Next-Generation Endocrine Therapies for Breast Cancer

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It has been more than 100 years since Beaston and Boyd independently reported that bilateral oophorectomy was an effective treatment or adjuvant for breast cancer, observations that together initiated the use of endocrine therapy for this disease.[1,2] Remarkably, these advances were made before the discovery of 17β-estradiol (E2) or the establishment of its role as a mitogen in breast cancer cells. Prophetically, Boyd surmised that some substance produced by the ovaries was having a positive impact on tumor growth and survival, but it took nearly 75 years to advance endocrine therapy beyond surgical oophorectomy and/or radiation-induced ovarian ablation. Notable in this regard was the work of Elwood Jensen, William Hoekstra, Jack Gorski, and David Toft, who, in the 1960s, defined the biochemical entity that we now know to be the estrogen receptor (ER), and the subsequent studies by Bert O'Malley, which demonstrated that ER was, in fact, a ligand-regulated transcription factor.[3-6] For many years prior to these discoveries, and absent any understanding of the molecular mechanism of ER action, there had been considerable interest and success in developing estrogen-like compounds for use as emergency contraceptives.[7] In the early 1970s, Craig Jordan was one of the first to capitalize on the availability of these drugs, which displayed different pharmacologic attributes (ie, mimicked or opposed the action of estrogens in reproductive tissues).[8,9] He demonstrated that one such antiestrogen, tamoxifen, which earlier had shown efficacy in the treatment of metastatic breast cancer, actually functioned as a direct competitive inhibitor of ER, and its activity in models of carcinogen-induced mammary tumors suggested that it was likely to have activity in the adjuvant setting.[10-12] This body of work also led to the establishment of a simple model of ER pharmacology that posited that upon binding an agonist, ER underwent a biochemical transformation that enabled it to regulate target gene transcription and that antagonists functioned simply by competitively inhibiting agonist binding to the receptor.[9] Within the confines of this model, it was considered that, notwithstanding improvements in affinity and pharmaceutical properties of drugs, additional discovery in this area would likely lead to only incremental advances in efficacy.

With the emergence and clinical success of aromatase inhibitors in the early 2000s, there was little interest in the pharmaceutical industry in the continued development of ER modulators for breast cancer.[13,14] However, there continued to be considerable research defining the mechanism of action of ER and in identifying the molecular determinants of ER pharmacology. This was driven in large part by two pharmacologic curiosities: (1) tamoxifen and another drug raloxifene, while functioning as antagonists in breast cancer cells, exhibited different degrees of estrogenic activity in different cells, and (2) in both patients and preclinical models of breast cancer, there was evidence that resistance to tamoxifen occurred when something happened in cells that enabled them to switch from recognizing tamoxifen as an antagonist to an agonist.[15-18] These observations framed the important question as to how the same drug, acting through the same receptor, could have different activities in different cells. Leveraging insights from our work and from other investigators, we developed a contemporary model to explain the molecular pharmacology of ER, which holds that (1) the overall conformation of ER is influenced by the nature of the ligand to which it is bound, (2) differences in ER conformation allow the differential presentation of protein-protein interaction surfaces on the receptor, and (3) the relative and absolute expression of functionally distinct receptor-interacting proteins (coregulators) dictate how differently conformed ER-ligand complexes are recognized in cells (Fig 1).[19-21] Thus, with respect to drug discovery, the primary exploitable feature of ER is the ability to use small-molecule ligands to manipulate its conformation, and this engenders different coregulator interactions.[21-23] Reflecting their ability to induce different alterations in ER structure and manifest tissue-selective agonist and antagonist activities, tamoxifen and raloxifene were reclassified as selective estrogen receptor modulators (SERMs).[24] These insights informed the discovery of new SERMs with unique clinical profiles such as lasofoxifene, bazedoxifene, pipendoxifene, ospemifene, and more recently H3B-6545, some of which are being evaluated as breast cancer therapeutics.[25-29]

Whereas SERMs have found utility in the treatment and prevention of osteoporosis, dyspareunia, and other symptoms associated with estrogen deprivation (menopause), there emerged a disappointingly long list of

ASSOCIATED CONTENT

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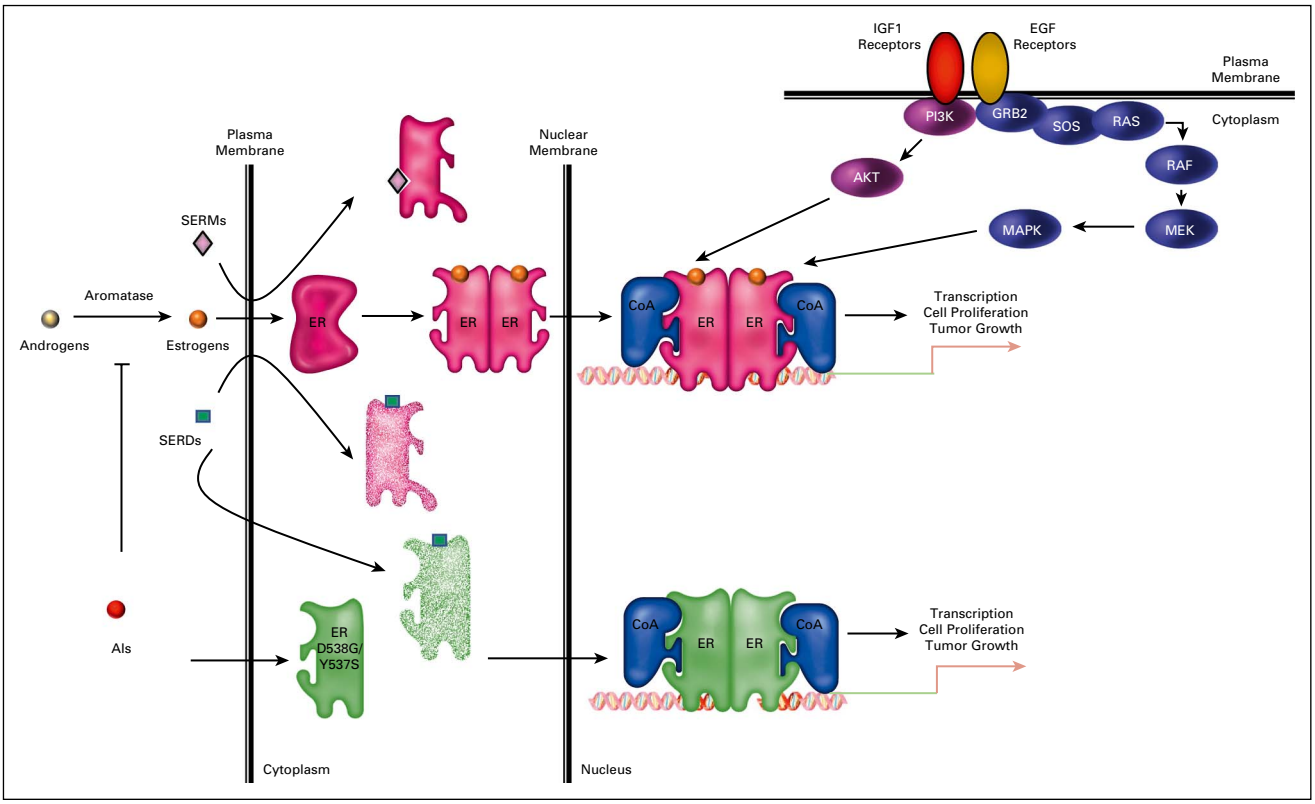

FIG 1. Endocrine therapy landscape for ER-positive breast cancer. SERMs such as tamoxifen inhibit ER-positive breast tumor growth by competitively blocking estrogen binding to the receptor, whereas AIs function by blocking the production of estrogens from androgens. These treatments are not curative as growth factor signaling pathways can mediate resistance by activating the receptor-CoA complex in the absence of hormone or when the receptor is occupied by an SERM. Treatment escape following AI therapy, and to a lesser extent SERM therapy, is also often accompanied by the expression of constitutively active ER mutants, most commonly ER-D538G and ER-Y537S. SERDs, such as fulvestrant and elacestrant (RAD1901), can circumvent some of the therapeutic liabilities of SERMs and AIs by degrading both wild-type and mutant receptors. AIs, aromatase inhibitors; AKT, protein kinase B; CoA, coactivator; EGF, epidermal growth factor; ER, estrogen receptor; GRB2, growth factor receptor-bound protein 2; IGF1, insulin-like growth factor 1; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; PI3K, phosphoinositide 3-kinase; RAF, Raf oncogene; RAS, Ras oncogene; SERD, selective estrogen receptor downregulator or degrader; SERM, selective estrogen receptor modulator; SOS, son of sevenless homolog 1.

next-generation SERMs that failed to show efficacy as second-line endocrine therapies in breast cancer.[30] Several related discoveries provided a potential explanation for these drug failures. The first was the observation that certain ER coregulators (eg, SRC1 and SRC3) were significantly overexpressed in advanced disease, which decreased the inhibitory activity of even the most antagonistic SERMs.[31] Further, it was demonstrated that breast cancer cells likely use the same mechanism, overexpression of coregulators, to circumvent the estrogen deprivation afforded by aromatase inhibitors.[32,33] Even more problematic from a therapeutic point of view was the observation that coregulators and ER itself were post-translationally modified upon the activation of several intracellular signaling pathways (eg, mitogen-activated protein kinase and phosphoinositide 3-kinase) and that this enabled ER to direct target gene transcription absent a canonical small-molecule ligand.[34,35] These insights reduced enthusiasm for further development of SERMs as therapeutics in advanced disease.

The observation that coregulator biology is frequently dysregulated in breast cancer and that ER can activate transcription absent a ligand suggested that removal of ER, rather than solely inhibiting its classical activities, may have particular utility in breast cancer. Indeed, this idea was supported by the observation in preclinical models that fulvestrant, a first-in-class selective estrogen receptor downregulator or degrader (SERD), was effective in animal models of endocrine therapy–resistant breast cancer.[36] Fulvestrant is approved for use as a second-line endocrine therapy, and despite the fact that it is an injectable with considerable pharmaceutical liabilities, its effectiveness in metastatic disease has validated the general SERD approach.[37-40] The early clinical experience with fulvestrant drove the search for effective oral SERDs, which have increased efficacy in the setting of metastatic disease and which would also be suitable for use in the adjuvant setting in patients at high risk for recurrence. To our knowledge, our group identified the first oral SERD etacstil (DPC974),

whose development, despite evidence of clinical efficacy, was discontinued for business reasons.[41] However, the clear understanding of the mechanism of action of this drug led others to pursue this therapeutic modality with the result that there are currently at least 13 oral SERDs (and two new classes of SERM) in clinical development for breast cancer (Fig 2). As described in the accompanying article, RAD1901 (elacestrant), a drug our group repurposed for breast cancer, having identified it to be an oral SERD, is the furthest along in development.[42-44] The positive clinical activity of RAD1901 in breast cancer reported by Bardia et al[42] bodes well for the success of the oral SERDs as a class and is instructive with respect to biomarkers that may predict positive response in patients. Preliminary efficacy data should be available for several other drugs of this class later this year.

In addition to wild-type ER (wtER), there has emerged considerable interest in understanding how SERDs work in breast (and gynecologic) cancers harboring ESR1 mutations, recently found to occur in approximately 40% of the metastatic lesions in patients who have progressed on aromatase inhibitors.[45-47] These mutations, which occur within the ligand-binding domain of ER, alter the pharmacology of the receptor, facilitate constitutive coregulator binding, and permit ligand-independent transcriptional activity.[46] They may also endow upon the receptor neomorphic pathologic activities.[48] Whereas it is believed that these mutants are directly involved in the regulation of processes that affect disease pathology, it remains to be determined how, given their low allelic frequency and the fact that they likely are coexpressed with wtER in most cells, they affect cancer cell biology. Indeed, we have recently demonstrated that the pharmacology of the most commonly occurring mutants is normalized in cells when wtER is present.[49] Intriguing to us is the possibility that the presence of ESR1 mutations in tumor cells may be a predictive biomarker that reads on the acute estrogen dependency of a tumor and thus may serve as a positive predictor of response to SERDs or even some SERMs. It is notable in this regard that although the sample size was small, it was reported in the accompanying study that the response to the SERD, elacestrant (RAD1901), was greater in patients in which an ESR1 mutation was detected (ORR 33% in patients harboring ESR1 mutations *v* 19% in all comers).[42] It may be possible to identify those patients who will most likely respond to second-line endocrine therapies by virtue of being able to detect ESR1 mutations in biopsied metastatic tumors or in circulating tumor DNA.

It is likely that most of the SERDs in development will demonstrate efficacy in cancers harboring either wild-type or mutant ESRs, and thus there is a need to consider how they can be distinguished in a clinically meaningful manner. Key differentiators will likely be tumor exposure, target engagement (ER turnover), and tolerability, issues that to date have significantly limited progress in this area. Some drugs appear to be associated with significant GI issues, and bradycardia is a potential liability of at least two SERDs in development.[50] These issues could limit the use of some SERDs in the adjuvant setting and possibly also in advanced disease, where they would likely be used in

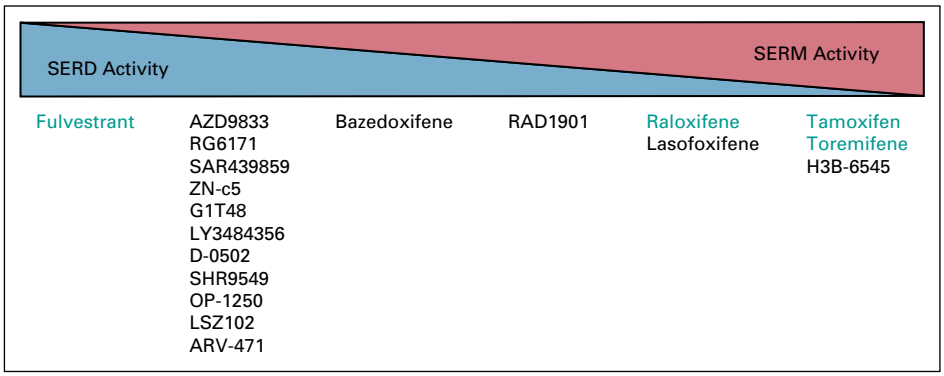

FIG 2. ER modulators that are currently approved for use in the treatment or prevention of ER-positive breast cancers or that are currently in clinical development. Those drugs (SERDs and SERMs) that are currently approved for clinical use in breast cancer are highlighted in green. Investigational drugs that are currently in development for breast cancer are as follows: AZD9833 (NCT04588298; *SERENA-3*), RG6171 (*giredestrant*) (NCT04576455), SAR439859 (*amcenestrant*) (NCT03284957; *AMEERA-1*), ZN-c5 (NCT03560531), G1T48 (*rintodestrant*) (NCT03455270), LY3844356 (NCT04188548; *EMBER*), D-0502 (NCT03471663), SHR9549 (NCT03596658), OP-1250 (NCT04505826), LSZ102 (NCT02734615), ARV-471 (NCT04072952), bazedoxifene (NCT02448771), RAD1901 (elacestrant) (NCT03778931; *EMERALD*), lasofoxifene (NCT03781063; *ELAINE-1*), and H3B-6545 (NCT04288089). The relative SERD or SERM activity reflects the authors' summary of the available literature and may change as more data become available from comparative studies. ER, estrogen receptor; SERD, selective estrogen receptor downregulator or degrader; SERM, selective estrogen receptor modulator.

combination with other drugs that have their own inherent liabilities (eg, CDK4/6, PI3K, and mTOR inhibitors).[51-53] Another important distinguishing feature of SERDs will be their differential ability to cross the blood-brain barrier, where they would be anticipated to inhibit the growth or progression of metastatic lesions. However, the significant functional differences in the murine and human blood-brain barriers make it difficult to predict human brain exposure of the various drugs at the current time. Further, some SERDs, by mechanisms that remain elusive, also protect against bone loss, and in the adjuvant setting, this is not only likely to be beneficial to bone health but may also decrease or prevent secondary metastasis.[50,54] Clearly, the positive or negative activity of these drugs in other ER-target tissues needs to be considered in evaluating their likely benefit in patients.

Finally, looking to the future, all the existing SERDs and SERMs were developed with the understanding that the most important target in breast tumors is ER expressed within the cancer cells. Thus, drugs were generally optimized for activity in cellular models of luminal breast cancer, and then activities were confirmed in xenograft tumor models as a surrogate for activity in metastatic disease. However, this established and traditional discovery path does not reflect the fact that in addition to cancer cells, ER is expressed in most cells within the tumor microenvironment and that the impact of inhibiting this receptor in these cells remains unknown. There is clearly a need to define how estrogens, SERMs, and SERDs affect tumor immunity through actions in T cells, macrophages, and other cells in the tumor stroma. Somewhat forgotten are the results of early studies using endocrine therapy that demonstrated that tamoxifen has considerable efficacy in patients whose tumors were biochemically ER-negative.[10] As compelling were data suggesting that although overall response to tamoxifen and the high-affinity ER agonist diethylstilbestrol were equivalent in patients with breast cancer, those patients taking the estrogen had a better overall survival.[55,56] Also important to consider is the most updated data from the Women's Health Initiative, which reported a reduced incidence of breast cancer in postmenopausal women receiving supplemental estrogen therapy.[57,58] The ongoing studies with SERDs (and SERMs) in breast cancer and the correlative studies associated with these trials may help to address some of these complex issues. However, it is our strongly held opinion that in the process of developing the next generation of endocrine therapies, we should take a step back and define the activities of ER in different cellular components of the tumor microenvironment and how they are influenced by different ER modulators. With this information in hand, we should be in a position to identify new drugs that retain their antagonist and/or SERD activity on ER within the tumor cells, but which also exert favorable activities in tumor-associated cells that contribute to the biology of tumors.

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