Mechanisms of action of selective estrogen receptor modulators and down-regulators

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INTRODUCTION

About two-thirds of breast cancers express the estrogen receptor (ER)-alpha protein. These ER-positive tumors are dependent on the ER and its cognate ligand, estrogen, for their growth, survival, and progression. Three major classes of endocrine therapy drugs, which differ by their basic mechanism of action, are in use for the treatment and/or prevention of ER-positive breast cancers. These therapies are all designed in one way or another to block ER function and signaling. Selective estrogen receptor modulators (SERMs) and selective estrogen receptor down-regulators (SERDs), the focus of this topic, are competitive inhibitors of estrogen binding to ERs. How SERMs such as tamoxifen and raloxifene and SERM/SERD hybrid (SSH) agents can have both antagonist and agonist actions on the ER in different tissues and the distinctive mechanisms of action of SERDs such as fulvestrant and new oral SERDs will be reviewed here. The emphasis will be on the effects of tamoxifen and SERDs on breast cancer. Additional material on the physiology of estrogen and ERs is presented elsewhere. (See "Molecular biology and physiology of estrogen action".)

The third class of endocrine therapy agent, aromatase inhibitors, are discussed in detail elsewhere. (See "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer" and "Treatment for hormone receptor-positive, HER2-negative advanced breast cancer" and "Selective estrogen receptor modulators and aromatase inhibitors for breast cancer prevention".)

SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)

Three agents are available that act as SERMs: tamoxifen, raloxifene, and toremifene [1]. All three agents are competitive inhibitors of estrogen binding to estrogen receptors (ERs), and all have mixed agonist and antagonist activity, depending on the target tissue. These mixed activities have led to the redesignation of this class of compounds from "anti-estrogens" to SERMs.

The mixed antagonist/agonist effect of SERMs on ERs can be illustrated by their physiological effects in postmenopausal women:

- SERMs provide some protection against menopausal bone loss, presumably due to their partial agonist activity (figure 1 and figure 2) [2-5]. However, the increase in bone density is substantially less than that seen with estrogen therapy. (See "Selective estrogen receptor modulators for prevention and treatment of osteoporosis".)

- SERMs lower serum total and low-density lipoprotein (LDL)-cholesterol concentrations (by 12 and 19 percent, respectively, in one report), although they do not increase serum high-density lipoprotein (HDL) cholesterol [4,6,7]. However, data confirming protection against cardiovascular disease for either drug or for estrogen itself are still controversial. (See "Managing the side effects of tamoxifen and aromatase inhibitors".)

- Tamoxifen's antagonist effect is particularly prominent with respect to breast cancer. Among women with ER-positive breast cancer, tamoxifen reduces the risk of recurrence and death when given as adjuvant therapy for early-stage disease and can provide palliation in those with metastatic disease [8,9]. However, as will be described below, some ER-positive breast cancers display primary resistance to tamoxifen, and all advanced breast cancers eventually become refractory to tamoxifen treatment (secondary resistance). Tamoxifen may also prevent the development of contralateral breast cancer, both in women with a prior diagnosis of breast cancer and in those women at high risk of breast cancer (figure 3) [7]. (See "Selective estrogen receptor modulators and aromatase inhibitors for breast cancer prevention" and "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer", section on 'Indications'.)

- Raloxifene has a similar protective effect against the development of invasive breast cancer, with a lower risk of thromboembolic events and cataracts but a higher risk of noninvasive (in situ) breast cancer [10].

- Both raloxifene and tamoxifen also induce hot flashes (an estrogen antagonist effect). Of interest, while tamoxifen clearly induces endometrial hyperplasia (an estrogen agonist effect) and increases the risk of developing endometrial cancer (table 1), raloxifene does not appear to have endometrioid agonistic effects; unlike tamoxifen, it does not increase the risk of uterine cancers. (See "Managing the side effects of tamoxifen and aromatase inhibitors" and "Selective estrogen receptor modulators and aromatase inhibitors for breast cancer prevention".)

SELECTIVE ESTROGEN RECEPTOR DOWN-REGULATORS (SERDS)

Fulvestrant — Fulvestrant, a competitive antagonist of estrogen binding to the estrogen receptor (ER), is approved for the treatment of breast cancer, and acts as an ER down-regulator. As opposed to the SERMs, fulvestrant is a "pure" ER antagonist with no known agonistic activity. Fulvestrant has been proved effective in advanced breast cancer as both first-line [11] and second-line [12] therapy. It is approved by the US Food and Drug Administration for the treatment of patients with advanced ER-positive breast cancer [13]. (See "Treatment for hormone receptor-positive, HER2-negative advanced breast cancer".)

- The more "pure" antiestrogenic activity of fulvestrant and its ability to degrade the ER protein is the underlying mechanism of action of this drug and explains the clinical efficacy in treating patients with ER-positive breast cancer [14-16], including patients who have developed resistance to tamoxifen or aromatase inhibitors (AIs) [12]. (See "Treatment for hormone receptor-positive, HER2-negative advanced breast cancer".)

- Unlike tamoxifen or AIs, fulvestrant has very low oral bioavailability and is administered as a monthly intramuscular injection. It is believed that the clinical efficacy of fulvestrant has been limited by the partial ER degradation seen in patients' tumors as opposed to the higher degradation levels seen in preclinical breast cancer models.

- The adverse effects reported in the multiple clinical studies with fulvestrant, which are in general comparable with the side effect profile of AIs, also support its systemic "pure" antiestrogenic activity.

- Strong dose-dependent biological effects of fulvestrant have been demonstrated in neoadjuvant studies. Increasing the fulvestrant dose leads to reduction in ER, its downstream product progesterone receptor (PR), and the proliferative Ki67 marker [15,16]. This dose-dependent reduction in tumor biomarkers is in line with the dose-dependent clinical efficacy seen in postmenopausal women with advanced breast cancer

in second-line treatment studies [17,18], as well as in the first-line setting through cross-trial comparisons [11,19]. (See "Treatment for hormone receptor-positive, HER2-negative advanced breast cancer".)

- In patients with ER-positive metastatic breast cancer, fulvestrant monotherapy or fulvestrant in combination with CDK 4/6 inhibitors can be used in first or subsequent line, or in combination with the PI3K-inhibitor alpelisib in at least second-line in patients whose tumors harbor *PIK3CA*-activating mutations [20]. (See "Treatment for hormone receptor-positive, HER2-negative advanced breast cancer", section on 'ESR1 wild-type'.)

  Ongoing trials continue to investigate the efficiency of fulvestrant in combination with other signaling molecule inhibitors (eg, with the AKT inhibitor capivasertib, NCT04305496).

Oral SERDs — Efforts to develop new agents with SERD properties with superior bioavailability, pharmacokinetics, and potent antiestrogenic activity in the breast have led to the discovery and characterization of second and third generations of SERDs [20-24].

- **Elacestrant** – Elacestrant (aka RAD1901) is a SERD that has regulatory approval in the United States for use in postmenopausal women and in men with *ESR1*-mutated advanced hormone receptor-positive HER2-negative breast cancer that has progressed on at least one line of prior endocrine therapy [25].

  The EMERALD Phase III trial of elacestrant (RAD1901) in metastatic breast cancer reported benefits in patients after progression on prior endocrine and CDK 4/6 inhibitor therapy [26], and is discussed in detail elsewhere. (See "Treatment for hormone receptor-positive, HER2-negative advanced breast cancer", section on 'ESR1 mutation-positive'.)

- **Others** – GDC-0810 is a novel nonsteroidal, oral SERD that demonstrates robust antitumor activity in tamoxifen-sensitive and resistant breast cancer xenografts, as well as in models that harbor *ESR1*-activating mutations [27,28], as described below. (See 'ESR1 gene mutations' below.)

Results from a phase I study show that GDC-0810 effectively engages its target, even in patients with *ESR1* mutations, and may provide clinical benefit for postmenopausal women with advanced ER-positive breast cancer [29]. AZD9496 is a second novel, potent, nonsteroidal, orally bioavailable SERD that has been shown to effectively inhibit the growth of ER-positive, endocrine-sensitive and resistant xenograft models [30]. This agent is in early-stage clinical development (NCT02248090).

Although GDC-0810 effectively engages its target, even in patients with *ESR1* mutations, and may provide clinical benefit for postmenopausal women with advanced ER-positive breast cancer, the manufacturer halted its further clinical development [29]. The oral SERDs giredestrant (GDC-9545) and amcenestrant (SAR439859) are being evaluated in clinical trials based on preclinical studies and early-phase trials in pretreated ER-positive metastatic breast cancer after progression on prior endocrine therapies, including in patients harboring *ESR1* mutations (NCT03332797 and NCT03284957, respectively) [21]. Camizestrant (AZD9833) is being evaluated as first-line therapy in advanced breast cancer in combination with palbociclib in the SERENA-3 trial (NCT04588298).

Imlunestrant (LY3484356) and rintodestrant (G1T48) are oral SERDs that demonstrated efficacy in preclinical models of ER-positive breast cancer with wild-type and *ESR1* mutations, and have also shown clinical efficacy in phase I trials in a cohort pretreated ER-positive metastatic breast cancer (NCT04647487 and NCT03455270, respectively). Finally, additional next generation oral SERDs are currently under early clinical development in phase I/I-II clinical trials.

Based on early results it is likely that most SERDs will be efficacious in patients with either wild-type or *ESR1* mutations, and we await definitive efficacy data from oral SERDs.

ER PROTACS – Proteolysis targeting chimeric (PROTAC) technology is an endogenous protein degradation strategy that can ubiquitinate target proteins, like ER, though the ubiquitin-proteasome system. It is hypothesized that ER PROTACS like ARV-471 will be best-in-class ER degraders because of their interactive MOA and broad tissue penetration, but these advantages need to be borne out in clinical trials. Data from an ongoing phase I–II clinical trial suggested some clinical activity of ARV-471 monotherapy in heavily pretreated patients with endocrine resistant metastatic breast cancer [31]. Concerns over PROTACS include their potential off-target side effects and possible acquired resistance to the core components of the E3 ligase complex.

SERM/SERD HYBRIDS

A new class of SERM/SERD hybrids (SSHs) has emerged, with improved agonist/antagonist tissue profiles, exhibiting some of the properties of both SERMs and SERDs. These agents represent possible future therapeutic options but remain investigational for the treatment of breast cancer at this time, pending further safety and efficacy data.

Bazedoxifene is an SSH compound that acts as an agonist in bone, but also effectively inhibits ER action in the reproductive system by inducing receptor degradation in these tissues.

Bazedoxifene has been approved for the treatment of osteoporosis in Europe and, in the United States, is approved in combination with conjugated estrogen for the treatment of postmenopausal symptoms [32]. This compound exhibits pure antiestrogenic activity in animal models of tamoxifen-sensitive and resistant breast cancer, and has the ability to degrade ER in breast tumors [33]. The combination of bazedoxifene with a cyclin-dependent kinase (CDK 4/6) inhibitor has shown therapeutic potential in models of breast tumors resistant to endocrine therapies or those expressing ER-alpha (*ESR1*) mutations [34] (see 'ESR1 gene mutations' below). Based on additional preclinical studies, there is an ongoing study testing its efficacy in the treatment of metastatic breast cancer when combined with a CDK 4/6 inhibitor (NCT02448771).

THE ESTROGEN RECEPTOR

Most receptors of the steroid family, with the exception of the ER, are classically viewed as "translocating receptors." That is, they move from a principally cytoplasmic distribution in the absence of hormone to a predominantly nuclear localization in hormone-stimulated cells. However, the ER appears to be predominantly nuclear both in the presence and absence of hormone. The ER operates as a ligand-dependent transcription factor; attachment of estrogen to the ER's ligand-binding domain results in either direct binding of the ER to estrogen response elements (ERE) in the promoter of target genes or to a protein-protein interaction with other transcription factors at their respective promoter sites [35-38].

Subsequently, the hormone-receptor complex is able to bind to estrogen-specific response elements that activate or repress expression of genes whose protein products are responsible for the physiologic actions of the hormone.

The ER shares many structural features with other members of the nuclear receptor superfamily with six components or "domains," A to F (figure 4) [36,37]. Estradiol and SERMs such as tamoxifen bind to the ligand-binding site in the E domain, which also mediates ER dimerization. The sequence-specific DNA binding function of the ER requires dimerization and resides in domain C. Domain D contains a nuclear localization signal. Regions that promote transcription activation functions are present in domains A/B (AF1) and E (AF2). (See "Molecular biology and physiology of estrogen action".)

Corepressors and coactivators — On a molecular level, we have only a limited understanding of how an individual SERM can act as an ER agonist in one tissue and as an antagonist in another. However, it is likely that the change in receptor conformation that follows binding of the ER by a SERM results in variable interactions with cofactors that are required for ER-mediated gene regulation. These nuclear proteins, termed coactivators and corepressors, are

able to interpret the difference between binding of different ligands (eg, estrogen or tamoxifen) to the ER. Coactivators increase the transcriptional activity of the ER by promoting an interaction between the receptor and the transcriptional apparatus that provides the machinery for gene activation and subsequent mRNA transcription [37]. By contrast, corepressors restrain ER activity, maintaining the receptor in a protein/DNA complex that does not promote transcription [39].

ER coactivators are exquisitely sensitive to the conformational changes that occur in the ligand-binding domain (LBD) [40-46]. Unlike estrogens, tamoxifen distorts the LBD, generating an abnormal receptor conformation that disrupts coactivator binding outside the LBD [43,47-49]. Subsequently, corepressor molecules are recruited to the ER, holding it in an inactive state [50].

Changes in the relative ratios and activity of coactivators and corepressors in breast cancer cells are implicated in the differential responsiveness of ERs to an agonist or an antagonist [51,52]. In addition, the acquired tumor ER mutations are increasingly being recognized [53-55], which appear to cause constitutive activation of ER within tumor cells, making them relatively resistant to SERMs. (See 'ESR1 gene mutations' below.)

Estrogen receptor-beta: A second ER isoform — The above characteristics describe ER-alpha (*ESR1*). A second isoform, ER-beta (*ESR2*), has been described that is highly homologous to *ESR1* in both the DNA binding and ligand-binding domains [56,57]. ER-beta binds estrogens with a similar affinity as *ESR1* and activates the expression of genes containing ERE in an estrogen-dependent manner [58].

In contrast to the hormone and DNA binding domains, *ESR1* and *ESR2* are not homologous in the N terminal A/B (transactivation) domains. *ESR2* does not contain a strong AF1 within its amino-terminus but, rather, contains a repressor domain that when removed, increases the overall transcriptional activity of the receptor. As a result, the transcriptional properties of *ESR1* and *ESR2* are dissimilar. (See "Molecular biology and physiology of estrogen action".)

Transcriptional activity of *ESR2* in response to estrogen is dependent upon the cell type, promoter, and the nature of the ligand. Tamoxifen, which shows agonist activity in some tissues upon binding to *ESR1*, has no agonistic activity when it interacts with *ESR2*. These differences appear to result from alterations in the amino-terminal A/B receptor domain, particularly AF1 [59]. Unlike *ESR1*, *ESR2* does not have a strong AF1 domain, and its AF2 domain appears to function independently within the receptor [60].

In addition, the partial agonist activity of tamoxifen that is manifest through *ESR1* can be completely abolished upon coexpression of *ESR2* [60-62]. When coexpressed in tumor cells,

ESR2 functions as a transdominant inhibitor of ESR1 transcriptional activity at subsaturating hormone levels and decreases overall cellular sensitivity to estradiol.

The discovery of *ESR2* has added further complexity to the molecular biology of the ER and its interaction with estrogens, SERMs, and selective estrogen receptor down-regulators (SERDs) in different tissues. Further study of these interactions, particularly using molecular methods such as gene expression profiling, may help explain the differential actions of tamoxifen and other SERMs, SERDs, and SERM/SERD hybrids (SSHs) on different tissues [63].

Information on the clinical significance of *ESR2* expression in breast cancer is limited. However, at least some data suggest that expression of *ESR2* is an independent marker for benefit from tamoxifen in women who have *ESR1*-negative tumors (in whom tamoxifen is usually not considered beneficial) [64]. These results raise the possibility that a subset of women who have *ESR1*-negative but *ESR2*-positive breast cancer may in fact derive some benefit from adjuvant tamoxifen. However, these data are very speculative, and at present, assay of breast tumors for *ESR2* is not routinely undertaken, in part because reagents that reliably assess ESR2 protein expression are not available.

INTERACTIONS OF SERDS AND SERMS WITH THE ER

Tamoxifen — A simple model of ER-alpha (*ESR1*) function is provided in the figure (figure 5). After estrogen or tamoxifen binds to the ligand-binding domain (LBD), the ER is released from heat shock protein (HSP)-90 and ER dimerization occurs. Sequence-specific DNA binding to an estrogen-responsive element (ERE) follows. In the presence of estrogen, mRNA transcription is promoted though AF2. Tamoxifen-bound ERs are shown as inactive, since tamoxifen inhibits AF2 function in breast cancer cells. However, this simple paradigm provides no insight into the tissue-specific mixed agonist/antagonist actions of SERMs such as tamoxifen [36]. As a result, more complex models are required (figure 6) [38].

Raloxifene — The newer SERMs such as raloxifene appear to have different tissue-specific effects from tamoxifen. The factors that determine the variable ER agonist and antagonist activity of raloxifene are not fully defined but are under active study [63]. Raloxifene should not be substituted for tamoxifen in the adjuvant or metastatic setting given that it has not been compared with tamoxifen in these settings. It is only approved for prevention. (See "Selective estrogen receptor modulators and aromatase inhibitors for breast cancer prevention", section on 'Raloxifene'.)

Like tamoxifen, raloxifene distorts the LBD of the ER, generating an abnormal receptor conformation that disrupts coactivator binding [62]. As a result, there is likely to be significant cross-resistance between tamoxifen and raloxifene, resulting in a relative lack of activity of raloxifene in tamoxifen-refractory breast cancer. The differing effects of raloxifene and tamoxifen on the uterus may be related to structural differences in the two compounds that influence the conformations of the ligand-receptor complexes, thereby determining which estrogen-responsive genes are modulated in specific tissues [65].

Alternatively, differences in tissue specificity compared with tamoxifen may be related to other unique aspects of the interaction of raloxifene with the ER. As an example, the human transforming growth factor-beta3 gene is activated by the ER in the presence of estrogen metabolites or estrogen antagonists such as raloxifene [66]. Activation is mediated by a polypurine sequence, termed the raloxifene response element (RFE), and does not require the DNA-binding domain of the estrogen receptor. Interaction of the estrogen receptor with the RFE appears to require a cellular adapter protein. The observation that individual estrogens and antagonists can modulate multiple DNA response elements may explain the tissue-selective estrogen agonist or antagonist activity of SERMs such as raloxifene.

Fulvestrant, oral SERDs, and SERM/SERD hybrids — Although the mechanisms underlying endocrine resistance are complex, multiple lines of clinical and preclinical studies suggest that in the majority of the patients with disease refractory to tamoxifen and/or aromatase inhibitors (AI), ER remains engaged and continues to contribute to the disease pathogenesis [67]. This evidence, which suggests that ER remains a viable therapeutic target in these resistant breast cancers, inspired the development of selective estrogen receptor down-regulator (SERD) agents, which degrade and eliminate the ER protein.

SERDs, such as fulvestrant, are distinguishable from tamoxifen and other SERMs both by their pharmacology and by their mechanisms of action (MOA). Fulvestrant is a high-affinity competitive antagonist of ER. Due to its similarity to the endogenous estrogen ligand, fulvestrant competes with estrogen binding to the LBD of ER. However, its long hydrophobic side chain confers fulvestrant with unique antiestrogenic properties. Fulvestrant binding to the ER, similar to other ER ligands and SERMs, causes dissociation of the receptor from its heat-shock chaperone proteins. However, because of its long side chain, receptor dimerization is sterically hindered and rapid proteasome-dependent ER degradation is induced [14,68]. Rapid degradation of ER following treatment with fulvestrant seems to play an important role in the abrogation of both ligand-dependent (induced by estrogen or SERMs) and ligand-independent (eg, induced by hyperactive growth factor signaling or by *ESR1* mutants) ER activity and signaling. Thus, the unique MOA of fulvestrant is probably accountable for the drug efficacy

observed preclinically and/or clinically, especially in the treatment of tumors that have developed resistance to prior tamoxifen or AI treatments or those that harbor constitutively active *ESR1* mutants. However, emerging preclinical and clinical evidence supports the notion that tumor cells harboring the constitutively active *ESR1* mutants possess at least partial resistance to fulvestrant [69].

Unfortunately, fulvestrant's poor pharmaceutical properties that prevent oral administration have limited its usefulness and potency. However, remarkable clinical activity and the increased understanding of its MOA, as well as the molecular mechanisms underlying the selective agonist/antagonist activity of SERMs, have promoted the development and characterization of a new generation of orally bioavailable SERD and SERM/SERD hybrid (SSH) compounds for the treatment of ER-positive breast cancer, especially in the context of endocrine resistance [27]. The oral SERD elacestrant is discussed in detail elsewhere. (See "Treatment for hormone receptor-positive, HER2-negative advanced breast cancer", section on 'ESR1 mutation-positive'.)

This figure depicts the molecular pharmacology of SERDs in the setting of tamoxifen resistance (figure 7). Resistance to tamoxifen under chronic exposure stems from the selection of a subpopulation of cells that express a compatible coactivator(s) that directs the pharmacologic switch of tamoxifen from an antagonist to an agonist. SERDs, such as GDC-0810, have activity in this setting because (1) they function as high affinity competitive antagonists, and (2) they induce a conformational change in the ER that does not support the exposure of the coregulator (coactivator) binding surface required for the agonist activity of estrogen and tamoxifen, but instead exposes a surface on the receptor that targets it for proteasome-dependent degradation [27]. This MOA can also explain the inhibitory activity and potential clinical efficacy of these SERDs, and probably of the emerging SSH compounds, in the setting of endocrine resistance that is related to constitutive ligand-independent ER activity under chronic exposure to AIs or in the presence of *ESR1* mutants.

The main results of the trials that evaluate the therapeutic benefit of fulvestrant are discussed separately. (See "Treatment for hormone receptor-positive, HER2-negative advanced breast cancer".)

TAMOXIFEN RESISTANCE IN BREAST CANCER

Resistance to tamoxifen may occur in patients taking drugs that alter CYP2D6 metabolism of the agent, for example selective serotonin reuptake inhibitors (SSRIs) (see 'Patients taking SSRIs' below). Additionally, research over the last two decades has identified that resistance to tamoxifen therapy may be intrinsic (de novo) resistance, in which ER-negative and many ER-

positive tumors do not respond to tamoxifen at the outset of therapy; or acquired, where ER-positive tumors that initially responded to tamoxifen subsequently fail to respond [38]. (See 'ESR1 gene mutations' below.)

Patients taking SSRIs — Tamoxifen is converted to its active metabolites (endoxifen and 4-hydroxytamoxifen) by two rate-limiting enzymes, cytochrome P450 2D6 (CYP2D6) and UDP-glucuronyltransferase-2B7 (UGT2B7) [70-73] (see 'Altered tamoxifen metabolism' below). Certain selective serotonin reuptake inhibitors (SSRIs), particularly paroxetine and fluoxetine, inhibit CYP2D6 (table 2). However, we do not routinely discontinue these medications in patients starting tamoxifen. However for patients with indications to start an SSRI while on tamoxifen, we typically initiate agents such as venlafaxine or citalopram, as these have a lesser effect on CYP2D6. (See "Management of psychiatric disorders in patients with cancer", section on 'Selective serotonin reuptake inhibitors' and "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects" and "Overview of long-term complications of therapy in breast cancer survivors and patterns of relapse", section on 'Hot flashes'.)

Studies have not demonstrated a difference in survival with the use of SSRIs among patients taking tamoxifen [74,75]. For example, in a retrospective study of almost 17,000 patients treated for stage 0 to II breast cancer with adjuvant tamoxifen, nearly half of whom also took antidepressants, the use of antidepressants was not associated with an increased risk of subsequent breast cancer at a median follow-up of six years [74]. Results did not vary according to which antidepressant was used, regardless of whether they inhibit CYP2D6 or not. Among patients who took paroxetine for at least 75 percent of their five-year course of tamoxifen, the hazard ratio for recurrent breast cancer was 0.85 (95% CI 0.54-1.32).

We do not check levels of tamoxifen or its metabolites in patients taking tamoxifen with other agents that may affect its metabolism. Although studies are examining whether serum levels of tamoxifen and its metabolites correlate with clinical outcomes [76], this is investigational and not used in routine clinical practice.

Intrinsic resistance — ER and progesterone receptor (PR) expression are the best predictors of response to tamoxifen; tamoxifen is ineffective in patients with ER-negative, PR-negative breast cancer. However, 25 percent of ER-positive, PR-positive tumors; two-thirds of ER-positive, PR-negative tumors; and approximately one-half of ER-negative, PR-positive tumors fail to respond to tamoxifen or develop early resistance to tamoxifen [77]. (See "Hormone receptors in breast cancer: Clinical utility and guideline recommendations to improve test accuracy".)

A number of factors may contribute to intrinsic tamoxifen resistance, including:

- Variable expression of the ER-alpha (*ESR1*) and beta (*ESR2*) isoforms

- Interference with binding of coactivators and corepressors
- Acquired mutations in the gene that encodes for *ESR1* and alternatively spliced mRNA variants of ER
- Dysregulation of growth factor receptors and cellular kinase pathways, such as existing or acquired mutations or amplifications in the HER family receptors, *FGFR1* amplification and PI3K/MAPK pathway alterations [78]
- Imbalance in the levels and/or activity of ER co-regulators due to amplification and activating mutations of ER co-activators [67] or inactivating mutations in ER co-repressors [79]
- Modulation of the activity of ER and its coregulatory proteins through increased expression of growth factors (eg, type 1 epidermal growth factor (EGF) receptor [EGFR1] and the type 2 EGFR, also called HER2)
- Inherited drug metabolizing CYP2D6 genotypes
- Mutations in the *BRCA1* gene, which appears to modulate expression of *ESR1*

While these mechanisms have been studied in the preclinical or early clinical setting, they do not affect routine clinical management at this time.

Expression of ER isoforms — In laboratory models, altered levels of *ESR1* and *ESR2* can deregulate estrogenic and antiestrogenic activities in target cells [60], and the relative changes in expression of *ESR1*/*ESR2* that occur during tumorigenesis parallel the marked changes in estrogen action that accompany this process [80]. These preclinical findings suggest that altered expression of ER isoforms may represent one mechanism of tamoxifen resistance [61,81]. However, the available data linking expression of *ESR2* with clinical tamoxifen resistance are conflicting [81-83]. Thus, the role of *ESR2* in tamoxifen resistance remains unclear.

Tissue-specific availability of coactivators and corepressors — Differential recruitment of coactivators and corepressors to the transcription complex depends upon differences between estrogen-bound ERs and tamoxifen-bound ERs. Tamoxifen distorts the LBD, generating a receptor conformation that disrupts coactivator binding outside the LBD [43,47-49]. Subsequently, corepressor molecules are recruited to the ER, holding it in an inactive state [50].

Since tamoxifen also induces ER dimerization and DNA binding, inactivation of the ER depends upon the net effect of tamoxifen on these functions and upon coactivator and corepressor interactions, which may differ between cell types and tumors [43,45]. As an example, a 160-

kilodalton ER-associated protein, ERAP160 (also known as steroid receptor coactivator 1 [SRC-1]), exhibits estradiol-dependent binding to the ER; the ability of the receptor to activate transcription parallels its ability to bind ERAP160 [43]. SERMs are unable to promote ERAP160 binding and can block the estrogen-dependent interaction of the ER and ERAP160 in a dose-dependent manner [43].

In addition, coactivator and corepressor proteins appear to play a major role in determining the tissue-specific agonist/antagonist profile of tamoxifen [51]. In some cells, tamoxifen-induced AF2 inhibition may be bypassed when enough coactivator function is recruited to the ligand-independent domain, AF1 [84]. In other cell types, available coactivator proteins might bind to and activate AF2 despite the presence of tamoxifen [45].

In the breast, tamoxifen (and raloxifene) induces recruitment of corepressors to ER target promoters. In endometrial cells, tamoxifen, but not raloxifene, recruits coactivators rather than corepressors to ER target genes that do not contain a classical estrogen response element (ERE) (c-myc and IGF-1). In addition, the estrogen agonist activity of tamoxifen in the endometrium requires a high level of SRC-1 expression [51].

Differences in coactivator/corepressor status among tumors may also help explain the variable response to tamoxifen in the primary treatment of ER-positive, metastatic breast cancer [52,77,85,86]. In addition, corepressor and coactivator expression levels may influence the development of secondary resistance to tamoxifen. In animal models, prolonged tamoxifen exposure alters the balance between coactivators and corepressors in favor of the agonist, growth-promoting properties of tamoxifen; the net effect is stimulation of growth despite the continued presence of tamoxifen [87]. This is accompanied by suppression of corepressor N-CoR levels in the tamoxifen-stimulated tumors when compared with their tamoxifen-sensitive counterparts [85].

ESR1 gene mutations — Mutation of a clinical target is a common mechanism utilized by cancer cells to avoid therapeutic agents. Studies using next-generation sequencing (NGS) report preliminary ER-alpha (*ESR1*)-mutant frequencies ranging from 1 to 3 percent in primary breast tumors [88] and 21 percent in metastatic breast cancers [89]. There is no direct clinical trial evidence for how best to treat patients with *ESR1* mutations, as most of the metastatic patients with *ESR1* mutations were treated with multiple hormonal agents. Various studies have indicated that these mutations confer partial resistance to conventional SERMs and selective estrogen receptor down-regulators (SERDs) (tamoxifen, and fulvestrant, respectively); therefore, effective treatment likely requires a more effective antiestrogen. Elacestrant (aka RAD1901) is a SERD that has regulatory approval in the United States for use in postmenopausal women and in men with *ESR1*-mutated advanced hormone receptor-positive HER2-negative breast cancer

that has progressed on at least one line of prior endocrine therapy [25], and is discussed in detail elsewhere. (See "Treatment for hormone receptor-positive, HER2-negative advanced breast cancer", section on 'ESR1 mutation-positive'.)

Two antiestrogens with mixed SERM/SERD activity, bazedoxifene and pipdendoxifene, have shown efficacy in preclinical models of tamoxifen resistance, with bazedoxifene demonstrating activity against a patient-derived xenograft (PDX) model expressing the *ESR1*-Y537S mutation [34]. Preclinical preliminary data from a PDX model suggest that an oral ER degrader (ARN-810) may also be useful to inhibit the growth of *ESR1*-Y537S-mutated cancers [90]. Whether inhibition of other survival/growth pathways, such as cyclin-dependent kinase (CDK 4/6) or mechanistic target of rapamycin (mTOR), in combination with agents with improved SERM/SERD activities will provide additional benefit or synergy in *ESR1*-mutant tumors remains to be determined.

ESR1 gene mutations frequently occur at phosphorylation sites in the ER that receive signals from important tyrosine and serine kinases [91]. (See 'Modulation of ER expression through second messengers' below.)

The *ESR1*-Y537N mutation was first discovered in a metastatic bone lesion [92], and the mutation occurs at a phosphorylation site for c-Src, an important tyrosine kinase that is hyper-activated in cancer and is involved in enhancing invasion and metastasis. The *ESR1*-K303R mutation was originally reported to occur in premalignant ductal breast hyperplasias, and later was found in invasive primary breast cancers by a number of laboratories, although specific sequencing methods are required to detect this mutation [93-96]. The *ESR1*-K303R mutation occurs at a site within the beginning of the receptor LBD that receives signals from several important cellular kinase cascades, including p21-activated kinase (PAK1), protein kinase A (PKA), and protein kinase B (also called AKT) [97]. Thus, these mutations occur at sites with fine-tuned regulation via ligand-independent signaling mechanisms.

ESR1 mutations occurring at mutational hot-spots near or surrounding the Y537 residue in the LBD of the receptor have been reported. The LBD hot-spot *ESR1* mutations maintain the receptor in an agonist conformation in the absence of hormone, thus they exhibit hormone-independent activity and are resistant to estrogen withdrawal or aromatase inhibitor (AI) growth inhibition [55,98].

Since the LBD mutations occur most frequently in hormone-refractory metastatic tumors and render the receptor hormone-independent, estrogen withdrawal with AI treatment may provide positive selection pressures during tumor progression. Anecdotal data suggest that *ESR1* mutations can emerge during hormone deprivation therapy using deep NGS [99]. An *ESR1*-D538G mutation was found in biopsies of a metastatic tumor and cell-free circulating DNA, but

was absent from the primary in a patient treated with AI therapy. *ESR1*-mutant allele frequency also significantly declined in a second circulating DNA sample taken from this patient during response to chemotherapy.

Acquired resistance to an AI in metastatic tumors can be explained by the presence of the mutation, and data demonstrate that these mutations arise in response to AIs. *ESR1* mutations are detected in 30 to 50 percent of patients progressing on first-line AI. A significant enrichment for *ESR1* mutations in metastatic tumors was confirmed in targeted sequencing of over 11,000 metastatic breast tumors (18.3 in breast tumor metastases versus 2.2 percent in primary local disease) [100]. The prevalence of hotspot *ESR1* mutations varied by site of metastasis; visceral tissues (liver, pleura, brain, and lung) had more *D538G* mutations (20 to 48 percent of *ESR1* mutations than all other hotspot mutations). By contrast, non-visceral sites like bone had significantly more *Y537S* mutations. Interestingly, peripheral tissues like chest wall tumors had more *E380Q ESR1* mutations, and local primary tumors and lymph node metastases exhibited mutations outside of the ligand binding domain with less pathogenic functions.

- ***ESR1* gene fusions** – *ESR1* gene fusions comprise a new class of recurrent somatic mutations that drives endocrine resistance and metastasis in ER-positive breast cancer [101,102]. There are largely two types of *ESR1* gene fusions [103]. In the first type, *ESR1* fusion transcripts retain the first two non-coding exons of *ESR1*, which are fused to various sequences from nearby genes, forming a promoter trap that activates aberrant expression of truncated and potentially oncogenic proteins. In the second type, the first six exons of *ESR1* are preserved and fused in-frame to partner sequences provided by various genes, forming different ER-fusion proteins. Most of these fusions lead to global endocrine resistance due to the loss of the ER LBD. This is a growing research field and key challenges that remain are diagnosis of these genomic fusions, determining their biology, and identifying the most effective treatments.

- **Liquid biopsies in assessing tumors over time** – Discordance in ER status can occur over time in approximately 20 percent of cases [104]. Reassessment of ER and human epidermal growth factor receptor 2 (HER2) status of metastatic disease is recommended in clinical guidelines [97], but still frequently omitted due to the invasive nature of tissue biopsies. It is hoped that eventually, therapeutic decisions may be made using real-time data from liquid biopsies, thereby improving outcomes in patients with discordant receptor status [105].

  The phase III PADA-1 trail was designed to evaluate the feasibility of preventing or delaying tumor progression in patients receiving first-line treatment with palbociclib plus an AI by switching from the AI to fulvestrant as soon as *ESR1* mutations became detectable

in the blood through analysis of circulating cell-free DNA [106]. This strategy was associated with a 39 percent reduction in risk of disease progression or death. In those patients who progressed, cross over was of short duration, suggesting the importance of early detection of *ESR1* mutations in the blood. A number of open questions remain including the significance of low allele frequencies, and polyclonal *ESR1* mutations in patient outcomes.

Primary breast tumors can be heterogeneous, and molecular analyses of metastatic breast cancers show that breast cancers indeed evolve over time, losing and/or gaining new changes. This evolution of breast cancer over time constitutes the rationale for assessing metastases to direct therapy in trials of precision medicine. Using liquid biopsies taken during metastatic dissemination, ER status discrepancies were confirmed in about 24 percent of circulating tumor cells from metastatic patients compared with the corresponding primary tumors [107].

Alternatively spliced ER — Alternatively spliced ER mRNA variants have been frequently identified in both normal and malignant breast tissues [108]. These mRNA variants lack one or several exons due to exon "skipping." Some of these variants bind to DNA, but not estrogen, activating transcription in an estrogen-independent manner. These properties imply a role in estrogen-independent growth, although they have not been investigated extensively as a cause of SERM resistance in human breast cancer. Interestingly, there appears to be a significant increase in expression of these exon-deleted variants in metastatic breast cancer when compared with the respective primary tumor [109].

Modulation of ER expression through second messengers — ER expression and function are also strongly influenced by nongenomic or additional mechanisms such as estrogen-independent growth factor signaling [110]. Both ER expression and ER function correlate with distinct patterns of growth factor receptor overexpression [111-119]. As an example, ER-negative tumors (as well as those that are ER positive but progesterone receptor negative [120,121]) overexpress proteins of the EGFR family, particularly EGFR and the HER2 protein [111-114,120]. In experimental systems, ER expression is suppressed when either the HER2 receptor or EGFR is activated, leading to refractoriness to hormone therapy [110,115-117]. In addition, chronic activation of ER-positive, HER2-positive breast cancer cell lines with heregulin, a ligand for the HER2 family of receptors, leads to down-regulation of ER expression and hormone independence [118,119].

One report suggests that this effect may be mediated by a corepressor termed metastasis-associated protein 1 (MTA1) corepressor and that it can be inhibited by trichostatin A, opening the possibility of pharmacologic reversal of resistance to antiestrogen therapy [117]. Others

suggest that the antagonist activity of tamoxifen on the ER may be diminished via an interaction between HER2 and AIB1 (also known as SRC-3), an ER coactivator [122].

Data linking nonestrogen growth factor signaling pathways to acquired tamoxifen resistance are discussed below. (See 'Acquired resistance' below.)

It appears likely that an appropriate growth factor environment is necessary for efficient mitogenesis in breast cancer cells, with steroid hormone and growth factor signaling pathways "cross talking" to reinforce each other's signaling [110]. One proposed model for both primary and secondary hormone resistance in breast cancer is that phenotypic changes in growth factor signaling pathways may perturb this balance of steroid hormone and growth factor interaction, providing a selective advantage for tumor cell proliferation. These changes may underlie in vivo endocrine unresponsiveness in breast cancer.

Modulation of ESR1 expression by BRCA1 — Germline mutations in the breast cancer susceptibility genes 1 and 2 (*BRCA1* and *BRCA2*) confer a genetic predisposition to breast and ovarian cancers. (See "Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes".)

At least some data suggest that patients with inherited *BRCA1* mutations derive less benefit from chemoprevention using tamoxifen than do those with *BRCA2* mutations, although the available studies are conflicting.

It has been proposed that the selective benefit of tamoxifen in high-risk patients could be attributable to differences in ER-alpha (*ESR1*) expression. While most sporadic and *BRCA2*-associated breast cancers are *ESR1* positive, the majority of *BRCA1*-associated tumors do not express *ESR1*, possibly because the BRCA1 protein may be able to bind to and inactivate the ER-alpha promoter on the *ESR1* [123].

Altered tamoxifen metabolism

Tamoxifen is converted to its active metabolites (endoxifen and 4-hydroxytamoxifen) by two rate-limiting enzymes, cytochrome P450 2D6 (CYP2D6) and UDP-glucuronyltransferase-2B7 (UGT2B7) [70-73]. Although several reports indicate that the inheritance of CYP2D6 polymorphisms may confer relative resistance to tamoxifen [124-131], other data indicate that these polymorphisms do not impact either toxicity or breast cancer outcomes [132-137]. In the absence of conclusive data, we do not routinely test for CYP2D6 genotype prior to the administration of tamoxifen. The approach to patients taking medications such as SSRIs, which interfere with CYP2D6 metabolism, is discussed below. (See 'Patients taking SSRIs' above.)

The largest prospective-retrospective studies (correlative studies from previously conducted prospective trials) are discussed below.

- Breast International Group (BIG) 1-98 – CYP2D6 genotyping was performed in 4393 (61 percent) women who were treated on the BIG 1-98 adjuvant endocrine therapy trial [133]. The proportion of patients classified as poor, intermediate, or extensive metabolizers was 8, 30, and 62 percent, respectively. There was no association between CYP2D6 genotype and breast cancer-free survival or the incidence of hot flashes among women treated with tamoxifen. Compared with extensive metabolizers, poor or intermediate metabolizers had no difference in the risk of breast cancer recurrence (hazard ratio [HR] for recurrence 0.86, 95% CI 0.60-1.24), but a higher risk for hot flashes (HR 1.24, 95% CI 0.96-1.59 for poor metabolizers; HR 1.23, 95% CI 1.05-1.43 for intermediate metabolizers).

- Arimidex, Tamoxifen, Alone or in Combination (ATAC) – Similarly, in a study of over 1800 postmenopausal patients with hormone-positive disease randomly assigned to tamoxifen or anastrozole, CYP2D6 genotype did not predict clinical benefit of adjuvant tamoxifen [134].

By contrast, an ad hoc group of investigators, the International Tamoxifen Pharmacogenomics Consortium, conducted a pooled analysis of selected studies that suggested that CYP2D6 status does affect outcomes of patients treated with tamoxifen. These data are as follows:

- International Tamoxifen Pharmacogenomics Consortium (ITPC) – The ITPC conducted an ad hoc analysis using data from 12 global research projects that contributed clinical and genetic data in almost 5000 patients treated with tamoxifen [136]. The main results were that reduced CYP2D6 metabolism is:

  - Significantly associated with a higher risk of recurrence (measured by the invasive disease-free survival [IDFS]; HR 1.25, 95% CI 1.06-1.47) when the analysis is restricted to postmenopausal women who underwent resection of a nonmetastatic, early-invasive breast cancer, were treated with tamoxifen monotherapy for an intended duration of five years, and were followed annually for recurrence (n = 1996 patients).

  It should be noted that an accompanying editorial raised concerns about the methodology and conclusions of the ITPC, specifically in regards to drawing conclusions based on an ad hoc subset analysis [138]. If the analysis included all samples (n = 4935) or was restricted to pre- and postmenopausal women treated with any duration of tamoxifen without the requirement of annual follow-up (HR 1.17, 95% CI 0.90-1.52; n = 2443), reduced CYP2D6 metabolism was not significantly associated with a shorter IDFS (HR 1.07, 95% CI 0.92-1.26).

One therapeutic strategy that is being explored to circumvent issues with CYP2D6 metabolism is use of the tamoxifen metabolite Z-endoxifen hydrochloride, whose affinity for ER far exceeds that of its parent compound tamoxifen. In a phase 1 study of women with AI-refractory metastatic breast cancer (NCT01327781), substantial antitumor activity was observed in patients with and without prior progression on tamoxifen as well as in patients with prior progression on fulvestrant [139,140]. Overall, the findings indicate that endoxifen is both well tolerated and antitumorigenic. A prospective randomized phase II study comparing endoxifen with tamoxifen is ongoing (NCT02311933).

Another strategy, using an increased dose of tamoxifen (40 mg orally daily) among patients with CYP2D6 hetero- or homozygous variants, did not achieve a higher rate of progression-free survival at six months relative to standard dosing (20 mg orally daily) [141].

The main results of the trials that evaluate the therapeutic benefit of tamoxifen are discussed separately. (See "Selective estrogen receptor modulators and aromatase inhibitors for breast cancer prevention", section on 'Tamoxifen'.)

Acquired resistance — Growth factor pathways also appear to play a central role in acquired resistance to tamoxifen. Signaling through EGFR and the HER2 receptor, as well as other growth factor receptors, appears to bypass the estrogen requirement for breast cancer cell growth and may drive initially ER-positive cells into an endocrine therapy-resistant state [122,142]. It is postulated that activation of growth factor pathways such as these modulates activity of ER or its regulators via phosphorylation, which alters ER function, especially its ability to interact with or to be inhibited by tamoxifen [118,143,144]. The net result is that an ER-positive cell becomes "hormone independent" and therefore resistant to tamoxifen.

Genomic studies have underscored key somatic mutations associated with intrinsic or acquired resistance to hormonal therapies (eg, [145]). A study of a large cohort of tumors that were previously exposed to hormonal therapy [146] identified increased number of alterations in genes involved in the mitogen-activated protein kinase (MAPK) pathway (eg, *EGFR, KRAS, NF1*), ER transcriptional regulators and other key transcription factors (eg, *CTCF, FOXA1*), and the *ERBB2* gene that codes for HER2. These mutations, which are largely non-concurrent with *ESR1* mutations, were associated with a shorter duration of response to subsequent hormonal therapies, suggesting their independent role in promoting endocrine resistance.

Emerging studies suggest that high levels of tumor EGFR expression may serve to identify those women for whom adjuvant tamoxifen provides little benefit [147]. However, EGFR expression might be associated with a poorer prognosis overall [148], and whether alternative adjuvant

strategies, either other forms of hormone therapy or chemotherapy, would alter the clinical course in these patients is uncertain. Prospective trials are required to address these issues.

The impact of HER2 expression on the response to tamoxifen is discussed separately. (See "HER2 and predicting response to therapy in breast cancer" and "Treatment for hormone receptor-positive, HER2-negative advanced breast cancer".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hereditary breast and ovarian cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient education: Breast cancer guide to diagnosis and treatment (Beyond the Basics)" and "Patient education: Medications for the prevention of breast cancer (Beyond the Basics)")

SUMMARY

- The selective estrogen receptor modulators (SERMs) tamoxifen, raloxifene, and toremifene are competitive inhibitors of estrogen binding to estrogen receptors (ERs); all have mixed agonist and antagonist activity, depending on the target tissue. (See 'Introduction' above.)

- Among women with ER-positive breast cancer, tamoxifen reduces the risk of recurrence and death when given as adjuvant therapy for early-stage disease and can provide palliation in those with metastatic disease. (See 'Introduction' above.)

- How an individual SERM can act as an ER agonist in one tissue and as an antagonist in another is not firmly established. However, it is likely that the change in receptor conformation that follows binding of the ER by a SERM results in variable interactions with cofactors that are required for ER-mediated gene regulation in different tissues. (See 'Corepressors and coactivators' above and 'Estrogen receptor-beta: A second ER isoform' above.)

- The newer SERMs such as raloxifene appear to have different tissue-specific effects from tamoxifen. The differing effects of raloxifene and tamoxifen on the uterus may be related to structural differences that influence which estrogen-responsive genes are modulated in specific tissues. Tamoxifen induces endometrial hyperplasia, an estrogen agonist effect, and increases the risk of developing endometrial cancer. Raloxifene does not appear to have endometrioid agonistic effects; unlike tamoxifen, it does not increase the risk of uterine cancers. Raloxifene has only been used for prevention, and should not be substituted for tamoxifen in the adjuvant or metastatic setting. (See 'Selective estrogen receptor modulators (SERMs)' above and 'Raloxifene' above.)

- Not all breast cancers respond to SERMs such as tamoxifen. Resistance to tamoxifen therapy may be intrinsic (de novo), in which ER-negative and many ER-positive tumors do not respond to tamoxifen at the outset of therapy, or acquired, where ER-positive tumors that initially responded to tamoxifen subsequently exploit the tamoxifen/ER complex as a stimulatory rather than inhibitory growth signal.

- Deep sequencing studies suggest a relatively common mechanism of acquired SERM resistance may be the acquisition of a somatic mutation in ER-alpha (*ESR1*) that causes an amino acid change in the ER ligand-binding domain (LBD), resulting in a constitutively active ER conformation. However, the clinical implications of this finding for treatment of women with ER-positive breast cancer have not yet been determined. (See 'Tamoxifen resistance in breast cancer' above.)

- Two antiestrogens with mixed SERM/selective estrogen receptor down-regulator (SERD) activity, bazedoxifene and pipdendoxifene, have shown efficacy in preclinical models of tamoxifen resistance, with bazedoxifene demonstrating activity against a model expressing the *ESR1*-Y537S mutation. However, the clinical implications of these findings have not yet been determined.

- Elacestrant is a selective estrogen receptor down-regulator (SERD) that has regulatory approval in the United States for use in postmenopausal women and in men with *ESR1*-mutated advanced hormone receptor-positive HER2-negative breast cancer that has progressed on at least one line of prior endocrine therapy. A number of other oral SERDS are currently in clinical trials, including giredestrant and camizestrant, after showing efficacy in preclinical models with either wild-type and *ESR1* mutations. The novel ER PROTAC ARV-471 is currently in phase I studies in combination with palbociclib. There are also a number of other oral SERDS in development and entering this clinical space. (See 'Fulvestrant, oral SERDs, and SERM/SERD hybrids' above.)

- A number of factors contribute to intrinsic resistance, including variable expression of the ER-alpha and beta isoforms, interference with binding of coactivators and corepressors, alternatively spliced ER mRNA variants, and modulation of ER activity through increased expression of growth factors. (See 'Intrinsic resistance' above.)

- Tamoxifen requires the cytochrome P450 CYP2D6 for conversion to one of its active metabolites. However, we do not evaluate for CYP2D6 genotype as a way to select patients for tamoxifen treatment. (See 'Intrinsic resistance' above.)

- While certain selective serotonin uptake inhibitors (SSRIs), particularly paroxetine and fluoxetine, inhibit CYP2D6, we do not routinely discontinue these medications in patients starting tamoxifen. However, for patients with indications to start an SSRI while on tamoxifen, we typically initiate agents such as venlafaxine or citalopram, as these have a lesser effect on CYP2D6.

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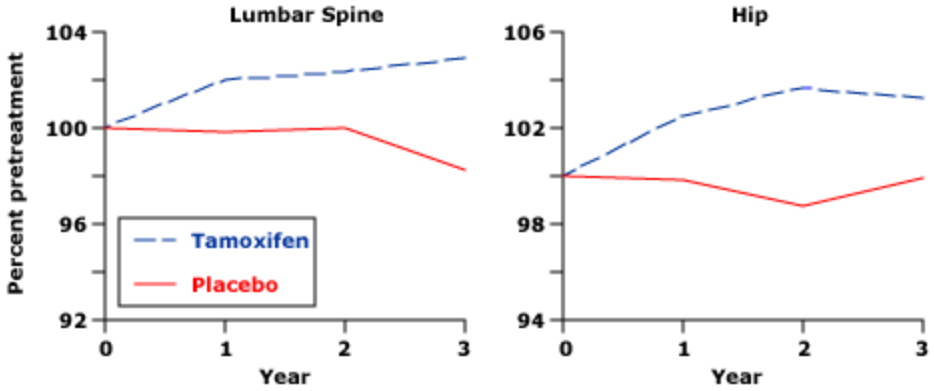
Topic 762 Version 41.0

GRAPHICS

Tamoxifen increases bone density in postmenopausal women

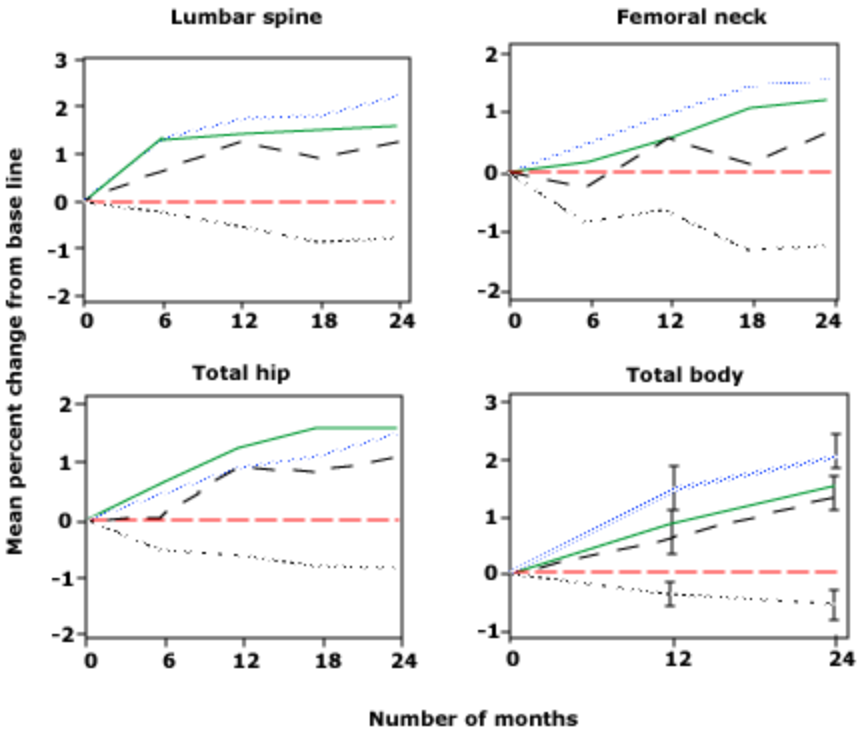


Change in bone mineral density in the lumbar spine and hip in postmenopausal women treated with tamoxifen or placebo. Tamoxifen was associated with an increase in bone density at both sites.

Data from: Powles TJ, Hickish T, Kanis JA, et al. Effect of tamoxifen on bone mineral density measured by dual-energy x-ray absorptiometry in healthy premenopausal and postmenopausal women. J Clin Oncol 1996; 14:78.

Graphic 56681 Version 3.0

Bone mineral density increases with raloxifene in postmenopausal women

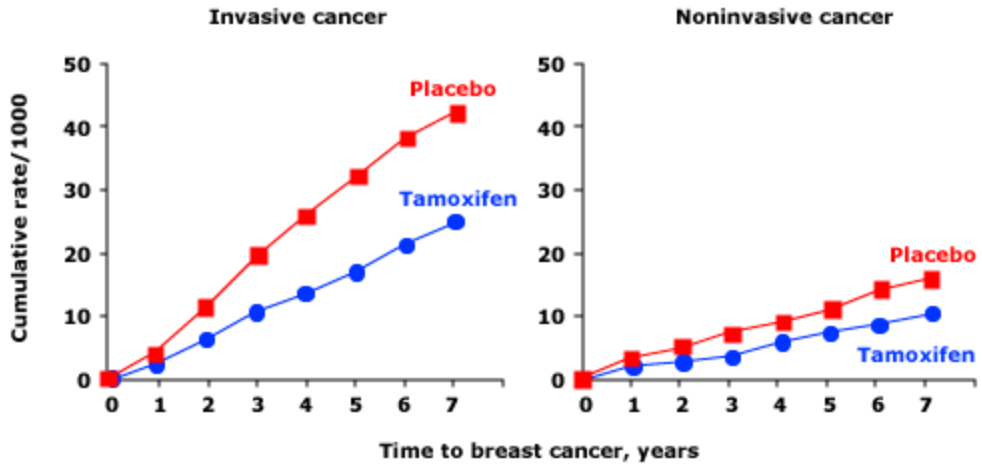


Administration of raloxifene at varying doses (30 mg, black dashed line; 60 mg, green line; 150 mg, blue dotted line) resulted in an increase in bone mineral density compared with placebo (black dotted line) in all sites tested over the two-year follow-up period.

Data from: Delmas PD, Bjarnason NH, Mitlak BH, et al. Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. N Engl J Med 1997; 337:1641.

Graphic 73629 Version 3.0

Cumulative rates per 1000 women of invasive and noninvasive breast cancer in NSABP P-1 participants by treatment group



Reproduced with permission from: Fisher B, Costantino JP, Lawrence D, et al. Tamoxifen for the prevention of breast cancer: Current status of the National Surgical Adjuvant Breast and Bowel Project P- 1 study. JNCI 2005; 97:1652. Copyright © 2005 Oxford University Press.

Graphic 60219 Version 2.0

Toxicities of tamoxifen for patients at high risk of breast cancer in NSABP P-01

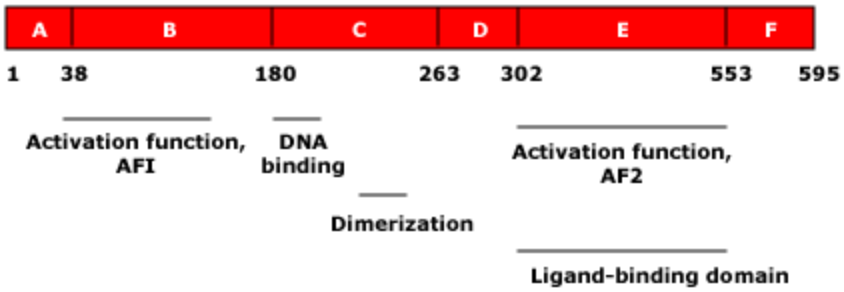
Adverse event	Annual rate per 1000 women				RR (95% CI)	
	Placebo		Tamoxifen			
	≤49 years	≥50 years	≤49 years	≥50 years	≤49 years	≥50 years
Cerebrovascular accident	0.5	1.7	0.57	2.5	1.13 (0.39-3.36)	1.47 (0.97-2.22)
Transient ischemic attack	0.44	1.10	0.25	1.09	0.57 (0.12-2.25)	0.99 (0.56-1.76)
Pulmonary embolism	0.13	0.44	0.25	0.96	2.01 (0.29-22.19)	2.16 (1.02-4.89)
Deep vein thrombosis	0.76	0.89	1.01	1.33	1.34 (0.59-3.10)	1.49 (0.84-2.68)
Invasive endometrial cancer	0.82	0.58	1.16	3.08	1.42 (0.55-3.81)	5.33 (2.47-13.17)

RR: risk ratio for women in the tamoxifen group relative to women in the placebo group; CI: confidence interval.

Data from: Fisher B, et al. J Natl Cancer Inst 2005; 97:1658.

Graphic 69836 Version 2.0

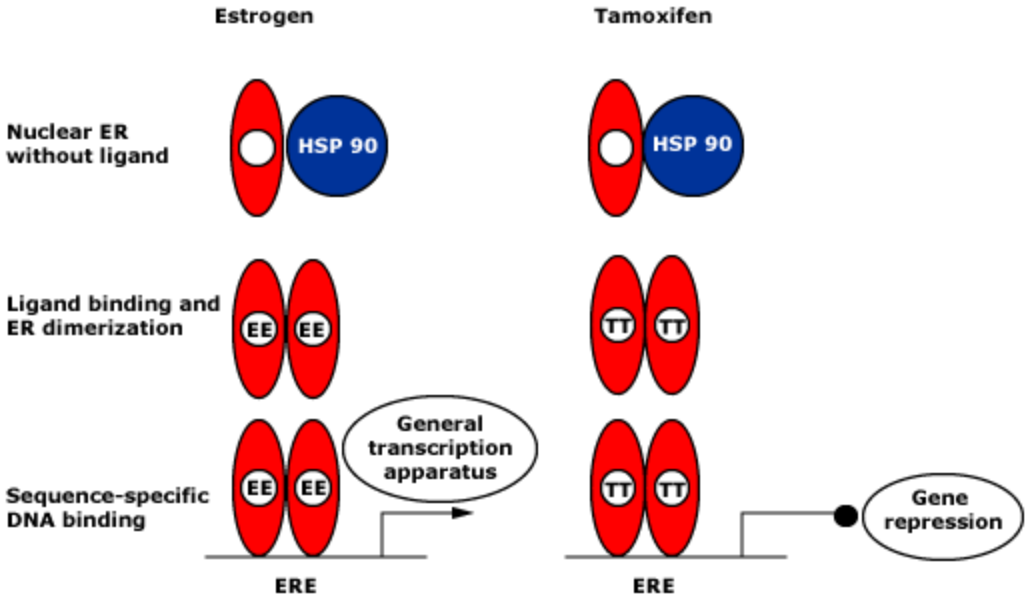
Structure of estrogen receptor (ER)



A to F represent different domains of the ER. Numbers represent amino acids from amino to carboxy termini.

Graphic 59876 Version 10.0

Simple model of estrogen (E) and tamoxifen (T) binding to the ligand binding domain of the estrogen receptor (ER)

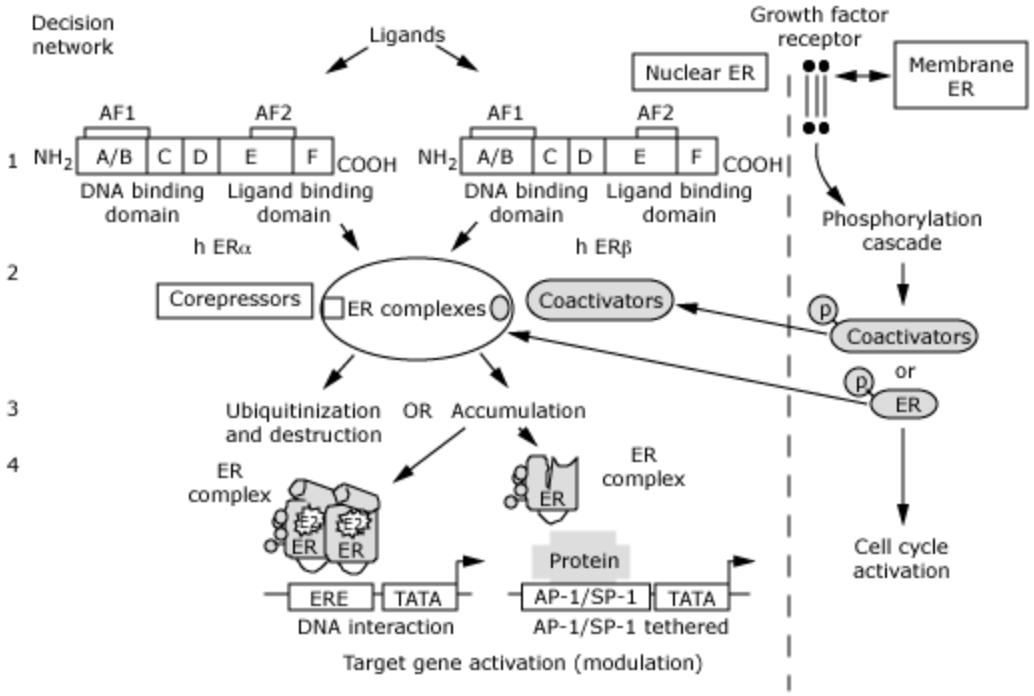


Basic model in which ligand (estrogen or tamoxifen) displaces heat shock protein (HSP), resulting in binding of ligand-receptor complex to estrogen receptor element (ERE) of gene promoter region. ER binding directly to the ERE is one mechanism, but ER can also instead tether DNA binding transcription factors for modulate genes without a classical ERE.

Arrow: gene activation; circle: gene repression.

Graphic 61233 Version 10.0

Complexity of SERM signal transduction



The decision network for estrogen or SERM action binding to nuclear estrogen receptor (ER) a or b receptor or membrane ER (decision 1). Receptor-specific or mixed specificity ligands bind to the ligand binding domain (E region) of the ERs to cause a ligand-specific perturbation in the receptor complex that creates opportunities for the complex to bind either coactivators or corepressors on the external surface (decision 2). The interactive proteins shunt the ER complex into transcriptionally active or inactive states. Although the expanding family of coregulators are being defined, this does not exclude the possibility that other interactive proteins could alter gene transcription through phosphorylation activation. This could be initiated rapidly either by membrane ER or constitutively through cell surface growth factor receptors. The next decision point (3) is where the complex or coregulators are ubiquitinated and destroyed by the proteasome or accumulate to become promiscuous estrogen-like complexes. Again, phosphorylation may play an important role in the activity of the ER complex. The decision (4) to interact with the machinery involved with gene transcription can shunt the signaling pathway from positive or negative regulation based upon the ER concerned, the ligand, or whether there is a direct interaction with an estrogen response element (ERE) or a tethered interaction to proteins at AP-1 or SP-1 sites. Overall, the decision network creates a complex regulatory system at target tissues or in cancer where a growth advantage can be exploited in response to antiestrogen therapies.

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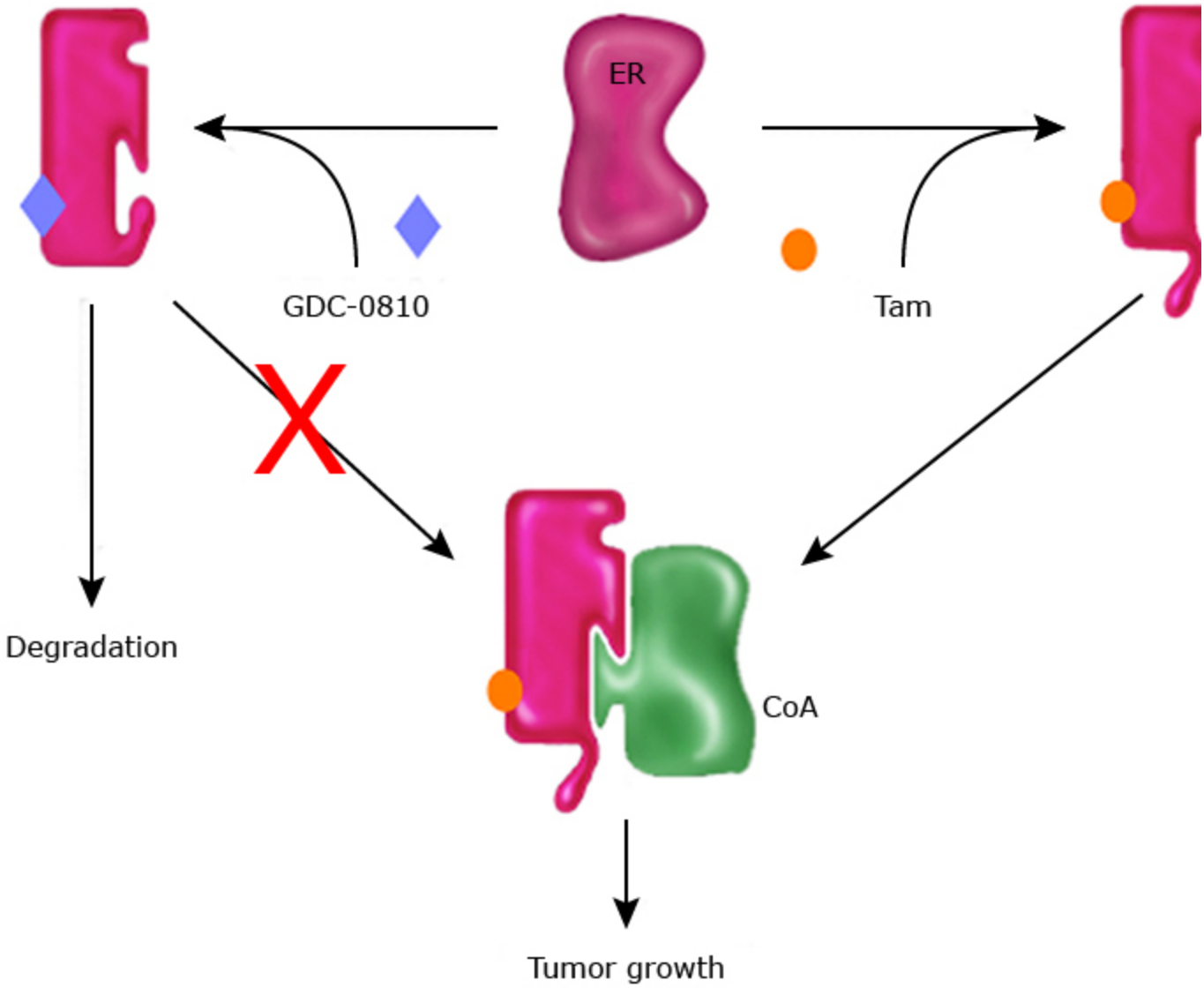
Graphic 75840 Version 2.0

Molecular pharmacology of SERDs in the setting of tamoxifen resistance



Molecular pharmacology of SERDs in the setting of tamoxifen resistance. Upon binding tamoxifen, ERα undergoes a specific conformational change that enables the presentation of protein-protein interaction surfaces for which in tamoxifen-sensitive cells there are no compatible coregulators. Thus, tamoxifen bindin commits ER down a "nonproductive" pathway, an activity that manifests as antagonism. It is proposed that chronic administration of tamoxifen, however, results in the selection of a subpopulation of cells that expres compatible coactivator (CoA). In this manner the pharmacology of tamoxifen "switches" from that of an antagonist to an agonist. SERDs, like GDC-0810, have activity in the setting of tamoxifen resistance because they (a) function as high affinity competitive antagonists, (b) induce a conformational change that is incompatible with coregulator interactions, and (c) target the receptor for proteasomal degradation.

Graphic 108029 Version 1.0

Cytochrome P450 2D6 (CYP2D6) inhibitors

Strong inhibitors	Moderate inhibitors
▪ Bupropion ▪ Dacomitinib ▪ Fluoxetine ▪ Paroxetine ▪ Quinidine ▪ Tipranavir	▪ Abiraterone ▪ Adagrasib ▪ Cinacalcet ▪ Darifenacin ▪ Darunavir ▪ Duloxetine ▪ Givosiran ▪ Lorcaserin ▪ Mirabegron ▪ Perhexiline* ▪ Rolapitant ▪ Terbinafine (systemic) ▪ Thioridazine

- This table lists strong and moderate CYP450 2D6 inhibitors; there are no known clinically relevant inducers of CYP2D6.
- Inhibitors of CYP2D6 metabolism listed above can alter serum concentrations of other drugs that are dependent on CYP2D6 liver enzymes for activation or elimination:
  - Codeine, tamoxifen, and tramadol are examples of drugs that require transformation by CYP2D6 to their active metabolite(s). The presence of CYP2D6 inhibitors can **decrease** efficacy of these drugs.
  - Amitriptyline, clozapine, desipramine, flecainide, haloperidol, nortriptyline, risperidone, and valbenazine are examples of drugs that are eliminated by CYP2D6 metabolism. The presence of CYP2D6 inhibitors can **increase** levels of these drugs.
- The specific effect of CYP2D6 inhibition on CYP2D6 substrate blood levels varies widely among individual patients because of variability in CYP2D6 function (ie, genetic polymorphism). Poor, intermediate, extensive, and ultrarapid CYP2D6 function types have been well characterized.
- These classifications are based upon US Food and Drug Administration (FDA) guidance.[1,2] Other sources may use a different classification system resulting in some agents being classified differently.
- For additional information on CYP2D6 drug metabolism, refer to the UpToDate topic review of pharmacogenomics, section on CYP2D6 variants, and clinical topic reviews of the use of these agents and their drug interactions.
- Specific drug interactions and management suggestions may be determined by using the Lexicomp drug interactions program included with UpToDate. Refer to UpToDate topics on specific agents and indications for further details.

CYP2D6: cytochrome P450 2D6.

* Not available in United States.

References:

1. *US Food and Drug Administration. Clinical drug interaction studies — Cytochrome P450 enzyme- and transporter-mediated drug interactions guidance for industry, January 2020. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-drug-interaction-studies-cytochrome-p450-enzyme-and-transporter-mediated-drug-interactions (Accessed on June 5, 2020).*
2. *US Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available at: FDA.gov website.*

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