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Cancer Stem Cells: Culprits in Endocrine Resistance and Racial Disparities in Breast Cancer Outcomes

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Abstract

Breast cancer stem cells (BCSCs) promote endocrine therapy (ET) resistance, also known as endocrine resistance in hormone receptor (HR) positive breast cancer. Endocrine resistance occurs via mechanisms that are not yet fully understood. In vitro, in vivo and clinical data suggest that signaling cascades such as Notch, hypoxia inducible factor (HIF), and integrin/Akt promote

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BCSC-mediated endocrine resistance. Once HR positive breast cancer patients relapse on ET, targeted therapy agents such as cyclin dependent kinase inhibitors are frequently implemented, though secondary resistance remains a threat. Here, we discuss Notch, HIF, and integrin/Akt pathway regulation of BCSC activity and potential strategies to target these pathways to counteract endocrine resistance. We also discuss a plausible link between elevated BCSC-regulatory gene levels and reduced survival observed among African American women with basal-like breast cancer which typically lacks HR expression. Should future studies reveal a similar link for patients with luminal breast cancer, then the use of agents that impede BCSC activity could prove highly effective in improving clinical outcomes among African American breast cancer patients.

Keywords

breast cancer; stem cells; endocrine resistance; endocrine therapy; disparities

1. Introduction

More than 500,000 women die from breast cancer each year worldwide. Most women are diagnosed with hormone receptor (HR) positive or luminal breast cancer since their tumors express the estrogen receptor (ER), the progesterone receptor (PR), and in rarer instances, human epidermal growth factor receptor 2 (Her2). Luminal breast cancer is further divided into two subtypes: luminal A and luminal B, with the luminal A subtype exhibiting the best prognosis [1]. Endocrine therapy (ET) entails blocking the binding of estrogen to the ER often designated as estrogen receptor alpha (ERα), or inhibiting aromatase which converts androgens into estrogens.

Selective estrogen receptor modulator tamoxifen, acts as an estrogen antagonist in breast tissues yet behaves as an estrogen agonist in cardiac tissues and bone [2]. Aromatase inhibitors (AIs) have largely replaced tamoxifen as first line therapy for luminal breast cancer due to their enhanced efficacy [3]. Thus, tamoxifen is primarily used in women who cannot tolerate AIs. In pre-menopausal patients, AIs alone are insufficient to decrease estrogen levels due to the production of estrogen from the ovaries. It is therefore necessary to suppress ovarian function, which is commonly and reversibly achieved using luteinizing hormone-releasing hormone analogs. Patients who develop AI resistance are often treated with the selective estrogen receptor down-regulator fulvestrant in combination with agents such as cyclin dependent kinase (CDK) inhibitors [4].

Though ET often shows tremendous efficacy, relapse occurs in more than 40% of patients [5]. When patients develop resistance to one form of ET, they are often treated with an alternate form of ET. However, resistance to alternate forms of ET frequently occurs. Emerging evidence suggests that ET often enriches the breast cancer stem cell (BCSC) population to ultimately promote relapse [6] (Figure 1A). Recently, AI-resistant cells were shown to exhibit high levels of stemness markers [7]. To eradicate BCSCs, it is necessary to identify cellular signaling pathways that promote BCSC development and function [8].

African American women experience higher rates of breast cancer mortality than European American women despite lower overall incidence [9]. Differences in tumor biology are

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believed to contribute to this survival disparity. This minireview will focus on molecular aberrations within breast cancer cells that promote stem cell survival and increase the risk of endocrine resistance onset. We will discuss the potential contribution of BCSCs to the breast cancer survival disparity observed among African American women. We will also discuss potential therapeutic strategies to overcome endocrine resistance based on preclinical and clinical studies.

2. Pathways that regulate BCSC activity in endocrine therapy resistance

Stem cells govern tissue development and homeostasis. BCSCs represent key drivers of metastasis and endocrine resistance as previously reviewed [10]. Signaling pathways that promote endocrine resistance frequently drive BCSC growth and function. For instance, an ERα splice variant promotes resistance by increasing ET-mediated enrichment of the BCSC population via activation of AKT/GSK3β signaling [11]. Notch and integrin/Akt signaling pathways are important players in stem cell function and involve hypoxia inducible factor alpha (HIF1α) to impact both BCSC actions and ET responsiveness (Figure 1B). In this manuscript, we will focus our discussion on the contributions of Notch, HIF, and integrin/Akt signaling to the BCSC population and endocrine resistance.

2.1 Notch signaling

The Notch pathway maintains the hematopoietic system and provides crucial cues to enable stem cells to grow, proliferate and differentiate [12]. Notch signaling is mediated by four Notch receptors (NOTCH1–4) and at least four functional ligands such as delta-like-ligand (DLL)-1, Jagged-1 (JAG1), and Jagged-2 (JAG2) as previously reviewed [13]. Notch signaling is aberrantly activated in cancer where it promotes self-renewal of cancer stem cell (CSC) growth [14]. Aberrant expression of Notch pathway mediators such as JAG1–2, DLL, and Hey is associated with poor prognosis in invasive breast cancer [15]. Increased JAG1 levels in breast cancer coincides with increased Notch signaling and cell cycle progression via cyclin D upregulation [16].

Undifferentiated CSCs rely heavily on aberrant Notch signaling [12]. Cross-talk interactions occur between the Notch receptor and ERα signaling with distinct implications for ET responsiveness [17]. This provides a rationale for using Notch inhibitors to enhance ET efficacy when treating $ERα^+$ endocrine-resistant breast cancer. Notch 4 can control BCSCs directly [18]. Specifically, pharmacological or genetic inhibition of Notch signaling reduces BCSC activity *in vitro* and tumor formation *in vivo* [18]. Hence, Notch 4 likely promotes the transcription of estrogen-responsive genes in the absence of estrogen.

NUMB, a negative regulator of Notch signaling, interacts with p53 to maintain asymmetric cell division, prevents ubiquitin-mediated proteolysis of the tumor suppressor p53, and consequently inhibits pluripotency and dysregulated expansion of CSCs [19]. NUMB-mediated regulation of Notch signaling is lost in nearly 50% of breast cancers due to ubiquitination and proteasomal degradation [20]. In CSCs, a NUMB-interacting protein, TBC1D15, is overexpressed, which initiates p53 degradation and the self-renewal of CSCs, contributing to Notch pathway-mediated tumorigenesis [21].

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Death-associated factor 6 (DAXX) is a negative regulator of NOTCH. DAXX expression levels inversely correlate with NOTCH in human ER+ breast tumor samples and DAXX restricts CSC survival *in vitro* and *in vivo* [22]. DAXX likely binds to and facilitates hypermethylation of promoters of CSC-stimulating genes like SOX2 to restrict CSC survival [22].

Hyperactivation of Notch signaling promotes the growth of endocrine-resistant breast cancer cells [23]. Short-term treatment with ET decreases cell proliferation but increases BCSC activity through JAG1-NOTCH4 receptor activation in cells from patient samples [6], which potentially results in more aggressive forms of luminal breast cancer [24]. Both fulvestrant and tamoxifen were found to promote Notch-mediated BCSC activity in patient derived cells and xenografts [6]. AI-resistant breast cancer cells and tumors also display Jag1-Notch signaling upregulation [6, 25]. Notch signaling is hyperactivated in endocrine-resistant breast cancer cells and at least indirectly confers resistance to PI3K inhibitors that are used to overcome endocrine resistance [26].

DAXX protein is stabilized by estrogen-mediated ER activation, but conversely ET rapidly destabilizes the DAXX protein, which increases CSC survival [22]. Silencing DAXX recapitulates the CSC-survival pattern seen with ET causing increased expression of NOTCH target genes. In general, ET suppresses oxidative phosphorylation and decreases ER expression to enrich stemness gene CD133 via interleukin 6/Notch signaling activation [27]. Taken together, ET agents appear to promote their own resistance at least in part via Notch signaling activation.

2.2 HIF signaling

Hypoxia inducible factors (HIFs) aid in promoting carcinogenesis [28]. The HIF-1 transcription factor is a heterodimer composed of an inducibly expressed HIF-1α and a constitutively expressed aryl hydrocarbon receptor nuclear translocator known as HIF-1β [29]. HIF-1α and HIF-1β possess a basic helix-loop-helix domain that dimerizes and binds to hypoxia-responsive elements on the promoters of target genes [29]. Under normoxia, HIF-1α undergoes hydroxylation at specific prolyl residues resulting in immediate ubiquitination and subsequent proteasomal degradation of the subunit. Under hypoxia, the stabilized HIF-1α interacts with coactivators such as p300 and CBP (Figure 1B) to modulate the transcription of target genes involved in cell survival, proliferation, and metastasis [30].

CSCs can repopulate tumors following therapy initiation leading to a more aggressive and resistant phenotype [31]. HIFs play important roles in maintaining the BCSC phenotype in response to hypoxia [32]. CSCs exhibit a pronounced shift towards aerobic glycolysis distinct from the remaining bulk tumor [33]. The CSC population nearly triples once breast cancer cells are cultured under hypoxic conditions [33]. We previously revealed that hypoxia exposure increases the population of breast cancer cells with stemness characteristics [34].

Increased expression of epithelial to mesenchymal transition (EMT) markers correlates with the upregulation of cyclooxygenase 2 (COX-2) and HIF-1α, while knockdown of NF-KB, COX-2, or HIF-1 prevents EMT [35]. COX-2 has been shown to induce BCSCs via activation of the prostaglandin E2 receptor EP4 [36]. Downstream targets of NFKB such as

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the insulin growth factor 2/inhibitor of DNA binding 1 axis promote BCSC activity irrespective of the breast cancer subtype [37]. *In vivo* knockdown experiments reveal that HIFs are necessary for CSC survival and tumor propagation while diminished HIF activity in CSCs reduces their ability to form tumors [38]. Culturing a subpopulation of cells under hypoxic conditions activates HIF-1α which then expands the subpopulation of cells that stain positive for CSC markers such as CD133 [39].

The breast cancer cell intrinsic transcription factor C/EBPδ promotes CSC-associated phenotypes by engaging two positive feed-back loops, in part by directly targeting the interleukin-6 (IL-6) receptor gene *IL6RA*, and thus amplifying IL-6 and HIF-1 signaling [40]. C/EBPδ mediates the innate immune response, which is enhanced by hypoxia and IL-6 signaling, important in ER+ cancer progression. Data also support a pro-tumorigenic role for C/EBPδ when expressed in tumor cells. In mouse models of breast cancer and in human breast cancer cell lines, deletion of C/EBPδ reduced expression of CSC factors, sphere formation, self-renewal, tumor growth and metastases. The results of this study provide a rationale for targeting CSCs to thwart metastasis and endocrine resistance [40].

The epigenetic reader zinc finger MYND-type containing 8 (ZMYND8) has been recently identified as a direct HIF target gene involved in a primary epigenetic mechanism of HIF activation and HIF-mediated breast cancer progression [41]. *ZMYND8* is induced by HIF-1α and HIF-2α in luminal, and triple negative breast cancer (TNBC) cells which do not express HRs or Her2. Elevated ZMYND8 tumor expression correlates with poor breast cancer survival. Genetic deletion of ZMYND8 decreases proliferation, migration, and invasion in cells, and inhibits breast tumor growth and lung metastases in mouse models.

Endocrine resistance associated with elevations in COX-2 is likely mediated by EP4 similarly to resistance involving other anticancer agents as reviewed previously [42]. NF-KB demonstrates an emerging role in endocrine resistance as reviewed previously [43]. Intermittent hypoxia has a greater propensity than normoxia to promote a metastatic phenotype in endocrine resistant breast cancer [44]. Stabilized HIF-1α induces rapid loss of the ER protein in a diverse group of breast cancer cells via proteolysis [45]. This reduced ER significantly attenuates ER-directed transcription and inhibits cell proliferation. Thus, recurrence in patients with ER positive tumors may stem from tumor cells residing in hypoxic environments.

Interestingly, ER^+ breast cancer cells are less sensitive to ET when hypoxic, while HIF2α levels are increased in endocrine-resistant cells [46]. ET exposure further increases HIF2α expression in these endocrine resistant cells. Ectopic expression of HIF2α in MCF-7 cells significantly decreases ET sensitivity, which further implicates HIF2α in endocrine resistance. HIF2α drives hypoxic induction of EGFR and EGFR induces HIF2α expression in a positive crosstalk. This HIF2-EGFR coregulatory crosstalk promotes endocrine resistance.

2.3 Integrin-Akt signaling

Integrins play a pivotal role in BCSC maintenance and survival. Integrins are heterodimeric cell surface receptors involved primarily in cell-matrix adhesion to control cellular features

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such as survival and differentiation [47]. Extracellular matrix components such as laminin bind to integrin receptors in mammalian cells to help establish communication between the intracellular component of the cell and the extracellular matrix [48]. Integrins are composed of non-covalently linked α and β subunits to result in more than 24 different combinations of αβ heterodimers [49]. Alternative mRNA splicing further enhances this diversity in integrins.

α6-integrin has been used to define multiple stem cell populations, including pluripotent, multipotent, and CSCs [50]. α6-integrin, also known as CD49f, is a putative biomarker for BCSCs [51]. α6-integrin not only maintains BCSC function but also promotes invasion and metastasis of cancer cells [52]. The α6B-integrin is a splice variant which promotes the BCSC population in breast cancer while the α6A-integrin splice variant lacks BCSC-promoting properties [53]. α6-integrin is typically expressed as a dimer with β1-integrin or β4-integrin in breast cancer [54]. β1-integrin, in conjunction with α6 integrin, helps maintain the mammary BCSC niche [55]. β4-integrin aids in identifying and stratifying BCSC-enriched mesenchymal-like TNBC cells [56]. Traditionally, high expression of α6-integrin has been associated with reduced survival in breast cancer patients [57]. One study examining the tumor tissues of 312 breast cancer patients revealed an association between α6-integrin and increased risk for disease recurrence and poor clinical outcomes [58].

BCSCs have been linked to endocrine resistance; agents such as tamoxifen and fulvestrant promote CSC activity in both patient derived samples and patient derived xenografts (PDXs) [6]. We have previously shown that α6-integrin is overexpressed in tamoxifen-resistant cells and in tumor sections from patients who relapsed on tamoxifen [59]. An α6-integrin blocking antibody suppressed α6-integrin expression and function to re-sensitize resistant breast cancer cells to tamoxifen. Others revealed that blocking β1 integrin reversed fibronectin-induced endocrine resistance in mammary tumor cells [60].

Emerging evidence suggest that α6-integrin promotes resistance to endocrine therapy-induced cell death in ER^+ breast tumors [61]. In a 2019 study, α6-integrin was included in a prognostic panel of BCSC markers used to calculate a relapse risk score (RRS) which classified patients into different risk groups to predict their propensity for relapse and resistance to hormone therapy. Of the 253 ER+ patients receiving hormone therapy, there was no difference in relapse-free survival (RFS) between treated patients and non-treated patients in the high-risk score group, while in the low-risk score group, patients in the treated group showed remarkably longer RFS than those in the non-treated group [62]. These findings suggest ER^+ breast cancer patients at high-risk for relapse based on elevated BCSC biomarker expression may not benefit from conventional ET.

The α6-integrin can induce FAK/Src activation to promote breast cancer progression and endocrine resistance [63]. Furthermore, α6β4-integrin/PI3K/Akt signaling has been linked to endocrine resistance [64]. Tamoxifen-resistant tumors exhibit high EGFR expression to activate kinases such as PI3K/Akt found downstream of the integrin heterodimers [60]. Pathways involving integrins and Akt signaling play a pivotal role in mediating resistance to anticancer agents. Akt activation can promote cross-talk between the ER and growth factor

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receptor signaling pathways which are implicated in endocrine resistance and BCSC maintenance.

Overexpression of epidermal growth factor receptor (EGFR) or HER2 and associated mitogen activated protein kinase activation in ER^+ breast cancer, confers endocrine resistance [65]. Under these conditions, extracellular regulated kinase 1/2 and AKt appear to be important downstream effectors of the resistance phenotype. Furthermore, insulin-like growth factor receptor 1 signaling is associated with endocrine resistance. Specifically, insulin growth factor (IGF)-1 regulates endogenous ER expression in breast cancer through transcriptional activation [66]. One mechanism whereby IGF signaling is believed to contribute to endocrine resistance is through the activation of Akt and subsequent phosphorylation of the ER, resulting in ligand-independent activation of ER and evasion of treatment-induced cell death [67]. Thus, integrins demonstrate the potential to regulate both the BCSC population and endocrine resistance (Figure 1B).

2.4 Targeting pathways that promote BCSC activity to counteract endocrine resistance

Since BCSCs are believed to be key drivers of self-renewal and relapse (Figure 1A), targeting this sub-population of cells is essential to overcoming endocrine resistance [6]. Current approaches to identify BCSCs rely heavily on specific cell surface ‘stemness’ markers which include CD133, ALDH, and α6-integrin [68]. Though selective inhibitors of Notch, HIF1alpha and integrin/Akt signaling have potential to target BCSCs, we and others have found that agonists for the aryl hydrocarbon receptor (AhR) signaling pathway also target the above-mentioned pathways. Prototypical AhR agonists such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) promote BCSC expansion via β-catenin and Akt signaling activation [69] In contrast, Stephen Safe and colleagues demonstrated that treatment of luminal breast cancer cells with TCDD resulted in proteasome-dependent degradation of AhR and ER [70]. This seminal study reveals the potential for AhR agonists to exhibit antiestrogenic actions. More recently, Safe and colleagues revealed that AhR loss promotes FOXM1 signaling to augment colonic stem cell renewal [71] to suggest the potential for AhR agonists to regulate BCSC activity. Interestingly, AhR activation has been shown to downregulate Notch signaling to suppress the self-renewal properties of luminal breast cancer cells. [72]

2.4.1 Inhibitors of Notch signaling—Pharmacological or genetic inhibition of Notch signaling reduces BCSC activity and tumor formation *in vivo* [18]. Notch signaling suppression is frequently achieved via γ-secretase inhibitors (GSIs) to prevent luminal breast cancer cells from acquiring an enriched luminobasal phenotype following ET [73]. This luminobasal population overlaps with the BCSC population which is resistant to ET. Preclinical and clinical studies revealed the potential for GSIs to decrease stemness cell markers in tumors and enhance efficacy of chemotherapy in breast cancer patients though more studies are needed to verify whether this holds true for those treated with ET [74]. Samples from patients with poorer outcomes after ET reveal that these tumors have high pre-treatment levels of ALDH1 expression and NOTCH4 activation, to suggest that JAG1-NOTCH4 signaling in ALDH-positive cell populations is a factor in endocrine resistance acquisition [6].

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Notch 4 signaling activity levels are 8-fold higher in BCSCs, which suggests a potential for them to prevent endocrine resistance [18]. Unfortunately, targeting NOTCH with neutralizing Notch antibodies, Notch-ligand decoys, GSIs, blocking peptides, or natural compounds has had mixed success clinically even after successful preclinical studies. However, a recent clinical trial involving Notch 1 specific inhibitor LY3039478 revealed that this agent was well tolerated though this study involved patients with solid tumors in general [75].

Global Notch inhibitors frequently fail in phase I/II clinical trials due to lack of efficacy and gastrointestinal toxicities [76]. As a result, targeting sites that indirectly impact Notch signaling offers more therapeutic potential. For instance, DAXX suppresses Notch signaling [22]. DAXX also suppresses the expression of key stemness-promoting genes such as SOX2 which thwarts BCSC proliferation following ET. Agents that stabilize DAXX thus show potential in treating endocrine resistance when used in combination with ET. RFS was significantly worse for ET-treated patients with tumors bearing low levels of DAXX to further support DAXX as a viable therapeutic target for overcoming endocrine resistance [76].

2.4.2 Inhibitors of HIF signaling—Few studies have examined the ability of HIF1α or HIF2α inhibitors to tackle endocrine resistance. Zolendronic acid counteracts endocrine resistance in luminal breast cancer via a mechanism that likely involves HIF1α inhibition [77]. AhR agonist Aminoflavone (AF) inhibits HIF1α [78] and we previously demonstrated that AF inhibits BCSCs and endocrine resistance [34, 59]. FM19G11, a HIF2α inhibitor treated in combination with ET restores ET sensitivity in resistant cells.

Recent *ex-vivo* work has found a direct correlation between intracellular ascorbate levels, activation of the HIF-1α pathway and patient survival in breast cancer [79]. In human breast cancer tissue (invasive ductal carcinoma), HIF-1α target genes were upregulated following increased HIF-1α activation and this was associated with higher tumor grade and stage, increased vascular invasion, as well as decreased disease-free survival (DFS) and disease-specific survival (DSS). Grade 1 tumors had higher ascorbate levels than grade 2 or 3 tumors and higher ascorbate levels were associated with less tumor necrosis, lower HIF-1α pathway activity as well as increased DFS and DSS.

Vandetanib (ZD6474), an approved clinical drug for thyroid cancer that targets HIF1α as well as vascular endothelial growth factor receptor 2 (VEGFR2) and EGFR tyrosine kinases is under preclinical investigation for treatment in breast cancer [80]. In a mouse model, Vandetanib effectively inhibited breast tumor growth [81]. Clinical trials are underway to evaluate the potential efficacy of Vandetanib in combination with fulvestrant to treat advanced AI-resistant breast cancer.

2.4.3 Integrin/Akt signaling inhibition—Recent studies suggest that inhibitors of integrin signaling have potential to combat endocrine resistance. Marina Simian and colleagues initially suggested that the tumor microenvironment has the potential to modulate tamoxifen resistance via the α6β1-integrin/Akt signaling pathway [60]. More recently, the β1-integrin was implicated in mediating tamoxifen resistance via the G protein-coupled ER

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in breast cancer cells [82]. EGFR inhibitors also suppress β1-integrin expression to reduce tamoxifen resistance [83].

TCDD promotes BCSC expansion via β-catenin and Akt signaling activation [69]. In contrast, we found that AFP 464, the pro-drug formulation of AF, not only reduces bulk tumor similar to other AhR agonists, but disrupts mammospheres (breast cancer spheroids) [34] derived from *in vitro* and *in vivo* models. We determined that AF inhibits α6-integrin-Src-Akt signaling to confer anticancer actions in tamoxifen-resistant cells and mammospheres [59].

3. Race associated differences in breast cancer survival

While race is often defined as a social construct, disparities in breast cancer outcomes have been observed among certain racial and ethnic groups. Both genetic and epigenetic factors drive underlying tumor biology to suggest that designating 'ancestry' groups proves more accurate in a biological context than self-reported 'race'. In most studies, the race/ethnicity designation given reflect the predominance toward the use of African ancestry in African Americans/Blacks as well as the use of European ancestry in white Americans/European Americans.

African American women are less likely to survive breast cancer than European American women and this disparity appears to be widening [84]. The average time to treatment initiation following diagnosis for African American patients is nearly twice as long as that for European American patients [85]. Delays in treatment adversely impact breast cancer survival. Moreover, differences in tumor biology between African American women and European American women are believed to impact responsiveness to therapy and influence survival [9].

3.1 Role of BCSCs in breast cancer survival disparity

Several studies reveal that populations with extensive African ancestry have a higher incidence of BCSCs compared to populations of European descent, including high levels of CD44 in TNBC [86]. This higher CD44 has been observed in both tumorigenic and nontumorigenic breast tissues from African Americans compared to European Americans [87]. Additionally, we found that biomarkers of BCSC composition, including ALDH expression in tumors, are elevated in more than 30% of tumors of African American and contemporary West African patients, compared to less than 25% of tumors from white American women and East African women who typically have higher European admixture [88]. These observations, made in the context of genetic ancestry groups rather than self-reported race groups, suggests genetic mechanisms that lead to distinct tumor characteristics due to distinct developmental pathways.

Genetic variations in the hippo signaling pathway known to regulate BCSC growth, increase the risk that African American patients will develop more aggressive forms of breast cancer [89]. High levels of 2-hydroxyglutamate in breast tumors occur more commonly among African American patients and are associated with a poor prognosis and a cancer stem-cell like transcriptional signature [90]. Furthermore, CSCs derived from African American

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patients tend to show an enhanced capacity to form mammospheres compared to those derived from European American patients [91].

3.2 Factors impacting luminal breast cancer survival with respect to ethnicity

The breast cancer survival gap between African American women and European American women was not apparent until the widespread clinical use of tamoxifen [92]. African American women under the age of 45 experience higher incidence of breast cancer and are up to three times more likely to die of breast cancer than age-matched European American women [84]. This diminished survival has been attributed to the decreased likelihood that African American women are diagnosed with luminal A breast cancer which is associated with a better prognosis. However, the survival disparity between African American and European American women diagnosed with luminal A breast cancer is actually greater than that of other breast tumor subtypes [93] even after accounting for socioeconomic status and education [94]. In fact, some studies reveal no statistically significant difference in survival disparity based on race for TNBC, while a significant survival disparity for luminal breast cancer remains [9] (Table 1).

A study of over 8000 patients in the Southeastern US (the most populous region of African Americans in the US) indicates that African Americans (n=3500+) had more than twice the mortality of white Americans in the same region (HR=2.67, 95%CI = 1.65–4.33) [94]. The Cancer Genome Atlas also reveals that the most pronounced disparities in breast cancer survival among African American patients are found in those with luminal breast cancer [95]. Though African American women of all age groups are less likely to receive a diagnosis of luminal A breast cancer, their risk of relapse is higher following a luminal A breast cancer diagnosis [96]. African American women are more likely to present with more aggressive forms of luminal A breast cancer than European American patients [97].

ESR1 mutations, particularly those that are activating, have been linked to endocrine-resistant breast cancer [98]. Such mutations rarely occur in the primary tumor but are frequent following relapse on fulvestrant and AIs [99]. More recently, alterations in ESR1 have been observed even with the use of CDK inhibitors in combination with ET [100, 101]. These mutations are believed to occur more frequently among African American patients which may account for some of the survival disparity observed following ET [9].

The mitosis associated enzyme Aurora kinase B has been shown to fuel the growth of tamoxifen- and fulvestrant-resistant cells to suggest its potential as a biomarker for endocrine resistance [102]. Furthermore, Aurora kinase B inhibitor barasertib effectively suppresses the growth of endocrine resistant cells [102]. High expression of 14–3-3ς, a regulator of Aurora B kinase, predicts a patient's likelihood to fail on ET [103]. Breast tumors from African American patients tend to exhibit elevated levels of Aurora kinase B suggesting that targeting this site may prove beneficial in treating these patients following relapse on ET [104].

Racial differences have been found in the adherence to adjuvant ET to impact survival among breast cancer patients [105] (Table 2). Some found that the racial disparity in luminal breast cancer survival is unrelated to differences in tumor stage or therapy initiation but

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rather to differences in tumor biology that may render them less responsive to ET [9]. In contrast, others found racial disparities in the initiation of adjuvant ET among African American luminal breast cancer patients and indicate that such patients are more apt to receive chemotherapy instead [106]. The latter study found African American patients are 17% less likely to initiate therapy within 12 months of diagnosis as compared to European American patients. Others found that African American luminal breast cancer patients consistently show worse clinical outcomes despite receiving similar forms of ET [107]. Differences in tumor biology and delays in treatment initiation likely both contribute to the racial disparity in luminal breast cancer survival.

African American women are more likely to present with tumors with weaker ER staining and are thus less likely to receive ET resulting in poorer outcomes [108]. Most recently, we reported that racial differences in breast cancer survival correlated with luminal master regulator gene expression levels [109]. In particular, FOXA1 exhibited the potential to serve as a predictive biomarker for survival based on race. Elevated FOXA1 levels correlate with endocrine resistance and increases in BCSC proliferation [110].

3.3 Clinical data on luminal breast cancer outcomes related to ethnicity

Most clinical trials evaluating agents to treat endocrine resistance provide minimal information related to the impact of ethnicity on efficacy and outcomes. The Trial Assigning Individualized Options for Treatment Rx (TAILORx) trial, primarily designed to address the role of adjuvant chemotherapy in addition to ET using the 21-gene recurrence score (RS) assay, provides crucial evidence to support racial/ethnic disparities in breast tumor biology for patients with $ER^+/HER2^-$ breast cancer [111]. Albain and colleagues recently published a report on the TAILORx trial which revealed that Black patients had worse clinical outcomes than white American patients despite having a similar 21-gene RS and undergoing similar therapies (Table 2) [111]. Furthermore, there was no therapeutic benefit from adjuvant chemotherapy for Black, Asian or Hispanic patients compared to white patients for the endpoints examined in the RS of 11–25 group. Reported clinical outcomes in various multivariate models show that Blacks performed worse than whites in DFS (HR of 1.43), RFS (HR of 1.85), overall survival (HR of 1.51) and relapse free interval (HR of 1.54).

Comorbidity data showed that more Black patients than white patients had hypertension and diabetes and were obese. All patients received standard local and systemic therapy with no differences in the use of chemotherapy and ET among patients during the trial. This study revealed higher recurrence risk for African American compared to white American patients with intermediate-risk 21-gene RS. When the 21-gene RS was low, Black and white American women similarly showed no benefit from adjuvant chemotherapy. It is important to note that while the TAILORx trial reveals the impact of tumor biology on racial disparities in clinical outcomes among breast cancer patients, this was a secondary aim in this study.

4. Clinical evaluation of agents designed to tackle endocrine resistance

Cyclin dependent kinase 4 (CDK4) promotes self-renewal within BCSCs in TNBC [112]. Whether CDK4 also promotes cancer stemness in luminal breast cancer is worth

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investigating since this may suggest why at least initially, CDK4/6 inhibitors enhance ET efficacy once patients relapse on ET. Insufficient elimination of BCSCs represents a key reason many combination therapies only marginally outperform established monotherapies.

A number of clinical trials have commenced to treat breast cancer patients who have relapsed on ET (Table 2). Combining CDK4/6 inhibitors with ET improves outcomes for both endocrine-sensitive and endocrine-resistant HR^+, $HER2^-$ breast cancer [113]. In the TREnd trial, CDK4/6 inhibitor palbociclib combined with AIs improves progression-free survival (PFS) compared to monotherapy in post-menopausal women with advanced HR^+, $HER2^-$ breast cancer previously treated with ET agents. Furthermore, patients who receive prior ET for more than 6 months show greater benefit from combination therapy than those who received prior ET for six months or less [114]. The authors did not provide a basis for this result though we speculate that more prolonged prior ET increases risk of developing resistance rendering these patients more responsive to combined treatment. In the absence of early resistance, combination therapy likely confers less overall benefit. The benefits of CDK4/6 inhibitors combined with AIs or fulvestrant are well documented in patients with advanced breast cancer who progress on prior ET [115]. In the PALOMA-3 trial, fulvestrant in combination with CDK4/6 inhibitor palbociclib improves PFS compared to fulvestrant alone and is recommended for the treatment of patients who relapse on AIs [116]. Preliminary results from the ALTERNATE trial show that no benefit exists in using fulvestrant or fulvestrant in combination with anastrozole in comparison to anastrozole alone for improving endocrine responsiveness.

Inhibitors of PI3K and mTOR signaling have been evaluated in combination with ET to combat endocrine resistance. For instance, combining everolimus with letrozole and goserelin, a gonadotropin-releasing hormone agonist, appears quite efficacious in premenopausal patients once they progress on tamoxifen in the MIRACLE trial [117]. The BOLERO-2 trial revealed that everolimus combined with AI improves PFS in women previously treated with AIs [118]. Due to safety concerns (BELLE-3 trial), buparlisib combined with fulvestrant may not be recommended, yet the authors still propose that other PI3K inhibitors in combination with ET might show therapeutic promise [119].

EGFR signaling promotes inflammation and cancer stem cell-like activity in inflammatory breast cancer to provide a rationale for EGFR inhibitors to thwart the BCSC population [120]. In the OVER trial, fulvestrant was unable to completely degrade the ER. The investigators attributed fulvestrant's reduced efficacy in part to the concomitant aortic insufficiency discharge that restores physiological postmenopausal levels of circulating estrogens. Targeting the EGFR/HER2 system should decrease circulating estrogens and ultimately improve fulvestrant's efficacy.

Breast cancer progression may occur due to insufficient inhibition of aromatase. It is plausible that changing the class of AIs (e.g., from type I, steroidal, to type II, non-steroidal) for use in combination with fulvestrant would improve fulvestrant's efficacy [120]. Long-term fulvestrant treatment has the potential to increase breast cancer cell proliferation to promote its own resistance. Since ER-mediated signaling remains suppressed in these cells, their restored growth may be related to the upregulation of alternate growth-stimulating

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pathways. This provides a rationale for the implementation of EGFR-tyrosine kinase inhibitors such as gefitinib to improve fulvestrant's efficacy in patients who have progressed on AIs.

5. Perspectives and Conclusions.

ET benefits many patients with luminal breast cancer although the emergence of resistance leading to relapse is a constant threat to sustained efficacy. Targeting signaling pathways that promote stemness is important to improving breast cancer survival. Though BCSCs contribute substantially to aggressive breast cancer subtypes (e.g., TNBC) and appear to promote the survival disparity seen among African American breast cancer patients, we hypothesize that these cells may play an even greater role in the luminal breast cancer survival disparity.

Indeed, the racial survival disparity is more pronounced with the luminal breast cancer subtype than with other subtypes. Few clinical trials have been implemented to examine the differences in responsiveness of patients to therapeutic approaches designed to combat endocrine resistance based on ethnicity. Even the TAILORx trial examined ethnicity as a secondary rather than a primary aim. Such studies are needed to inform clinicians of the most appropriate ET for patients. More studies are needed to determine whether the survival disparity found among African American patients is linked to an increased chance they will experience endocrine resistance and relapse due to elevated BCSC markers.

Although CDK4/6 inhibitors and mTOR inhibitors are recommended in patients who have relapsed on ET, these targeted therapies have their limitations in combating endocrine resistance which threatens favorable clinical outcomes. The development of agents that target BCSCs has the potential to extend ET efficacy and prevent endocrine resistance to improve overall breast cancer survival, particularly among African American women.

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Abbreviations:

BCSC	breast cancer stem cell
CSC	cancer stem cell

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ER	estrogen receptor
ERα	estrogen receptor alpha
PR	progesterone receptor
Her2	human epidermal growth factor receptor 2
ET	endocrine therapy
EGFR	epidermal growth factor receptor
CDK	cyclin dependent kinase
mTOR	mammalian target of rapamycin
AhR	aryl hydrocarbon receptor
AF	Aminoflavone
PI3K	phosphatidyl inositol-3-kinase
HIF	Hypoxia inducible factor
HIF1α	hypoxia inducible factor 1 alpha
HIF2α	hypoxia inducible factor 2 alpha
IGF	insulin growth factor
ALDH	aldehyde dehydrogenase
DAXX	death associated factor 6
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
CDK4	cyclin dependent kinase 4
PFS	progression-free survival
COX-2	cyclooxygenase 2
EMT	epithelial to mesenchymal transition
TNBC	triple-negative breast cancer
IL-6	interleukin-6
PDX	patient derived xenograft
RFS	relapse-free survival
RRS	relapse risk score
PFS	progression-free survival
DFS	disease-free survival

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DSS	disease-specific survival
VEGFR2	vascular endothelial growth factor receptor 2
ZMYND8	zinc finger MYND-type containing 8
GSIs	γ-secretase inhibitors
DLL	delta-like-ligand
JAG1	Jagged-1
JAG2	Jagged-2
TAILORx	Trial Assigning Individualized Options for Treatment Rx
AIs	aromatase inhibitors
HRE	hypoxia response element
ADAM	disintegrin metalloprotease
NUMB	phosphotyrosine binding protein
CBP	CREB binding protein
NID	notch inhibitor domain
AC	activating complex
FAK	focal adhesion kinase

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Highlights

- Endocrine therapy is highly efficacious though some patients experience relapse.
- Breast cancer stem cells (BCSCs) contribute to endocrine resistance and relapse.
- BCSCs likely play a causal role in racial disparities observed in breast cancer.
- Targeting BCSCs is expected to improve luminal breast cancer patient outcomes.

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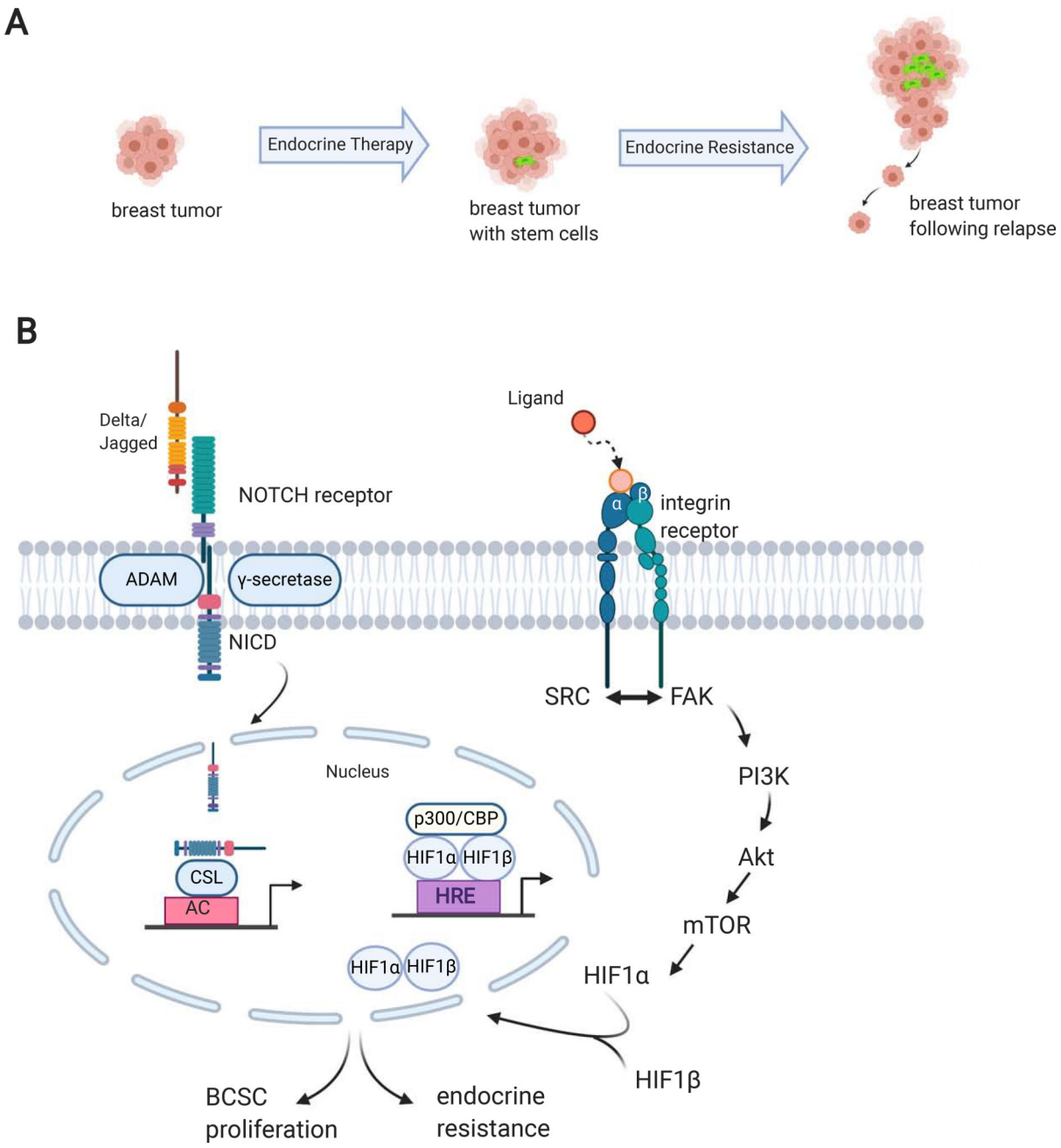

Figure 1. Endocrine therapy promotes breast cancer stem cell formation leading to resistance and tumor relapse.

(A) Breast tumors contain miniscule amounts of breast cancer stem cells (BCSCs). Endocrine therapy enriches for the cells (green) which eventually leads to endocrine resistance as evidenced by disease progression. Alternate forms of endocrine therapy are often initially effective but BCSC enrichment remains a threat. BCSCs undergo self-renewal and metastasize leading to relapse. The resultant tumors are nonresponsive to further endocrine therapy. (B) ligands for the Notch receptor (Delta/Jagged), bind to promote transactivation followed by proteolytic cleavages mediated by ADAM and later γ-secretase. The Notch intracellular domain (NID) is then released into the cytoplasm and translocates

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into the nucleus where it is able to bind to the CSL transcription factor which binds to the activation complex (AC) of target genes. Alternatively, ligands for the integrin receptor bind to activate Src and the focal adhesion kinase (FAK) and this promotes a cascade of events leading to PI3K/Akt/mTOR activation. During hypoxia, mTOR is able to activate HIF1α which can then translocate into the nucleus after joining with HIF1β to bind to the hypoxia response element (HRE) of target genes along with co-activators p300 and CBP. These processes ultimately promote the growth and expansion of BCSCs and endocrine resistance.

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Table 1

Studies Reporting Luminal Breast Cancer Survival and Clinical Outcomes Among African American and European American Patients

References	Title	Project goal	Key findings
Rauscher et al [9]	Racial disparity in survival from estrogen and progesterone receptor positive breast cancer: implications for reducing breast cancer mortality disparities	To elucidate factors contributing to survival disparity observed among AA women with luminal breast cancer	• The observed racial disparity in luminal breast cancer survival did not appear to be due to differences in tumor stage, grade or therapy initiation.
Collin, et al [94]	Racial Disparities in Breast Cancer Outcomes in the Metropolitan Atlanta Area: New Insights and Approaches for Health Equity	To evaluate racial disparities in breast cancer outcomes among patients residing in the Atlanta metro area	• The largest disparities in breast cancer survival between AA with EA patients were found with those diagnosed with luminal breast cancer. • Interestingly, these disparities were more pronounced among women of high social economic status.
Huo, et al [95]	Comparison of Breast Cancer Molecular Features and Survival by African and European Ancestry in The Cancer Genome Atlas	To compare breast cancer molecular features and survival in tumors among AA and EA patients using TCGA	• Overall AA breast cancer patients had a higher mortality rate with the breast cancer free interval differences greatest among those with basal like tumors. • However, tumors from AA luminal breast cancer patients were found to exhibit risk of relapse scores that were statistically higher than that of EA patients.
Troester, et al [96]	Racial Differences in PAM50 Subtypes in the Carolina Breast Cancer Study	To evaluate racial differences in the relative frequency of molecular subtypes and tumor biology and assesses whether differences in tumor genomics persist even within clinically defined subgroups	• Black women of all ages had a statistically significantly lower frequency of luminal A breast cancer. • All other subtype frequencies were higher in Black women. Among clinically HR+/HER2- cases, Risk of Recurrence (ROR) scores were statistically significantly higher among Black women.
O'Brien, et al [97]	Intrinsic Breast Tumor Subtypes, Race, and Long-Term Survival in the Carolina Breast Cancer Study	To identify differences in breast cancer-specific mortality across four "intrinsic" tumor subtypes: luminal A, luminal B, basal-like, and human epidermal growth factor receptor 2 positive/ estrogen receptor negative (HER2+/ER−) in AA women	• Breast cancer mortality was higher for participants with $HER2^{+}$/ERand basal-like breast cancer compared with luminal A and B. • African Americans had higher breast cancer-specific mortality than whites, but the effect of race was statistically significant only among women with luminal A breast cancer.
Farias, et al [105]	Racial differences in long-term adjuvant endocrine therapy adherence and mortality among Medicaid-insured breast cancer patients in Texas: Findings from TCR-Medicaid linked data	To determine racial differences in the adherence to ET and mortality among Medicaid patients in TX	• Long-term adherence is suboptimal particularly among AA patients on Medicaid. • AA women were less likely to use adjuvant ET and more likely to discontinue therapy as compared to EA women. • Discontinuation was associated with higher risk of all-cause and cancer-specific mortality irrespective of hormone receptor status.
Reeder-Hayes, et al [106]	Racial Disparities in Initiation of Adjuvant Endocrine Therapy of Early Breast Cancer	To determine whether racial disparities exist in therapy initiation	• AA women were less likely to initiate ET than EA women and more likely to undergo chemotherapy. This represents an important contributor to the racial survival disparity.

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References	Title	Project goal	Key findings
Tichy, et al [107]	Race, Response to Chemotherapy, and Outcome Within Clinical Breast Cancer Subtypes	To identify racial differences in response to chemotherapeutic response and long-term survival among breast cancer patients	• Black women had worse time to recurrence though there was no significant difference in overall survival. • Black women with ER+ breast experienced worse outcomes though relative sensitivity to chemotherapy appeared not to play a role.
Purrington et al. [108]	Racial differences in estrogen receptor staining levels and implications for treatment and survival among estrogen receptor positive, HER2-negative invasive breast cancers	To determine the relationship between race, percent ER staining, treatment, and clinical outcomes	• AA women are more likely to have tumors with weak ER stain than EA women. • Women with tumors found to weakly stain for ER are less likely to receive ET irrespective of race. • Increased mortality is associated with AA race and weak ER tumor staining.
Byun et al [109]	Racial Differences in the Association Between Luminal Master Regulator Gene Expression Levels and Breast Cancer Survival	To uncover biological factors underlying the racial breast cancer survival disparity by comparing functional expression and prognostic significance of master transcriptional regulators of luminal differentiation.	• Luminal master regulatory genes ESRI, FOXA1 and GATA3 show significant differential expression based on race which correlates with survival. • Downstream regulons to these genes also correlated highly with race and survival.

Abbreviations: TCR, Texas Cancer Registry; AA, African American; EA, European American; ER, estrogen receptor; TN, triple negative; AET, adjuvant endocrine therapy; HER, human epidermal growth factor receptor; ET, endocrine therapy.

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Table 2

Clinical Trials Aimed at Treating Patients Who Have Progressed on Endocrine Therapy or Evaluating Clinical Outcomes in luminal breast cancer patients

Trial Name	Study Type	Phase	Treatment	Study Description	Trial Identifier
TREnd	Interventional	II	palbociclib/palbociclib + ET*	Asses the monotherapy and combination therapy activity of palbociclib with endocrine therapy in patients who have progressed on first- or second-line ET agents	NCT02549430
MIRACLE	Interventional	II	everolimus	Evaluation of everolimus in first-line endocrine treatment of premenopausal MBC patients after progression on tamoxifen	NCT02313051
BOLERO-2	Interventional	III	everolimus + exemestane	To compare the efficacy and safety exemestane + everolimus to exemestane + placebo in postmenopausal MBC patients refractory to previous letrozole or anastrozole	NCT00863655
BELLE-3	Interventional	III	buparlisib + fulvestrant	To determine the efficacy and safety of buparlisib + fulvestrant in postmenopausal HR-positive, HER2-negative women who progressed on or after mTOR inhibitor-based treatment	NCT01633060
OVER	Interventional	III	fulvestrant ± lapatinib ± AI	Comparing the efficacy of fulvestrant in combination with lapatinib or AIs in MBC patients progressing on AIs	NCT02394496
ALTERNATE	Interventional	III	fulvestrant	To determine whether neoadjuvant endocrine therapy with fulvestrant or fulvestrant + anastrozole is more efficacious than anastrozole when given before surgery to reduce tumor size and inhibit growth	NCT01953588
PALOMA-3	Interventional	III	palbociclib + fulvestrant	To demonstrate the superiority of palbociclib with fulvestrant over fulvestrant alone in prolonging PFS in MBC patients that progressed after ET	
TAILORx	Interventional	III	ET +/− chemotherapy	To evaluate clinical outcomes in patients with HR+, Her2-breast cancer following ET with or without chemotherapy.	NCT00310180

Abbreviations: endocrine therapy (ET), human epidermal growth factor receptor 2 (Her2), mammalian target of rapamycin (mTOR), metastatic breast cancer (MBC), progression free survival (PFS), aromatase inhibitors (AIs). *ET includes anastrozole, letrozole, exemestane, fulvestrant and in the case of the TAILORx trial, tamoxifen.