REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Systemic Therapy for Estrogen Receptor–Positive, HER2-Negative Breast Cancer

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Breast cancers that are positive for estrogen receptor (ER) and negative for human epidermal growth factor receptor 2 (HER2) (hereafter referred to as ER-positive) are the most common subset of breast cancers, accounting for 65% of cases of breast cancer among women less than 50 years of age and 75% of cases among older women.[1] Estrogen binding to ER stimulates receptor-regulated transcription, which in turn promotes tumor-cell growth and proliferation. Hormone-based treatments for ER-positive tumors deplete estrogen production, interrupt ER signaling, degrade ER, or alter ER-regulated signaling or proliferation pathways (Fig. 1).

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Pathological and Genetic Features of ER-Positive Tumors

ER-positive breast cancer is heterogeneous. Tumors vary with respect to quantitative levels of ER, progesterone receptor (PR) expression (which is ER-driven), histologic grade, degree of proliferation (as measured by Ki-67 labeling or other indexes), patterns of gene expression, and the type and frequency of genomic alterations. These features are highly interrelated (Fig. 2 and Table 1), with important clinical implications. Low-grade (well-differentiated) tumors have higher ER and PR expression and lower rates of proliferation, whereas intermediate- and high-grade tumors may have lower levels of ER and may lack PR expression, with higher rates of cell proliferation (Fig. 2).[2] Most ER-positive tumors are the ductal histologic subtype; however, 15% are the lobular subtype, which is associated with loss of the cell-adhesion protein E-cadherin, resulting in loss of cell cohesion and tumor growth in a "single-file" pattern (Fig. 2). Uncommon histologic subtypes, such as cribriform and tubular carcinomas, are invariably characterized by strong ER expression, a low grade, and an excellent prognosis.[3]

Hereditary cancer genes account for 8 to 10% of ER-positive cancers; such genes include *CHEK2* (1% of cases) and genes associated with homologous recombination deficiency, such as *BRCA1* (2%), *BRCA2* (2%), *ATM* (0.5 to 1%), and *PALB2* (0.5 to 1%).[4] The prevalence of hereditary mutations in ER-positive breast cancer is highest among patients who are younger than 40 years of age (approximately 15%) and declines progressively with increasing age (approximately 10% among women 40 to 60 years of age and approximately 5% among those over the age of 70 years). Although *BRCA1* mutations are disproportionately associated with cancers lacking ER and HER2, most breast cancers arising in *BRCA2*, *PALB2*, *CHEK2*, and *ATM* mutation carriers are ER-positive, mirroring the distribution of sporadic cases.[5,6] Systemic therapy for early-stage hereditary breast cancers does not differ from systemic therapy for nonhereditary cases. As with sporadic cancers, hereditary

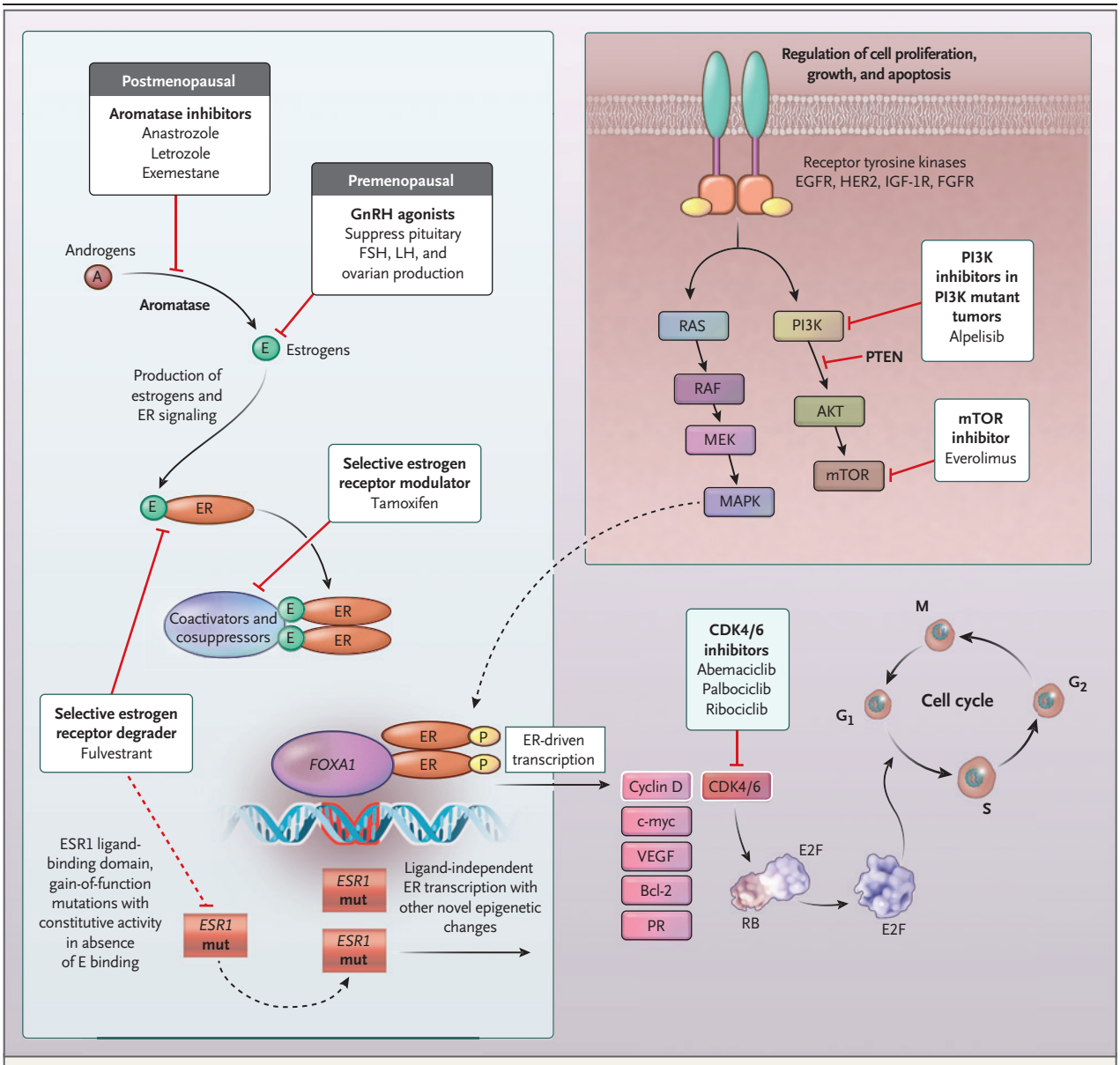

Figure 1. Mechanisms of Action and Resistance in Estrogen Receptor (ER)–Targeted Therapy.

Estrogen production and ER signaling are drivers of breast cancer tumorigenesis, growth or proliferation, and metastasis and are the focus of drugs that are effective in the treatment of early-stage breast cancer. Novel targeted treatments, in combination with endocrine therapy, can improve outcomes in advanced breast cancer and inhibit the activity of key pathways in cell growth, proliferation, and metastasis. Mutations in the ER gene *ESR1* (*ESR1* mut) or epigenetic changes in c-myc, cyclin D, and epidermal growth factor receptor (EGFR) are associated with resistance to endocrine therapy. Loss of retinoblastoma protein (RB) is associated with resistance to cyclin-dependent kinase 4 and 6 (CDK4/6) inhibition in advanced breast cancer. AKT, fibroblast growth factor receptor (FGFR), and human epidermal growth factor receptor 2 (HER2) represent overexpression, amplification, or mutation implicated in either endocrine therapy or CDK4/6 inhibition. FSH denotes follicle-stimulating hormone, GnRH gonadotropin-releasing hormone, IGF-1R insulin-like growth factor 1 receptor, LH luteinizing hormone, mTOR mammalian target of rapamycin, P progesterone, PI3K phosphatidylinositol 3-kinase, and PR progesterone receptor.

cancers can be treated with breast-conserving surgery and radiation therapy, though many patients carrying such mutations choose mastectomy (including contralateral mastectomy) instead of breast conservation in order to prevent a second breast cancer.[7]

Genomic sequencing and profiling based on patterns of RNA expression among genes known

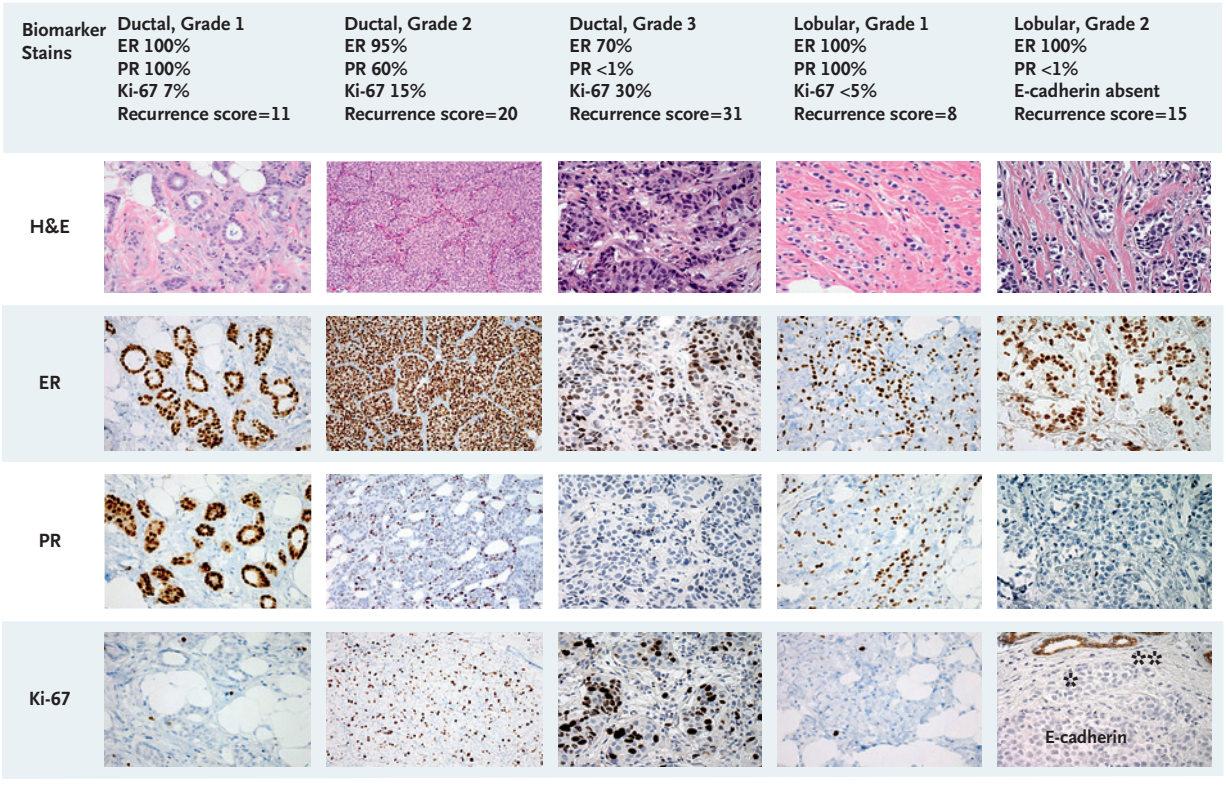

Figure 2. Pathological Features of ER-Positive, HER2-Negative Breast Cancers.

The photomicrographs show the spectrum of pathological features of ER-positive breast cancers and common relationships among tumor grade; ER, PR, and Ki-67 expression (an indicator of cellular proliferation); and recurrence score (ranging from 0 to 100, with higher scores indicating a greater chemotherapeutic benefit and lower scores indicating a lower risk of recurrence in the absence of chemotherapy). Duct formation among the ductal carcinomas ranges from low to high, and the lobular carcinomas display the classic "single file" pattern of tumor growth. The photomicrographs show routine immunohistochemical biomarker stains, with quantitative estimates of the degree of expression. Low-grade tumors have greater degrees of ER and PR expression than intermediate- or high-grade tumors and, conversely, have lower percentages of Ki-67 expression, indicative of lower rates of tumor proliferation. The photomicrograph of the grade 2 lobular tumor (bottom row, right) shows immunohistochemical staining for E-cadherin expression on normal ductal tissue (double asterisk) but an absence of expression on lobular carcinoma cells (asterisk). H&E denotes hematoxylin and eosin.

to be important in tumor pathogenesis and prognosis have corroborated the pathobiologic heterogeneity of ER-positive tumors and the relationships among grade, proliferation, and patterns of gene expression (Table 1 and Fig. 2).[8,9] ER-positive cancers with genomic luminal A, lower-risk signatures tend to be strongly ER-positive and PR-positive, with a lower grade, less proliferation, and a better prognosis; luminal B, higher-risk signatures correlate with lower expression of ER, PR, or both, a higher grade, and greater proliferation (Table 1),[10,11] with a higher risk of recurrence. Genomic assays, including the 21-gene recurrence score, the 70-gene assay, and the 50-gene intrinsic subtype, tend to correlate with one another with respect to recurrence risk for ER-positive tumors, with broad but imprecise concordance with the results of routine pathological assessment.[12-14] Histologic ascertainment of grade, ER and PR status, and proliferation assessed according to Ki-67 labeling can serve as a limited surrogate for genomic classifiers,[15] but thresholds for Ki-67 are not standardized,[10] and persistent challenges complicate the determination of tumor grade.[16]

PROGNOSTIC FACTORS

Integrating anatomical stage (tumor size and nodal status) with tumor grade and genomic

Table 1. Associations among Tumor Subtype, Pathological Features, Genomic Biomarkers, and Outcomes in Early-Stage, Estrogen Receptor–Positive Breast Cancer.*

Variable	Luminal A Subtype	Spectrum between Luminal A and Luminal B	Luminal B Subtype
Pathological grade	1 (low); well differentiated	2 (intermediate); moderately differentiated	3 (high); poorly differentiated
ER expression	+++	++ to +++	+ to ++
PR expression	++ to +++	0 to +++	0 to ++
Ki-67 proliferation index (%)	<10	10 to 20	>20
21-Gene recurrence score†	<11	11 to 25	>25
Other genomic signatures‡	Lower	Lower to higher	Higher
Recurrence risk	Lower	Lower to higher	Higher
Effect of endocrine therapy (regardless of stage)	+++	++ to +++	++ to +++
Effect of chemotherapy (may depend on stage)	0	0 to +	+++

* Intrinsic subtypes luminal A and luminal B are at opposite ends of a spectrum of relationships among histologic grade, estrogen receptor (ER) and progesterone receptor (PR) expression, measures of tumor proliferation, genomic signatures, and treatment effects. These relationships, which are not necessarily direct or linear, suggest that the likely benefit of adjuvant endocrine and chemotherapeutic treatment depends on the tumor subtype. The number of plus signs indicates the relative degrees of ER and PR expression and treatment effect.

† The 21-gene recurrence score ranges from 0 to 100, with higher scores indicating a greater chemotherapeutic benefit and lower scores indicating a lower risk of recurrence in the absence of chemotherapy.

‡ Other genomic signatures include the 70-gene signature (MammaPrint), the Breast Cancer Index, EndoPredict, and the Genomic Grade Index.

signatures provides refined prognostic estimates for the clinical spectrum of ER-positive breast cancers.[17-21] Smaller tumors with luminal A features in the absence of nodal involvement have the lowest risk of recurrence. Incremental changes in anatomical stage and, separately, biologic risk factors such as grade, proliferation, ER expression, and genomic signatures increase the risk of recurrence. The same prognostic factors for metastatic recurrence also predict local and regional recurrence after surgery and radiation therapy.[22-24] Cancers in premenopausal women younger than 40 years of age tend to have lower levels of ER, a higher tumor grade, and adverse genomic signatures, as compared with cancers in older, postmenopausal women. These features, along with a higher stage at diagnosis and the persistence of ovarian function, largely account for the effect of age on prognosis.[2,11,25] Recurrence rates for ER-positive cancers are relatively constant over many years, and tumors may recur over a long arc of time. At least half of recurrences arise 5 years after diagnosis, and events beyond 10 years are not uncommon.[26,27] The risk factors for early recurrence (in the first 5 years after diagnosis) and for late recurrence (more than 5 years after diagnosis) are largely the same: higher nodal and tumor stage, higher grade, and adverse genomic assays.[11,27-29]

ADJUVANT TREATMENT

ENDOCRINE THERAPY

Adjuvant endocrine therapy for 5 to 10 years is recommended for nearly all patients with ER-positive breast cancer to prevent metastatic disease, local–regional recurrence, and contralateral tumors.[30] Endocrine treatment is effective for luminal A and luminal B tumor subtypes.[31] Five years of treatment with tamoxifen, a selective modulator of ER function (Fig. 1), has been the traditional standard of care, regardless of menopausal status, reducing both distant and local–regional recurrence by 10 to 30% when ER expression is moderate and by 40 to 50% when ER expression is high, with carryover effects lasting 15 or more years.[30] Even at the lower end of the risk spectrum — subcentimeter, node-negative tumors — adjuvant endocrine therapy improves outcomes.[32] Tamoxifen is metabolized

by the hepatic enzyme CYP2D6, but genotypic variation in *CYP2D6* has not been shown to affect the benefit of tamoxifen therapy, and testing is not recommended.[33]

The extent of ER expression is a key determinant of the benefit from endocrine therapy. Women with cancers that are negative for both ER and PR do not benefit from adjuvant endocrine treatment.[30] One percent of breast cancers are classified as ER-negative but PR-positive, perhaps reflecting undetectable levels of ER expression; these tumors are associated with intermediate outcomes between those for ER-positive cases and those for ER-negative, PR-negative cases.[34] Very low ER expression (immunohistochemical staining of only 1 to 10% of tumor cells), which is found in 2 to 3% of hormone receptor–positive cancers, can confer sensitivity to endocrine treatment, though only a minority of such tumors carry genomic signatures that are typical of ER-positive cancers, and endocrine treatment is less valuable when ER expression is weak than when it is more robust.[30,35-37]

In recent years, the options for adjuvant endocrine treatment have broadened beyond tamoxifen. Aromatase inhibitors block the conversion of androgens into estrogens (Fig. 1), suppressing residual estrogen levels by more than 90% in postmenopausal women. These agents are contraindicated in premenopausal women who are not undergoing ovarian suppression, because compensatory physiological responses induce ovarian estrogen production. Aromatase inhibitor therapy results in a greater reduction in the risk of recurrence than 5 years of tamoxifen, such that most postmenopausal women should consider aromatase inhibitor treatment either as initial therapy or after 2 to 3 years of tamoxifen.[38] For women presenting with stage I or IIA cancers — the most common stage at diagnosis in countries where screening mammography is routine — the numerical advantage of aromatase inhibitor–based treatment over tamoxifen alone is modest: a 3% reduction in recurrence and a 2% reduction in mortality at 10 years. Aromatase inhibitors are of more value in the treatment of higher-risk cancers (according to stage or biologic features) because of the underlying prognosis[39] and in the treatment of lobular cancers.[40] Extending the duration of treatment from 5 to 10 years with either tamoxifen[41] or aromatase inhibitors[42,43] reduces the risk of recurrence, as compared with just 5 years of treatment. Patients at increased risk for a late recurrence because of nodal status or adverse biologic features of the tumor probably derive the greatest benefit from extended therapy; however, extended aromatase inhibitor treatment in years 8 through 10 is likely to confer a modest benefit, at most.[44,45] The decision to extend therapy should incorporate the patient's preferences, informed by the estimated risk of recurrence beyond year 5, and the toxic effects of therapy to date (Figs. 3 and 4).

Chemotherapy frequently causes premature ovarian failure, especially in women 40 years of age or older. In retrospective analyses, women with ER-positive breast cancer and chemotherapy-induced amenorrhea had a more favorable prognosis than those who remained premenopausal, suggesting an endocrine effect that confounds the traditional interpretation of the benefit of chemotherapy in younger women.[46] Prospective studies show that gonadotropin-releasing hormone (GnRH) agonist therapy for ovarian suppression (Fig. 1) reduces the risk of recurrence when added to either tamoxifen or an aromatase inhibitor, particularly among younger women (<40 years of age) and those with higher-stage cancer or adverse tumor biologic features (luminal B, lower ER expression, and higher grade and Ki-67 proliferation index).[47,48] As observed in trials involving postmenopausal women, aromatase inhibitors may offer additional risk reduction, as compared with tamoxifen, among women undergoing ovarian suppression. By contrast, among women with ER-positive tumors associated with a very favorable prognosis — typically, stage I, low-grade tumors not treated with chemotherapy — ovarian suppression has a limited benefit in reducing recurrence, as compared with tamoxifen alone.[47-49] Ascertaining menopausal status in women receiving adjuvant therapy can be challenging, because GnRH agonists occasionally provide incomplete ovarian suppression, particularly in younger women not receiving chemotherapy, and because women with chemotherapy-induced amenorrhea may recover ovarian function.[50] If the status of residual ovarian function is uncertain, GnRH agonist therapy or surgical oophorectomy to ensure postmenopausal endocrine function — or tamoxifen-

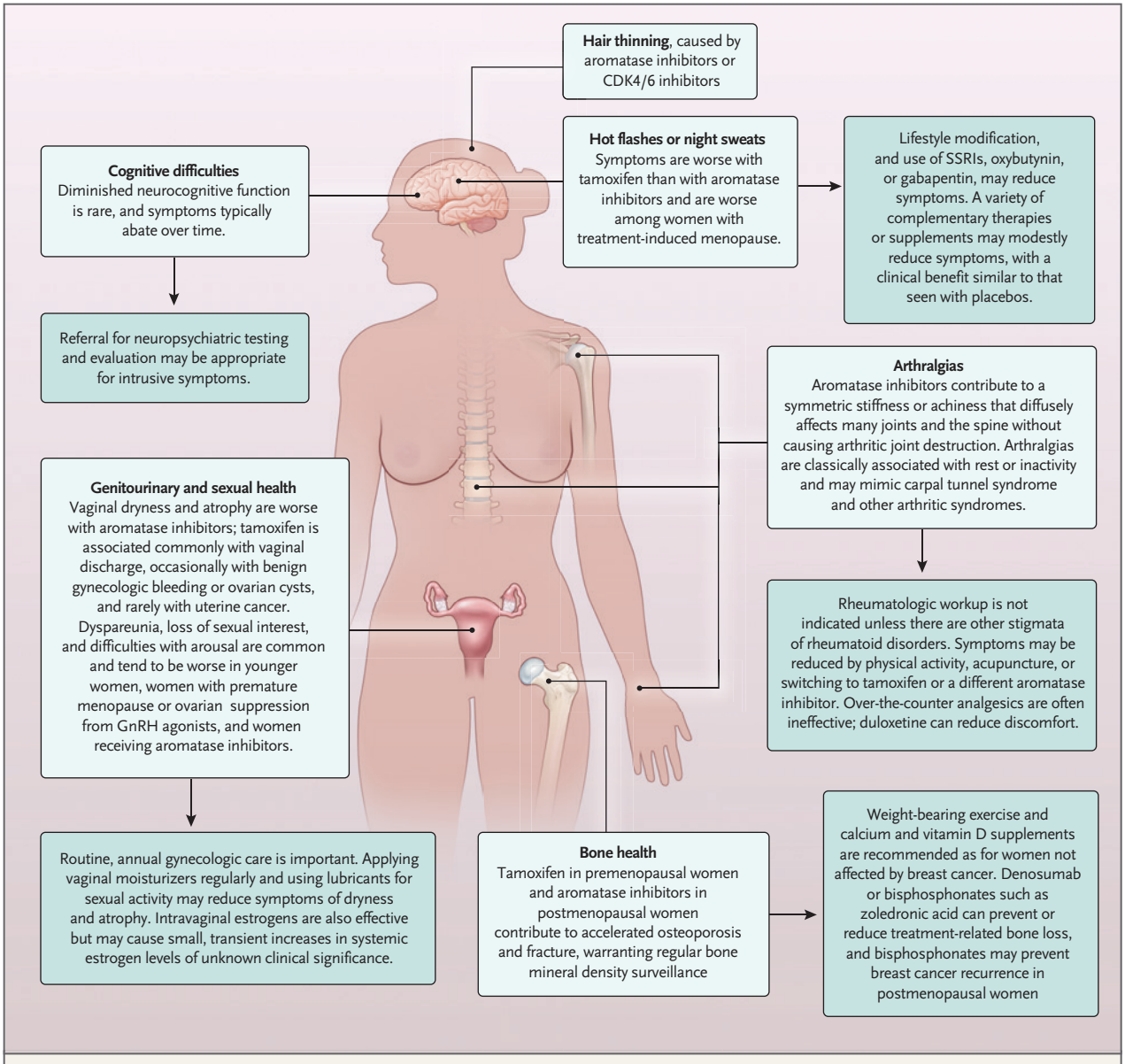

Figure 3. Side Effects of Endocrine Therapy for ER-Positive Breast Cancer.

Hormonal treatments used for estrogen deprivation or ER modulation have side effects across multiple aspects of health and well-being. Nonadherence to adjuvant endocrine therapy is common. Factors associated with nonadherence include extremes of age (young or old), low socioeconomic status, treatment-related symptoms, out-of-pocket costs, longer durations of therapy, and coexisting conditions. SSRI denotes selective serotonin-reuptake inhibitor.

based treatment instead of aromatase inhibitor therapy — should be considered.

Adjuvant endocrine therapy has myriad and prevalent side effects, many of them chronic, ranging from common problems affecting daily life to rare, serious complications (Fig. 3). Tamoxifen and aromatase inhibitors have different adverse effect profiles that may affect treatment selection. Both agents cause menopausal vasomotor symptoms such as hot flashes and night sweats, contributing to sleep disturbance and fatigue. Nonhormonal management options include oxybutynin, gabapentin, antidepressants such as venlafaxine or citalopram, which are un-

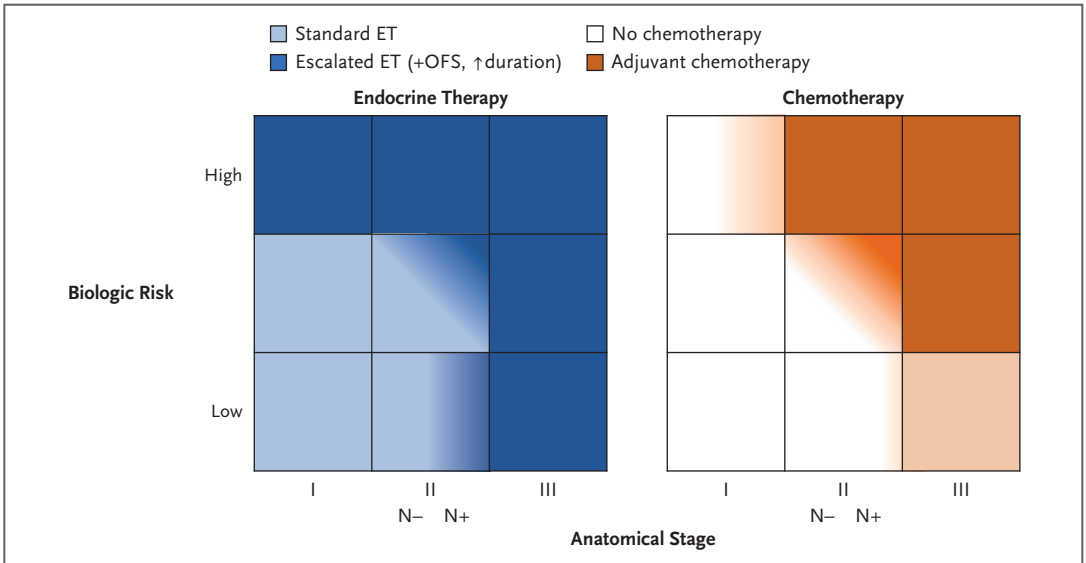

Figure 4. Integrated Model of Treatment Decision Making in Early-Stage, ER-Positive Breast Cancer.

Adequate therapy for ER-positive breast cancer is determined by considering the risk of recurrence and the likelihood of a benefit from treatment. The risk of recurrence depends on both the anatomical stage of the cancer and the biologic risk posed by the tumor, reflecting quantitative ER and PR expression, grade, proliferation index, and genomic signature. Proportional risk reduction with endocrine treatment is relatively consistent among disease stages and biologic features. Thus, with increasing anatomical or biologic risk, there is a progressively greater absolute benefit from escalated therapy (an extended duration of endocrine therapy [ET] or the addition of ovarian-function suppression [OFS]). The benefits of chemotherapy are also related to stage and biologic features (ER expression, tumor grade, degree of proliferation, and genomic findings) and are seen primarily in the treatment of tumors with higher-risk grade, proliferation, and genomic features. On the basis of both tumor stage and biologic features, many women may not require adjuvant chemotherapy. N– denotes node-negative, and N+ node-positive.

likely to interfere with tamoxifen metabolism, and hypnosis, as well as lifestyle adaptations to avoid precipitants of symptoms.[51] Tamoxifen carries rare risks of uterine cancer and deep-vein thrombosis, whereas aromatase inhibitors generate more genitourinary symptoms and bone issues, including arthralgias and osteoporosis. Side effects, especially hot flashes and arthralgias, along with coexisting conditions and socioeconomic status, are major reasons for nonadherence to therapy.[52,53] Counseling patients to anticipate side effects and providing interventions as appropriate can mitigate symptoms. The three approved aromatase inhibitors (anastrozole, letrozole, and exemestane) are equally efficacious and have similar side-effect profiles. However, for women in whom one aromatase inhibitor is associated with an unacceptable side-effect profile, switching to another one[52] or to tamoxifen may prove acceptable, whereas exercise, duloxetine, or acupuncture may reduce musculoskeletal symptoms.[54] When added to adjuvant endocrine therapy, bisphosphonates such as zoledronic acid mitigate osteoporosis in breast cancer survivors and may lower the risk of recurrence among women who are postmenopausal and those receiving GnRH agonists.[55,56] Ovarian suppression intensifies most treatment-related symptoms, especially hot flashes and night sweats, bone health, and sexual health.[57,58] Topical estrogens can alleviate symptoms of vaginal atrophy and improve sexual functioning but may result in transient, trace systemic absorption of estrogens.[59] Some patients report distressing cognitive effects that diminish the quality of life after both endocrine therapy and chemotherapy.[60,61] Neuropsychiatric testing is usually normal, and an effect on daily functioning is uncommon. Symptoms generally abate over time.[51] When the benefits are modest, clinicians must weigh the patient-reported side effects of endocrine therapy against the potential therapeutic gains.

CHEMOTHERAPY

An understanding of tumor heterogeneity and the availability of RNA expression–based genomic assays for risk stratification have prompted a reassessment of the role of adjuvant chemotherapy for ER-positive breast cancer. Neither meta-analyses nor traditional biomarker studies have delineated the tumors that warrant chemotherapy, since chemotherapy appears to provide a benefit for tumors of all stages and subtypes. However, an appreciation of the relationships among ER expression, grade, and degree of proliferation (Table 1 and Fig. 2) has led to the development of genomic tools that redefine the role of adjuvant chemotherapy.[11] Prospective, randomized trials have shown that adding chemotherapy to endocrine therapy is of no benefit among postmenopausal women with node-negative, ER-positive tumors bearing low-risk genomic signatures, defined by a 21-gene recurrence score of 25 or less (on a scale of 0 to 100, with higher scores indicating a greater chemotherapeutic benefit and lower scores indicating a lower risk of recurrence in the absence of chemotherapy) or a "low" result for risk on the 70-gene assay.[62,63] Similarly, chemotherapy does not reduce the risk of recurrence among postmenopausal women with ER-positive breast cancers and limited axillary-node involvement (1 to 3 positive nodes) and a low-risk genomic profile (e.g., a recurrence score of 25 or less).[64] Genomic assays also have prognostic value among premenopausal women, including women younger than 40 years of age, regardless of nodal status.[65] When added to standard endocrine therapy, adjuvant chemotherapy leads to a modest risk reduction among premenopausal women with cancers that have low-risk genomic profiles and either are node-negative[62] or involve 1 to 3 axillary lymph nodes.[64] Among such women, the risk reduction associated with chemotherapy is probably due in large part to the confounding factor of chemotherapy-induced menopause,[66] which suggests that much of the risk reduction might be achieved with ovarian suppression. By contrast, adjuvant chemotherapy with regimens that include taxanes and alkylators, and in high-risk cases, anthracyclines, is typically warranted for women with tumors larger than 1 cm in diameter, node-positive disease, or both who have higher-risk genomic features (e.g., a recurrence score of >25).[67] Chemotherapy is rarely indicated for women with ER-positive tumors who have disease at the lowest stage (<1 cm in diameter and node-negative) or who are in the oldest age group (>75 years), since it is unlikely to have a substantial effect on risk reduction or survival.

NEOADJUVANT THERAPY

Neoadjuvant (preoperative) therapy can improve surgical options for women with larger breast cancers, nodal involvement, or both. ER-positive tumors may respond to neoadjuvant chemotherapy, but a complete pathological response is uncommon, although it occurs more frequently in luminal B cancers or those with a higher genomic score than in luminal A cancers or those with a lower score.[68,69] Historically reserved for older women or women not considered to be candidates for chemotherapy, neoadjuvant endocrine therapy for 6 months or more is associated with high rates of clinical response and can enable breast-conserving surgery in women requiring mastectomy at baseline, though a complete pathological response is rare.[70,71] Neoadjuvant endocrine therapy can result in clinical response rates that are similar to those with chemotherapy in selected women with lower-grade, luminal A–like cancers.[72,73] Selection of patients for neoadjuvant treatment may be individualized on the basis of genomic information from core biopsies; tumors with low recurrence scores tend to respond well to neoadjuvant endocrine therapy, whereas tumors with higher scores warrant up-front chemotherapy.[69,74,75] Tumors that have substantial down-staging with neoadjuvant endocrine treatment while remaining strongly ER-positive with low Ki-67 levels at the time of surgery have an excellent long-term prognosis, even without chemotherapy.[76]

Both traditional measures of disease stage (tumor size and nodal status) and biologic features of the tumor reflect continuous spectra of risk that can be used to tailor adjuvant therapy in women with ER-positive breast cancer (Fig. 4). Incremental increases in stage or adverse biologic characteristics portend a greater risk of recurrence despite adjuvant treatments. Lower-stage tumors with low-risk biologic features rarely warrant chemotherapy; the outcomes are favorable with 5 years of adjuvant treatment con-

sisting of either tamoxifen or an aromatase inhibitor. With a higher anatomical stage or adverse biologic features of the tumor, progressively larger benefits are associated with intensified adjuvant endocrine approaches, including aromatase inhibitor treatment instead of or in sequence with tamoxifen, an extended duration of endocrine therapy beyond 5 years, and ovarian suppression. Nodal status remains a powerful marker of risk but does not by itself determine whether chemotherapy is warranted. For women with stage 1 or 2, ER-positive breast cancers, knowing the stage, grade, presence or absence of lymphovascular invasion, and genomic score allows clinicians and patients to frame accurately the likely benefit of chemotherapy,[11,18,21,62] make better informed treatment decisions,[77,78] and in the majority of instances, avoid adjuvant chemotherapy, the benefits of which are largely restricted to tumors with higher-risk genomic signatures.

ER-positive tumors at a higher stage (i.e., disease with extensive nodal involvement, stage III cancers, or both) generally carry sufficient risk to justify chemotherapy, regardless of the results of genomic testing. The role of chemotherapy in biologically favorable, higher-stage cancers has not yet been defined, though it is likely to be modest at best.[79] Patients with ER-positive, HER2-positive tumors (10% of all women with breast cancer)[1] receive HER2-directed therapies with chemotherapy and standard endocrine treatments. Nearly all breast cancers in men (99%) are ER-positive. Treatment decisions for these cancers are based on the same considerations as treatment decisions for breast cancer in women, though tamoxifen is the preferred hormonal agent for men.[80]

RESISTANCE TO ENDOCRINE THERAPIES

Multiple factors contribute to resistance to endocrine therapies and tumor recurrence or progression. The selective pressure from antiestrogens, particularly aromatase inhibitors, gives rise to acquired mutations in the ligand-binding domain of ER in nearly half of recurrent or progressing ER-positive cancers (Fig. 1).[81-83] These gain-of-function mutations in the ER gene *ESR1* enable constitutive activity of ER in the absence of estrogen, alter ER-based transcription, and are associated with a diminished benefit of ongoing aromatase inhibitor therapy, though selective ER degraders (SERDs) can still be effective.[84,85] Metastatic ER-positive cancers have more genomic alterations than primary tumors, including acquired mutations in *HER2*, *AKT1*, and other genes (Fig. 1).[86,87] A small subset of recurrent cancers have lost ER expression.[88] Epigenetic reprogramming of ER transcription, upregulation of *FOXA1*, *cyclin D*, *c-myc*, and altered expression of receptor tyrosine kinases can diminish the effects of antiestrogen treatments and promote pathways associated with proliferation and metastasis (Fig. 1).[89]

ENDOCRINE THERAPY FOR METASTATIC CANCER

Metastatic ER-positive breast cancer presents in protean ways; common sites of recurrence include bone and bone marrow, lymph nodes, pleura or lungs, liver, and skin. Central nervous system metastasis is less common than in other breast cancer subtypes. Lobular cancers show a predilection for serosal surfaces, causing pleural effusions, abdominal carcinomatosis, and gastrointestinal tract infiltration. Endocrine-based therapy is the standard of care as initial therapy for metastatic disease, except in patients with markedly symptomatic breast cancer and visceral crisis, which warrant initial chemotherapy. The selection of endocrine agents is governed by the prior adjuvant therapy, if administered (Table 2). Continued administration of treatment until tumor progression occurs is the norm; most patients receive multiple lines of endocrine therapy before tumors are refractory to endocrine-based approaches and require palliative chemotherapy. Premenopausal women with advanced ER-positive cancer should undergo ovarian suppression, which improves survival. Treatment with an aromatase inhibitor or tamoxifen is effective in controlling advanced disease and can be reintroduced in previously treated patients, especially if prior therapy was discontinued more than 1 year earlier. Fulvestrant, a SERD that binds to ER and functionally eradicates the receptor (Fig. 1), is active in tumors that are refractory to tamoxifen or aromatase inhibitor therapy,[90] including those with *ESR1* mutations.[85] In combination with an

Table 2. Endocrine Treatment and Targeted Therapy for ER-Positive, Metastatic Breast Cancer.*

Variable	Endocrine Treatment†		Targeted Therapy
	Early-Stage Disease Untreated or Treated with Adjuvant Tamoxifen	Early-Stage Disease Treated with Adjuvant Aromatase Inhibitor, with or without Tamoxifen	
First-line therapy	Aromatase inhibitor	Fulvestrant	CDK4/6 inhibitor
Second-line therapy	Fulvestrant	Tamoxifen, aromatase inhibitor, or fulvestrant	Alpelisib (if *PIK3CA* mutation is present) or everolimus
Third-line therapy and beyond	Chemotherapy or any one of the following (with targeted therapy if not already given): tamoxifen, aromatase inhibitor, or fulvestrant‡	Tamoxifen, aromatase inhibitor, or fulvestrant (with targeted therapy if not already given) or chemotherapy‡	

* For patients with visceral crisis from metastatic breast cancer, initial treatment with chemotherapy is an option, with endocrine-based treatments initiated after a therapeutic response to the chemotherapy has been observed.
† Premenopausal women with metastatic breast cancer should undergo ovarian suppression, followed by the same treatment approach that is used for postmenopausal women.
‡ In selected cases — typically, indolent tumors with minimal visceral disease — ongoing endocrine therapy, including progestins (e.g., megestrol or medroxyprogesterone) or estrogens, reintroduction of antiestrogens, or withdrawal of estrogen therapy may be effective.

aromatase inhibitor, fulvestrant may improve survival, particularly among women who have not received prior endocrine therapy.[91]

TARGETED THERAPIES

Cyclin-dependent kinases 4 and 6 (CDK4/6) are important regulators of cell-cycle progression in many cell types, including ER-positive breast cancer (Fig. 1). In randomized trials, adding CDK4/6 inhibitors (palbociclib, ribociclib, or abemaciclib) to either aromatase inhibitors in first-line therapy or fulvestrant in second-line therapy for advanced breast cancer improved progression-free and overall survival among both premenopausal and postmenopausal women and delayed the time to initiation of other cytotoxic chemotherapy.[92-95] Endocrine therapy plus CDK4/6 inhibition is as clinically effective as chemotherapy for first-line treatment of advanced cancer and as neoadjuvant treatment.[95,96] Resistance to CDK4/6 inhibition appears to be mediated through *RB1* loss or genomic changes in other growth factor and cell regulatory pathways (Fig. 1).[97] Large, randomized trials of adjuvant treatment with CDK4/6 inhibitors added to endocrine therapy for high-risk, early-stage breast cancer have had discordant results. Abemaciclib, but not palbociclib, reduced the risk of recurrence during 1 to 2 years of follow-up among patients who had breast cancer with multiple positive nodes, nearly all of whom had also received adjuvant chemotherapy.[98,99] Longer maturation of these trials and reports from similar ongoing studies are awaited to define the effect of CDK4/6 inhibitors on the natural history of ER-positive, early-stage breast cancer. CDK4/6 inhibitor treatment can be associated with neutropenia, diarrhea, fatigue, and in rare cases, pneumonitis.

Additional targeted therapies can improve tumor control in refractory, ER-positive breast cancers and are often added to sequential lines of endocrine treatment after the administration of CDK4/6 inhibitors. The phosphatidylinositol 3-kinase–AKT–mammalian target of rapamycin (PI3K–AKT–mTOR) signaling pathway controls aspects of cell growth in ER-positive breast cancers (Fig. 1). Between 30 and 40% of ER-positive tumors harbor an activating mutation in the alpha isoform of PI3K (*PIK3CA*), measurable on tumor or cell-free DNA. Alpelisib, an alpha-selective PI3K inhibitor, improves progression-free survival when added to fulvestrant for tumors with mutated *PIK3CA* but not for those with wild-type *PIK3CA*.[100] The mTOR inhibitor everolimus can improve progression-free survival when added to endocrine therapy in previously treated,

ER-positive breast cancer.[101] Alpelisib and everolimus can cause rash, diarrhea, hyperglycemia, and mucositis. In selected cases of indolent, advanced cancers, reintroduction of antiestrogen therapies after treatment interruption or use of low-dose estrogen or progestins can be of clinical value (Table 2). When tumors are refractory to endocrine treatment, chemotherapy can offer a substantial palliative benefit, and most women receive multiple lines of treatment with single-agent, sequential chemotherapeutic agents such as capecitabine, taxanes and other microtubule inhibitors, alkylators, other antimetabolites, or anthracyclines.[102]

The poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitors olaparib and talazoparib are each associated with high clinical response rates (>60%) among women with ER-positive breast cancers harboring germline *BRCA1*, *BRCA2*, or *PALB2* mutations.[103-105] Emerging therapies, including next-generation SERDs, AKT inhibitors, and other agents, hold promise in the treatment of advanced breast cancer. Sacituzumab govitecan, an anti-Trop-2–specific antibody–drug conjugate, yielded a response rate of 30% among patients previously treated with endocrine and chemotherapy for advanced breast cancer.[106] Trials of immunotherapy for ER-positive breast cancer are ongoing. As compared with other breast cancer subtypes, ER-positive tumors, particularly luminal A cancers, are characterized by a smaller tumor burden, lower levels of tumor-infiltrating lymphocytes, lower expression of programmed death 1 and its ligand (PD-1 and PD-L1), and less frequent DNA mismatch repair deficiency — features that are predictive of a benefit from checkpoint inhibitor–based immunotherapy.[107,108]

CONCLUSIONS

Breast cancer is a global public health concern, and many national health services and professional associations have promulgated comprehensive treatment guidelines (for links to current guidelines, see the Supplementary Appendix, available with the full text of this article at NEJM.org). Collectively, the emerging insights into the biology of ER-positive tumors, combined with new diagnostic tests, treatments, and a better understanding of the side effects of therapy and how to address them, allow for therapy to be highly tailored and individualized in order to achieve the best results for women with this heterogeneous and prevalent type of breast cancer.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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