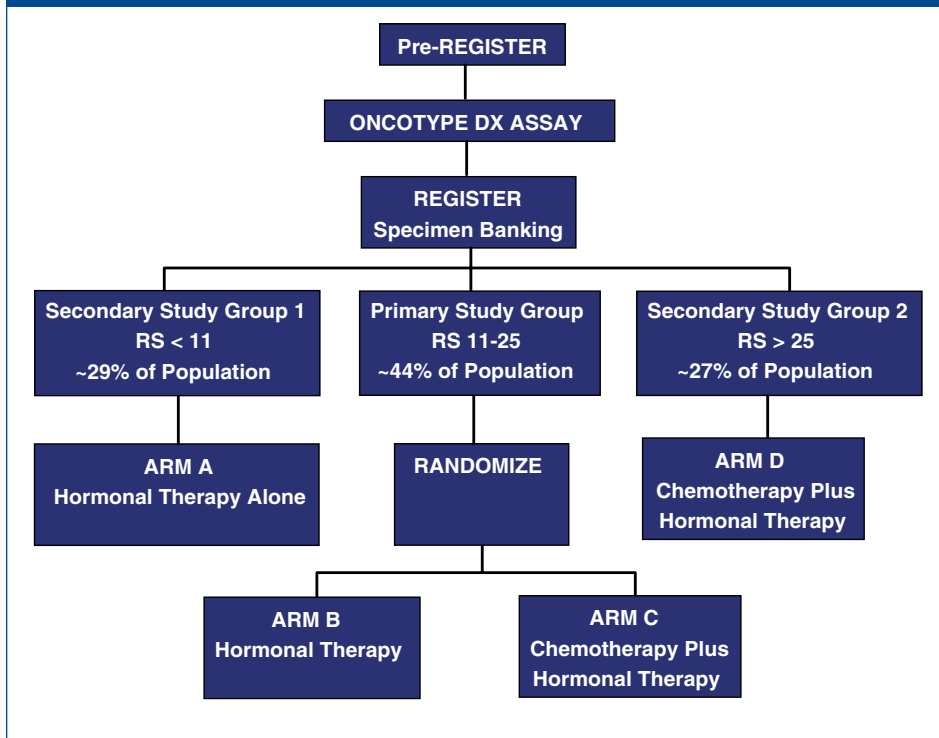
The central challenge is to subclassify ER+ breast cancers into groups that have distinct clinical outcomes and treatment approaches so that the management of the disease can be optimized. While RNA-based gene expression data has provided some clues, this approach will be widely supplemented by information at the DNA level using genome-wide microarray comparative genomic hybridization (aCGH). This technique allows the profiling of DNA copy number at high resolution (gene-by-

Figure 4.—Distance recurrence rate according to risk categories predicted by recurrence score. (From Paik et al,⁶ with permission.)



No. at Risk	0	2	4	6	8	10	11	12	13
Low risk	338	328	313	298	276	258	231	170	38
Intermediate risk	149	139	128	116	104	96	80	66	16
High risk	181	154	137	119	105	91	83	63	13

Figure 5.—Design of PACCT1:TAILORx Trial.



gene) so that gene amplifications or loss can be correlated with clinical outcomes. Genomic DNA isolated from tumor samples are fluorescently labeled with Cy5 and hybridized to cDNA micorarrays imprinted with thousands of genes along with the reference DNA (labeled with Cy3). Hybridization arrays are then analyzed for DNA copy number at various genomic loci. When used in conjunction with data obtained from gene expression arrays, a substantial impact on gene expression was observed due to gene copy number changes.^{10,11} In addition to copy number changes, DNA sequencing of tumor genomic material can be considered essential so that a complete picture of the somatic mutations indicative of underlying disease can be identified. This has been made possible by the availability of reference DNA sequences from the Human Genome Project and the high-throughput DNA sequencing facilities. Information on tumor somatic genetic mutations would complement gene expression data and would likely reveal the underlying

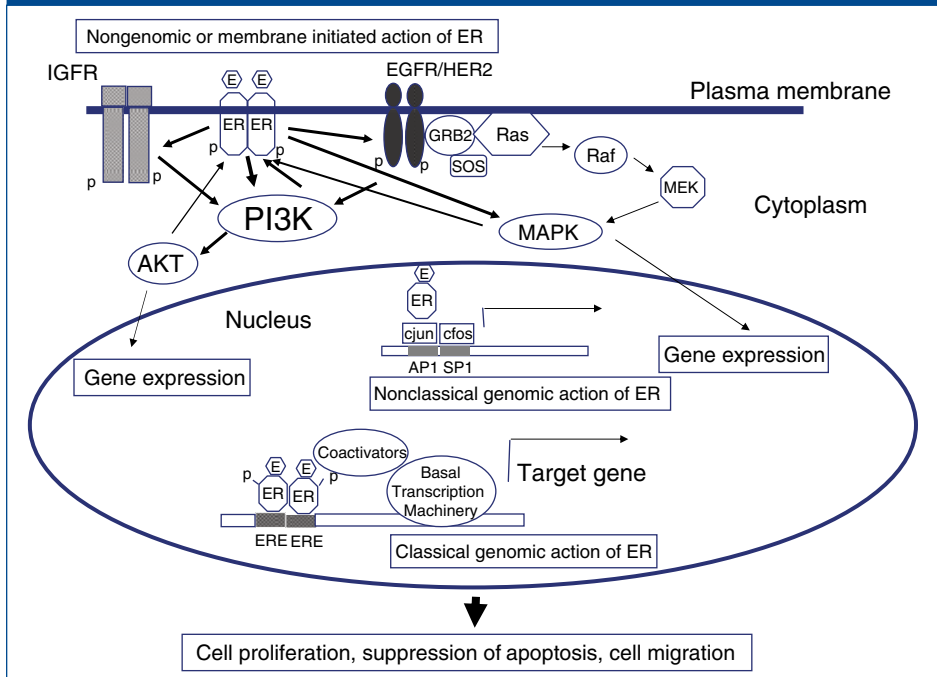
molecular mechanisms. Unraveling the tumor genome to decipher the genetic anomalies that drive a particular tumor phenotype is still in its infancy, but is now feasible with recent advances in genomic technologies.

APPLICATION OF NEW INSIGHTS INTO ESTROGEN ACTION

Clearly another key development stems from an improvement in our knowledge of estrogen action. For example, it is now recognized that there are at least two estrogen receptors, ER- α and ER- β .¹² The role of ER- β in endocrine therapy of breast cancer has not been completely elucidated. Both ER genes belong to the family of nuclear hormone receptors. The ER genes encode an N-terminal domain with a hormone-independent transcriptional function 1 (AF1), a DNA-binding domain, a dimerization domain, and a C-terminal hormone-binding domain with a hormone-dependent transcriptional activation function 2 (AF2). Binding of estrogen

activates ER through phosphorylation, dissociation from heat shock protein, conformational change, and dimerization. Classically, activated ER functions as a transcription factor in the nucleus to regulate gene expression through its direct interaction with the estrogen response elements (ERE) located upstream of estrogen-regulated genes (so called genomic action of ER). A number of co-regulatory molecules, co-activators, and co-repressors interact with the ER-estrogen complex and modulate the transcriptional activity of ER. In addition to transcriptional regulation through ERE, ER interacts with other transcription factors such as Fos-Jun complex to regulate genes containing alternative DNA sequences such as activator protein 1, transcription factor Sp1, and other sites (nonclassical mode of transcriptional regulation). Many genes regulated by ER are important for cell proliferation and apoptosis. In addition to the genomic action, another fundamental function of ER is to activate cytoplasmic signal transduction molecules through the action of membrane-associated ER (nongenomic actions of estrogen or membrane-initiated steroid signaling).¹² The nongenomic action of ER results in activation of growth factor receptors including insulin-like growth factor-1 receptor (IGF-1R), epidermal growth factor receptor (EGFR) and HER2, cellular tyrosine kinases, mitogen-activated protein kinases (MAPKs), phosphatidylinositol 3-kinase, Akt, and Src.¹³⁻²⁰ These later actions strongly emphasize the cross-talk between estrogen and peptide growth factor signaling and it seems likely that in the future we will be able to exploit this knowledge to address the problem of breast cancer heterogeneity and endocrine therapy resistance.²¹ As the catalog of somatic mutations that are documented in human breast cancer increases, it is

Figure 6.—Estrogen and peptide growth factor pathway. E = estrogen; ER = estrogen receptor; ERE = estrogen response element.



remarkable how many of them occur in genes that participate in the estrogen and peptide growth factor signaling network (Figure 6). A common theme is emerging whereby these key mutations generate constitutive or unregulated signals that abrogate the normal “lineage dependencies” that were inherited from the progenitor cell in the breast duct epithelium. A few examples, including HER2/*neu* and the PI3K/Akt signaling pathway as the key signaling pathway underlying the molecular mechanisms of endocrine resistance, will be discussed in more detail in the following sections.

HER2/*NEU* AND TREATMENT RESISTANCE

HER2 (HER2/*neu* or *c-erb-b2*) is a proto-oncogene located on chromosome 17q21.²² Although subsequently found to be the same gene, *neu*, *c-erb-b2*, and HER2 were discovered through 3 independent investigations in the 1980s, with *neu* identified as a transforming gene from ethylnitrosourea-induced rat neuroblastoma and *c-erb-b2* and

HER2 by sequence homology to the retroviral gene *v-erb-b*.²³⁻²⁵ The encoded 185 Kd protein contains intracellular, transmembrane, and cytoplasmic domains and belongs to a 4-member family of closely related growth factor receptors that includes HER1 (EGFR/*c-erb-b1*), HER2 (*c-erb-b2*), HER3 (*c-erb-b3*), and HER4 (*c-erb-b4*).²⁶ The oncogenic potential of HER2/*neu* overexpression has been demonstrated in both cell lines and animal models. One example is the MMTV-HER2 transgenic mouse which develops mammary tumors.²⁷ The exact mechanism of HER2 activation has not been fully understood and no ligands have been identified for this receptor. It is thought that heterodimerization with other members of the EGFR family or spontaneous homodimerization of HER2 initiates receptor phosphorylation and downstream signaling events.²⁸ This can be achieved by the binding of *neu* differentiation factors (NDF) or heregulins to HER3 or HER4 or the binding of EGF or transforming growth factor- α (TGF- α) to the EGFR.²⁸

HER2 overexpression/amplification occurs in 20% to 30% of breast cancer and is associated with higher histology grades, lower expression of ER, and progesterone receptors (PR) and worse clinical outcomes.^{29,30} Nonetheless, about 10% of ER+ breast cancer has HER2 gene amplification,²⁹ and ER+ tumors that exhibit HER2 gene amplification exhibit a lower dependence on estrogen and resistance to endocrine interventions. This is likely due to hyperactivation of MAPK and downregulation of ER due to HER2 overexpression.³¹ Implanted into ovariectomized athymic nude mice, an ER+ breast cancer cell line (MCF-7) transfected with HER2 demonstrated resistance to tamoxifen, although its growth was still estrogen dependent, supporting the possibility of endocrine resistance due to HER2 overexpression in breast cancer.³² Other studies indicate that HER2 overexpression reduces that dependence to estrogen.^{33,34} Consistent with the preclinical finding of tamoxifen resistance, HER2 overexpression leads to a dramatically reduced response rate to tamoxifen in ER+ metastatic breast cancer.³⁵⁻³⁷ HER2 overexpression has also been correlated with shorter disease-free and overall survival in the subset of patients treated with tamoxifen for early-stage breast cancer.^{38,39} In the setting of neoadjuvant therapy, a double-blinded, randomized, phase III neoadjuvant endocrine therapy trial comparing 4 months of letrozole with tamoxifen demonstrated superiority of letrozole with higher response rate (60% vs 41%, $P = .004$) and higher proportion of patients undergoing subsequent breast conservation surgery (48% vs 31%, $P = .036$).⁴⁰ Importantly, the most dramatic difference in response rate was observed in the subgroup of patients who had ER+ and HER2 and/or HER1 overexpressing tumors (88% vs 22%, $P = .0004$).⁴⁰

These studies raised the possibility of aromatase inhibitors in overcoming endocrine resistance conferred by HER2 overexpression. To address this issue further, the proliferative marker Ki67 was assessed. Intriguingly, less suppression of Ki67 following letrozole therapy was observed for HER2 amplified tumors when compared to HER2 nonamplified tumors, although a similar clinical response rate to letrozole was observed for these two groups of patients.⁴¹ This indicates a continued proliferation despite estrogen deprivation and could imply therapeutic resistance that may manifest later in the course of the disease.

Exciting data published recently shows that the use of the HER2-targeting monoclonal antibody trastuzumab reduces the relapse rate in ER+ HER2+ tumors and so for tumors that exhibit endocrine resistance in this setting, a targeted adjuvant option to improve outcomes is emerging. This will not be the whole story, however, because patients with ER+ HER2+ tumors treated with a combination of letrozole and trastuzumab in the advanced disease setting only respond about 25% of the time.⁴² These data suggest that common somatic mutations in the estrogen receptor growth factor network may work in concert to reduce the efficacy of both endocrine treatment and trastuzumab.

THE PHOSPHATIDYLINOSITOL 3-KINASE (PI3K) SIGNALING CASCADE AND TREATMENT RESISTANCE

There is emerging evidence that somatic mutations in genes encoding components of the phosphatidylinositol 3-kinase (PI3K) signaling cascade hold the key to improving the outcome of both endocrine therapy and trastuzumab treatment.^{43,44}

Class Ia PI3Ks play a pivotal role in mediating cellular response to a wide range of trophic signals including soluble growth factors and attachment to the extracellular matrix.^{45,46} The enzyme is a heterodimer composed of the regulatory subunits and the one of three p110 catalytic subunits (p110 α , p110 β , or p110 δ). The enzyme is activated by a direct interaction between the regulatory subunit and the phosphotyrosine residues of activated growth factor receptors or adaptor proteins. The activated PI3K phosphorylates plasma membrane lipid phosphatidylinositol-4,5-bisphosphate at the 3'-OH position of the inositol ring to form the important second messenger phosphatidylinositol 3,4,5-trisphosphate (PIP₃). PIP₃ in turn activates downstream signaling pathways, including the serine-threonine kinase Akt, and subsequent induction of a coordinated set of events leading to cell growth, migration, and survival.⁴⁶ The termination of PI3K signaling can be mediated by phosphatases. The lipid phosphatase PTEN (phosphatase and tensin homologue deleted from chromosome 10) is a powerful negative regulator of the PI3K/Akt pathway that acts by dephosphorylating phosphatidylinositol trisphosphate and plays an important role in regulating cell cycle and apoptosis.⁴⁷⁻⁵² Consistent with the important role of PI3K signaling in cellular signal transduction, the p110 α catalytic subunit (PIK3CA) was found to be a transforming oncogene,⁵³ and loss of PTEN stimulates tumor development in mice.⁵⁴ Germline mutation of PTEN causes Cowden disease, which is an autosomal dominant genetic disorder with significantly increased risk of breast (lifetime risk of > 50%), thyroid, and skin cancer.⁵⁵

Recently, activating mutations in the PIK3CA gene encoding the

PI3K p110 α catalytic subunit were identified in ~ 20% to 40% of breast tumors, which were more prevalent than TP53 mutation and HER2/*neu* amplification in the same tumor set.⁵⁶⁻⁵⁹ Mutations have been identified within exons 1, 2, 4, 5, 7, 9, 12, 13, 18, and 20, with the majority clustered in the "hotspot" regions in exons 9 (the helical domain) and 20 (the kinase domain).^{56,59} At least one hotspot mutation appears to increase the kinase activity.⁶⁰ PIK3CA mutations appear to correlate with larger tumor size, lymph node metastasis, positive ER status, and positive PR status in two of the larger studies.^{57,58} Patients with PIK3CA mutations showed significantly worse cancer-specific survival ($P = .004$).⁵⁸ Multivariate analysis, including nodal status, histology grade, tumor size, and TP53 mutations, indicated that PIK3CA mutation was an independent prognostic factor for worse survival in patients with ER+ and HER2 nonamplified tumors.⁵⁸

PTEN gene mutations which result in loss of PTEN expression or function and constitutive PI3K pathway signaling have also been observed in sporadic cancers, occurring in up to 50% of breast tumors.⁶¹ Loss of PTEN by immunohistochemistry staining has been associated with lymph node metastasis and poor breast cancer outcome with worse rates of disease recurrence and disease-related death.^{62,63} Unlike mutations of PIK3CA, reduced PTEN expression is associated with reduced expression of ER^{44,64} and PIK3CA gene mutations may be mutually exclusive with PTEN loss, although this is controversial.⁵⁷ Importantly, a strong association was observed between reduced PTEN expression and failure to respond to tamoxifen therapy in patients with ER+ breast cancer.⁴⁴

It has been shown in vitro that the PI3K/Akt pathway interacts with the

ER pathway and confers endocrine resistance.⁶⁵⁻⁶⁷ Studies using breast cancer cell lines demonstrated that the PI3K/Akt signaling pathway led to estrogen-independent activation of ER- α , with phosphorylation of ER and subsequent upregulation of estrogen-regulated *pS2* gene, *Bcl-2*, and macrophage inhibitory cytokine 1.⁶⁷ In addition, overexpression of Akt protected breast cancer cells from tamoxifen-induced apoptosis.⁶⁷ Treatment with PI3K inhibitor LY294002 enhanced the apoptotic effect of tamoxifen.^{65,67} Similarly, the mTOR inhibitor RAD001 potentiated the antitumor effect of both tamoxifen and letrozole in breast cancer cells.⁶⁸ An important observation which might have therapeutic implications is that reduced PTEN expression in breast cancer cells confers susceptibility to mTOR, the downstream target of Akt, and inhibitors of PI3K or mTOR restore endocrine responsiveness in breast cancer cells with aberrant Akt activity.^{69,70}

Collectively, these observations suggest that genomic alterations leading to constitutive activation of the PI3K pathway, or specific components of this pathway, exist in the majority of breast cancers. Therefore, this presents an opportunity for treating breast cancer with PI3K pathway inhibitors to circumvent endocrine resistance. The preclinical studies stated above provided rationale for the combination strategy to target both the ER and the PI3K/Akt signaling pathway. Direct inhibitors of PI3K are probably too toxic for clinical development. However, derivatives of rapamycin including CCI-779 and RAD001, which are specific inhibitors to the PI3K/Akt pathway target mTOR, are currently under clinical trial development for breast cancer treatment. Although these trials have only recently begun, early results from

a phase II trial with the rapamycin analogue CCI-779 in a cohort of patients with advanced disease indicated that objective responses were seen in a subset of patients.⁷¹ Interestingly, patients responding to treatment had tumors with HER2 overexpression and/or loss of PTEN expression, which is consistent with preclinical data discussed earlier.⁷¹

Based on the potential synergistic effect of letrozole and mTOR inhibitors, a phase II study was designed comparing the combination of letrozole and CCI-779 to letrozole alone in patients with advanced or metastatic breast cancer. Preliminary results of the study were reported at the recent San Antonio Breast Cancer Symposium in 2005.⁷² All patients received 2.5 mg letrozole and were randomized to receive either letrozole alone, CCI-779 at a 10-mg daily schedule, or CCI-779 at a 30-mg intermittent schedule (daily for 5 days every 2 weeks). As of 7 April 2005, 92 patients enrolled (daily: $n = 33$; intermittent: $n = 30$; letrozole alone: $n = 29$). The combination was found to be well tolerated, with the most common grade 3-4 toxicity being hyperglycemia. Patients treated with the combination of letrozole and CCI-779 at the 30-mg intermittent dosing had a longer median progression-free survival (PFS) (10 mg daily: 11.5 months; 30 mg intermittent: 13.2 months; letrozole alone: 11.6 months), a higher estimated rate of PFS at 16 months (10 mg daily: 39%; 30 mg intermittent: 45%; letrozole alone: 27%), and less disease progression and death (10 mg daily: 48%; 30 mg intermittent: 37%; letrozole alone: 62%) than patients in the other 2 cohorts. A phase III, randomized, double-blind study was conducted to further evaluate the combination of letrozole, with or without 30 mg intermittent dosing of CCI-779 daily. However, the study was terminated in March 2006 after the planned interim

analysis showed that it is unlikely to achieve the targeted level of efficacy for the combination therapy compared to letrozole alone.⁷³ RAD001 is also being tested in combination with letrozole in clinical trials.⁷⁴ The question remains whether there is a subpopulation of patients who would benefit the most from the combination therapy, but one might reasonably suspect that it would be the population of patients with tumors that carry mutations in the PI3K pathway.

SUMMARY

This paper presents the argument that the presence of deregulating mutations in the ER growth factor signaling pathway creates a molecular “glass ceiling” that limits further improvement of breast cancer endocrine therapy with agents that target ER alone. A better understanding of the functional and clinical consequences of the spectrum of somatic mutations in ER+ breast cancer is therefore essential if further progress in breast cancer endocrine treatment is to be made. When we have cataloged all the relevant somatic mutations that impact on the efficacy of endocrine therapy not only will we be able to identify patients with a poor prognosis despite treatment, but this knowledge will show where the opportunities for targeted interventions lie, allowing us to break through the glass ceiling to produce the next round of truly impressive gains in the treatment of ER+ breast cancer.

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Learning Assessment

Please choose the one best answer for each question and mark the appropriate box on the evaluation form on page 36.

- In premenopausal women with estrogen receptor–positive (ER+) metastatic breast cancer
 - LHRH agonists are equivalent to surgical ovariectomy
 - the combination of an LHRH agonist and tamoxifen is superior to the LHRH agonists alone
 - aromatase inhibitors (AIs) are equivalent to tamoxifen
 - both a and b are correct
- Clinical trials comparing AIs to tamoxifen as first-line therapy for postmenopausal advanced ER+ breast cancer have demonstrated that
 - AIs are at least equivalent to tamoxifen
 - tamoxifen was usually superior in efficacy but associated with more complications
 - AIs were generally superior to tamoxifen but also had a high incidence of serious adverse reactions
 - tamoxifen was better tolerated than AIs but overall equivalent
- In a pooled analysis of two large trials comparing fulvestrant and anastrozole in women with advanced breast cancer who had relapsed or progressed following endocrine therapy,
 - fulvestrant was superior to anastrozole
 - anastrozole was superior to fulvestrant
 - time to progression and time to treatment failure were equivalent for anastrozole and fulvestrant
 - there was a high incidence of thromboembolic events
- In premenopausal women with advanced breast cancer, AIs should
 - always be given as a single agent
 - be given in combination with tamoxifen
 - always be given in combination with ovarian function suppression
 - not be used
- The primary difference between the nonsteroidal AI (anastrozole and letrozole) and the steroidal AI (exemestane) is that
 - binding of the nonsteroidal AI to the enzyme is reversible; however, binding of the steroidal AI is irreversible
 - binding of the steroidal AI to the membrane is reversible; however, binding of the nonsteroidal AI is irreversible
 - the steroidal AI can only be administered via intramuscular injection
 - the nonsteroidal AI must be administered twice daily
- The BIG FEMTA trial demonstrated that 5 years of adjuvant letrozole
 - provided equivalent benefit in terms of disease-free survival (DFS) and time to recurrence (TTR) as 5 years of tamoxifen
 - improved both the event-free survival and breast cancer–free survival as compared to tamoxifen
 - resulted in event-free survival slightly inferior to tamoxifen
 - was associated with more hot flashes and vaginal bleeding than tamoxifen
- In 2005, the American Society of Clinical Oncology Technology Assessment Panel recommended that adjuvant hormonal therapy for postmenopausal women with hormone receptor–positive breast cancer include
 - tamoxifen, reserving AIs if needed for management of recurrent disease
 - an aromatase inhibitor as initial therapy or after treatment with tamoxifen
 - LHRH agonist plus tamoxifen or an AI as adjuvant therapy
 - a combination of tamoxifen and an AI for 2 or 3 years
- When compared to tamoxifen, anastrozole, letrozole, and exemestane in the ATAC, BIG 1-98, and IES trials, respectively, were associated with
 - fewer thromboembolic events
 - more thromboembolic events
 - a similar frequency of thromboembolic events
 - more endometrial cancer
- The presence of luminal subtype B ER+ tumors compared to luminal subtype A ER+ tumors
 - has been associated with significantly worse overall survival and relapse-free survival
 - has been associated with significantly improved overall survival and relapse-free survival
 - has a similar prognosis
 - reduced incidence of hepatic and brain metastases
- Retrospective molecular profiling analysis of the NSABP B-14 and B-20 clinical trials using the Oncotype DX assay reported that women with
 - high quantitative ER and low recurrence score (RS) were most likely to benefit from tamoxifen
 - high RS were most likely to benefit from chemotherapy
 - low quantitative ER and low RS were most likely to benefit from chemotherapy
 - both a and b are correct
- The subset of ER+ tumors that also exhibit HER2 gene amplification
 - are very sensitive to endocrine therapy
 - are more likely to respond to tamoxifen than AIs in women with metastatic disease
 - have been shown to be more responsive to letrozole than tamoxifen in a neoadjuvant trial
 - both a and b are correct
- PIK3CA mutations appear to correlate with
 - larger tumor size, ER+ status, and longer survival
 - smaller tumor size, ER-negative status, and longer survival
 - ER+ status, shorter survival, and positive lymph nodes
 - ER-negative status, shorter survival, and positive lymph nodes
- Reduced expression of PTEN is associated with
 - failure to respond to tamoxifen in ER+ tumors
 - susceptibility to mTOR
 - resistance to mTOR
 - both a and b are correct

Evaluation Form

Name and Address Information (please print clearly)

Print name, credentials Physician Other

Mailing address for statement of credit

City/State/ZIP code

E-mail address*

Telephone (with area code)

Fax (with area code)

Position/Title

*Participants who provide an e-mail address and satisfactorily complete the activity will receive their statement of credit via e-mail.

Evaluation

Excellent Good Satisfactory Poor

Accuracy and timeliness of the content	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Relevance to your daily practice	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Freedom from commercial bias	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Extent to which learning objectives were met	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Overall quality of this activity	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Usefulness of learning materials as future reference	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

What is the most important thing you learned from this activity? (check all that apply)

- Current treatment options Diagnostic strategies
 Clinical trial information New treatment options
 Other _____

What questions do you still have regarding this topic? (check all that apply)

- Clinical trial information Side effect management None
 Applicability to other populations Other _____

Why did you participate in this activity? (check all that apply)

- Amount of CE credit Convenience Format (live, Internet, CD-ROM, etc)
 Importance of the topic Quality of the faculty Other

What professional changes do you anticipate as a result of participating in this activity? (check all that apply)

- Current treatment strategy Enhanced ability to educate colleagues Improved patient education
 Treatment options Diagnostic strategies Quality of life issues
 Offering new therapies Other _____

Topics for future activities _____

May we contact you via mail or e-mail to assess the usefulness of this activity? Yes No

Would you like to join our private mailing list and receive notifications of our newest CE activities through our monthly Meniscus Educational Institute (MEI) CE Activities Update e-newsletter? Yes No I've already joined

How did you hear about this educational activity? (please check only one)

- Direct mail (eg, brochure) E-mail announcement
 Hyperlink from another Internet site MEI CE Activities Update e-newsletter
 Meniscus Limited Web site Sales representative Other _____

I hereby verify that I participated in this educational activity for _____ minutes, including the evaluation.

Signature _____ Date _____

Answers

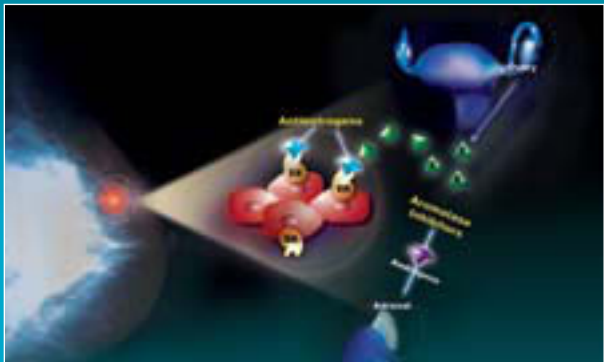
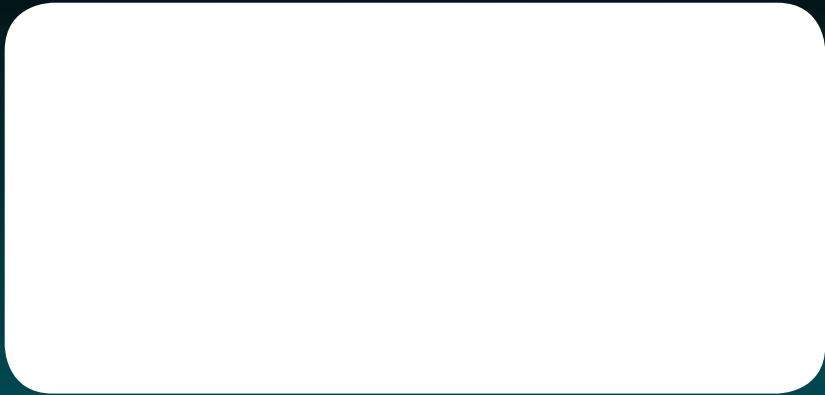
(REFER TO THE LEARNING ASSESSMENT ON PAGE 35)

	a	b	c	d
1.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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11.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



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TRANSLATING ADVANCES *IN HORMONAL THERAPIES FOR BREAST CANCER INTO CLINICAL PRACTICE*