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Overcoming Endocrine Resistance in Breast Cancer

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Summary

Estrogen receptor-positive (ER^+) breast cancer is the most common breast cancer subtype. Treatment of ER^+ breast cancer comprises interventions that suppress estrogen production and/or target the ER directly (overall labeled as endocrine therapy). While endocrine therapy has considerably reduced recurrence and mortality from breast cancer, *de novo* and acquired resistance to this treatment remains a major challenge. An increasing number of mechanisms of endocrine resistance have been reported, including somatic alterations, epigenetic changes, and changes in the tumor microenvironment. Here, we review recent advances in delineating mechanisms of resistance to endocrine therapies and potential strategies to overcome such resistance.

Introduction

Over 250,000 breast cancers are diagnosed each year in the U.S (Siegel et al., 2020). Of these, nearly 80% are estrogen receptor-positive (ER^+) (DeSantis et al., 2019). The vast majority of these tumors are initially dependent on activation of ER by the steroid hormone estrogen. Estrogen-induced activation of ERα and ERβ nuclear receptors promotes proliferation and survival of both normal and cancerous breast tissue through transcription of pro-survival genes (genomic regulation) and activation of cellular signaling (non-genomic regulation). Upon binding to estrogen, ER dimerizes and translocates to the nucleus, where ER dimers bind coactivators (CoA) to form a transcriptionally active ER complex (Figure 1A). Estrogens, including the hormone estradiol, play an obligate role in the growth and

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Author contributions

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D.R.S. prepared the figures.

Declaration of Interests

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development of female mammary and reproductive physiology (Nilsson et al., 2001). Seminal studies in genetically engineered mice have shown that the mammary glands of adult females that lack ER or estradiol are rudimentary and exhibit blunted pre- and post-pubertal ductal branching morphogenesis (Couse and Korach, 1999). Estrogen-bound ER induces cell cycle progression in part by inducing expression of *MYC* and *CCND1* (Cyclin D1) (Prall et al., 1998). Estrogen-stimulated ER also amplifies mitogenic signaling by upregulating the transcription of several growth factors that are important to mammary development, including TGFα, IGF-1, amphiregulin, and EGF (Bocchinfuso and Korach, 1997). The estrogen-ER driven mechanisms that govern normal mammary gland development also orchestrate mammary hyperplasia and tumorigenesis. The relative resistance of ER-knockout mice to oncogene-induced malignant transformation further underscores the importance of ER in breast tumorigenesis (Couse and Korach, 1999). Owing to the strong dependency of breast tumorigenesis on the estrogen-ER axis, estrogen suppression and ER antagonists have remained the mainstay of ER^+ breast cancer treatment for several decades (Figure 1).

Endocrine therapies, such as selective ER modulators (SERMs), selective ER downregulators (SERDs), and aromatase inhibitors (AIs) are approved for adjuvant treatment of patients with ER^+ breast cancer (Aggelis and Johnston, 2019). AIs (e.g., letrozole, anastrazole, exemestane) deplete systemic estrogen levels in postmenopausal patients by blocking the conversion of androgens to estrogens (Figure 1B). SERMs (e.g., tamoxifen) compete with estrogen for binding to ER, have mixed agonist/antagonist capacities, and are primarily used in pre-menopausal patients (Figure 1C). SERDs (e.g., fulvestrant) are thought to act primarily by inducing ER protein degradation or blocking ER transcriptional activity (Wardell et al., 2011; Wittmann et al., 2007). However, a recent study suggests that fulvestrant and similar ER antagonists suppress ER activity primarily by impairing intra-nuclear ER mobility (Figure 1D) (Guan et al., 2019). A number of oral SERDs, with potentially better pharmacological properties than fulvestrant, are being developed (Fanning and Greene, 2019). In this review, we summarize mechanisms associated with and/or causal to resistance to estrogen suppression, or inactivation of ER by other means (SERMs/SERDs). Although “endocrine resistance” properly refers to resistance to estrogen suppression, here we use the term broadly to refer to resistance to estrogen or ER suppression.

In randomized clinical trials, endocrine therapies have considerably reduced cancer recurrence and mortality (Lin and Winer, 2008), underscoring the high efficacy of these agents in early-stage breast cancers. However, up to 20% of patients diagnosed with operable ER^+ tumors recur with metastatic disease (Pan et al., 2017), although this estimate may decrease with more modern treatments. Moreover, endocrine resistance inevitably occurs in ER^+ metastatic breast cancer (MBC), the primary focus of this review. Loss of ER expression occurs in a minority (~10%) of endocrine-resistant breast cancers (Shiino et al., 2016). Instead, endocrine resistance is commonly driven by ligand-independent ER reactivation (Miller et al., 2011a). This can occur through gain-of-function mutations in ER, altered interactions of ER with coactivators/corepressors, or via engagement of compensatory cross-talk between ER and growth factor receptors and oncogenic signaling pathways (Figure 2) (Ma et al., 2015). For example, high EGFR or HER2 expression has

been shown to dampen the therapeutic efficacy of tamoxifen in ER^+ breast cancers (Borg et al., 1994; Newby et al., 1997). Upon adaptation and/or resistance to antiestrogens, growth factor-driven mitogenic and survival pathways (i.e., PI3K/mTOR, RAS/RAF/MEK/ERK) can drive reactivation of ER transcription in the absence of estradiol. Genomic alterations in components of these pathways represent a common mechanism of endocrine resistance. These resistant tumors are typically dependent upon both the aberrantly activated survival pathway and ER, and in most cases combined inhibition of both pathways is more effective (Andre et al., 2019; Hortobagyi et al., 2016b; Turner et al., 2015). Mitogenic pathway-mediated ER reactivation has been shown to involve CDK4/6-cyclin D1-dependent inactivation of Rb and de-repression of E2F transcription factors, and is, thus, sensitive to CDK4/6 inhibition (Miller et al., 2011a). Accordingly, addition of CDK4/6 inhibitors (e.g., palbociclib, ribociclib, abemaciclib) to antiestrogens have markedly prolonged progression-free survival (PFS) compared to antiestrogens alone in patients with ER^+ MBC. We recognize that some of the resistance mechanisms we describe herein may be abrogated by the addition of CDK4/6 inhibitors to antiestrogens. However, they may still be relevant drivers of endocrine resistance in early-stage tumors.

Both laboratory-based and clinical approaches have recently been used to discover novel mechanisms of endocrine resistance. These include (i) molecular profiling of biopsies from patients enrolled in short presurgical and neoadjuvant therapeutic trials and correlations of the molecular alterations with antiproliferative response (Dunbier et al., 2013; Giltnane et al., 2017; Guerrero-Zotano et al., 2018); (ii) next-gen sequencing of matched pre- and post-progression tumor biopsies and/or plasma ctDNA from patients with acquired drug resistance (O'Leary et al., 2018; Razavi et al., 2018); and (iii) high-throughput functional genetic screens (siRNA, CRISPR, etc.) to identify genes that mediate resistance (Fox et al., 2011; Miller et al., 2011a; Nagarajan et al., 2020; Xiao et al., 2018; Xu et al., 2020). Additional evidence to associate molecular alterations with endocrine resistance has come from exceptional clinical responses and positive results in randomized clinical trials with targeted therapies in genotype-selected cohorts of patients with ER^+ breast cancer (Andre et al., 2019; Smyth et al., 2020).

Somatic alterations

Recent large-scale DNA sequencing efforts of ER^+ breast tumors have illuminated the breadth of somatic alterations associated with poor response to endocrine therapy (*de novo* resistance) or acquired following long-term treatment (acquired resistance) (Table 1) (Angus et al., 2019; Bertucci et al., 2019; Griffith et al., 2018; O'Leary et al., 2018; Razavi et al., 2018). In some cases, there are functional data to causally link these alterations with drug resistance (i.e., *HER2*, *NF1*, *FGFR*, *ESR1*) (Figure 3), whereas in other cases such causality is less clear. One limitation of these landscape studies is the low number of intra-patient matched biopsies to rigorously address whether treatment leads to the enrichment and/or acquisition of somatic alterations.

Alterations in ER and aromatase

For many cancer therapies, mutations in the drug target itself are often the preferential mechanism by which the tumor escapes drug inhibition. Point mutations in *ESR1*, the gene encoding ERα were first reported over two decades ago (Zhang et al., 1997). However, it was only recently appreciated that acquired mutations in the ligand-binding domain (LBD) of *ESR1* are frequent drivers of resistance in ER^+ MBC (Jeselsohn et al., 2014; Merenbakh-Lamin et al., 2013; Robinson et al., 2013; Toy et al., 2013). These mutations are found in ~20% of recurrent ER^+ breast cancers, usually acquired following long-term treatment with AIs or tamoxifen (Jeselsohn et al., 2014; Razavi et al., 2018). The prevalence of *ESR1* mutations in plasma ctDNA in similar populations is even higher (Fribbens et al., 2016; Schiavon et al., 2015). These LBD point mutations (most commonly at Y537 and D538) allow hormone-independent ER transcriptional activity, leading to resistance to AIs and decreased sensitivity to tamoxifen and fulvestrant (Jeselsohn et al., 2015). The structural bases for this constitutive activity have been described in detail (Katzenellenbogen et al., 2018). Briefly, the Y537 and D538 mutations stabilize helix 12 (H12) in the active conformation, similar to wild-type (WT) ER when bound to estrogen. This enables binding of co-activators in the absence of ligand and decreases affinity for estrogen and tamoxifen. Jeselsohn et al. showed that the Y537S and D538G mutants also show allele-specific differences in their cistromes and transcriptomes that enhance transcription of metastasis-associated genes. This could be reversed by combining fulvestrant with a CDK7 inhibitor, suggesting a potential therapeutic strategy for tumors with these *ESR1* mutations (Jeselsohn et al., 2018). Similarly, the Y537S and D538G mutants displayed enhanced interactions with coactivators such as steroid receptor coactivator (SRC) family members, which could be potential targets in tumors with these *ESR1* mutations (Gates et al., 2018).

While the LBD mutations reduce the potency of fulvestrant (Toy et al., 2017), next-generation oral SERMs or SERDs that target both WT and mutant ER are in clinical development (Table 2) (Fanning and Greene, 2019). For example, GDC-9545 and elacestrant are oral SERDs that have shown preliminary clinical activity in *ESR1*-mutant MBCs, some of which had progressed on prior SERDs; these agents demonstrated acceptable toxicity profiles (Jhaveri et al., 2020; Kaklamani et al., 2020). Similarly, the oral SERD AZD9496 reduced on-treatment *ESR1*-mutant ctDNA levels (Paoletti et al., 2018) and GDC-0810 (now discontinued) reduced ^{18}F-fluoroestradiol (FES) uptake by positron emission tomography (PET) in patients with *ESR1* mutations (Joseph et al., 2016). The selective estrogen receptor covalent antagonist (SERCA) H3B-6545 covalently binds the Cys530 residue of both WT and mutant ERα, enforcing an irreversible antagonist conformation (Puyang et al., 2018).

Proteolysis targeting chimeras (PROTACs), hetero-bifunctional small molecules that recruit an E3-ubiquiting ligase to the target protein, have the potential to degrade both WT and mutant ER by binding to a region that is shared between mutant and WT (Figure 1E). For example, the PROTAC ARV-471 degrades the Y537S and D538G mutants and inhibits tumor growth in a patient-derived xenograft (PDX) harboring $ESR1^{Y537S}$ (Flanagan et al., 2019). We speculate that use of agents that target both mutant and WT ER earlier in the course of breast cancer treatment may prevent the acquisition of LBD mutations.

ESR1 amplifications and gene fusions have been found in ER^+ breast cancers, albeit at much lower frequencies than point mutations (Lei et al., 2019). Whether *ESR1* amplification is associated with resistance to endocrine therapy remains unclear. Stable *ESR1* in-frame gene fusions were first reported in 2013 (Li et al., 2013) and have since been found in at least 1% of MBCs (usually in tumors resistant to endocrine therapy) (Hartmaier et al., 2018), although the frequency is likely higher considering capture-based targeted exon sequencing often fails to detect fusions. Most *ESR1* gene fusions retain the N-terminal DNA binding domain of the ER fused to diverse C-terminal partner genes, thereby excluding the ER LBD. Lei et al. showed that these fusion proteins drive estrogen-independent ER transcriptional activity, cell proliferation, cell motility, and metastasis. Breast cancer cells and a PDX expressing these fusion products remained sensitive to CDK4/6 inhibition (Lei et al., 2018), suggesting that addition of CDK4/6i to endocrine therapy in the adjuvant setting may prevent acquisition of these fusions.

CYP19A1, the gene encoding aromatase, is also altered in AI-resistant tumors. Magnani et al. reported *CYP19A1* amplifications in 21.5% of AI-treated, relapsed patients, but <2% in primary tumors. *CYP19A1* amplification increases aromatase activity and leads to recruitment of ER to target genes in the absence of exogenous estrogen, thus inducing resistance to estrogen suppression with nonsteroidal AIs. *CYP19A1*-amplified cells remained sensitive to fulvestrant and irreversible AIs such as exemestane (Magnani et al., 2017). Inclusion of *CYP19A1* on targeted sequencing panels may reveal a subset of AI-resistant tumors that would be strong candidates for treatment with SERDs.

Alterations in RTKs

HER2 (ERBB2) amplification has long been known to reduce sensitivity to anti-estrogen treatment, primarily through activation of alternate survival pathways (ie, PI3K-AKT and MAPK pathways) (Figure 2) (Kurokawa et al., 2000). Therefore, the current standard of care for $ER^+/HER2^+$ tumors is a combination of anti-estrogens and HER2 inhibitors. More recently, *HER2*-activating mutations have been implicated in both intrinsic and acquired resistance to endocrine therapies (Croessmann et al., 2019; Nayar et al., 2019), and are found in ~5% of endocrine-resistant MBCs (Razavi et al., 2018). ER^+ breast cancer cells and xenografts expressing activating HER2 mutants were resistant to estrogen deprivation and fulvestrant, and also responded poorly to the HER2 tyrosine kinase inhibitor neratinib (Croessmann et al., 2019; Nayar et al., 2019). However, combined blockade of HER2 and the ER were synergistic *in vitro* and *in vivo*, and the combination of neratinib with fulvestrant has shown promise in ER^+ MBCs harboring *HER2* mutations (Smyth et al., 2020).

Razavi et al. reported *EGFR* amplification in 1.7% of endocrine-resistant MBCs, including acquired amplifications in matched post-treatment tissue. Ectopic expression of EGFR promoted fulvestrant resistance, which could be reversed by combining fulvestrant with an EGFR or ERK inhibitor (Razavi et al., 2018). Amplification of the locus containing *FGFR1* is found in ~15% of ER^+ MBCs and is associated with *de novo* endocrine resistance (Giltnane et al., 2017). In addition to the pro-survival effects of membrane-bound FGFR1-driven signaling, nuclear FGFR1 was found to associate with the ER and promote estrogen-

independent transcription of ER-target genes and estrogen-independent cell proliferation; the combination of an FGFR inhibitor and fulvestrant blocked the growth of ER^+/FGFR1-amplified cell lines and tumors (Formisano et al., 2017). Clinical studies combining FGFR inhibitors and fulvestrant (and also palbociclib) in ER^+ MBCs are ongoing (NCT03238196, NCT04024436). FGFR4 overexpression and hotspot mutations are associated with endocrine-resistant lobular MBC (Levine et al., 2019); the combination of endocrine therapy with an FGFR4-selective inhibitor such as fisogatinib (Kim et al., 2019) is an attractive strategy in these patients.

PI3K pathway alterations

Components of the PI3K pathway (including *PIK3CA, PTEN*, and *AKT1*) are frequently mutated in ER^+ breast cancers (Cancer Genome Atlas, 2012). Aberrant activation of the PI3K pathway promotes acquired resistance to estrogen depletion in preclinical models (Miller et al., 2010; Sanchez et al., 2011). Clinically, however, *PIK3CA* mutations are generally associated with a good prognosis in patients with early-stage ER^+ tumors (Kalinsky et al., 2009; Loi et al., 2010) and *PIK3CA* mutation rates are no different between primary and endocrine-resistant metastatic tumors (Razavi et al., 2018). Nonetheless, in patients with ER^+ MBC, the addition of PI3K pathway antagonists has improved outcome of patients, particularly those with tumors harboring activating *PIK3CA* mutations. For example, alpelisib, a specific inhibitor of the *PIK3CA* product PI3Kα, was recently approved in combination with fulvestrant in ER^+ MBCs harboring *PIK3CA* mutations (Andre et al., 2019). The mTORC1 inhibitor everolimus, which blocks a critical signaling node downstream PI3K, is approved in combination with aromatase inhibitors for MBCs that have progressed on endocrine therapy, regardless of *PIK3CA* mutational status (Baselga et al., 2012; Hortobagyi et al., 2016a). The AKT inhibitor capivasertib in combination with fulvestrant has also shown preliminary efficacy in endocrine-resistant ER^+ breast cancers (Jones et al., 2019; Turner et al., 2020). This combination may be particularly effective in ER^+ breast cancers with *AKT1* mutations (Hyman et al., 2017; Turner et al., 2020). *AKT1* and *PTEN* mutations are more frequent in advanced/metastatic ER^+ breast cancers (Angus et al., 2019; Pearson et al., 2020). Acquired hotspot mutations in *PIK3CA* have been reported following progression on either fulvestrant alone or in combination with CDK4/6 inhibitors (CDK4/6i) (O'Leary et al., 2018). Importantly, *PIK3CA*-mutant cancers that had progressed on CDK4/6i-containing regimens remained sensitive to alpelisib $^+$ fulvestrant (Andre et al., 2019).

Amplification of the 17q23 locus has also been associated with endocrine resistance (Giltnane et al., 2017; Rueda et al., 2019). We recently reported that overexpression of the *PRR11* gene on this amplicon promotes estrogen-independent growth via activation of the PI3K pathway in ER^+ breast cancer cell lines (Lee et al., 2020), adding an additional mechanism by which the PI3K pathway is altered in ER^+ breast cancers.

MAPK pathway alterations

Components of the MAPK pathway, including *NF1, KRAS/NRAS/HRAS, BRAF*, and *MAP2K1* are frequently mutated in many cancer types, yet rarely mutated in primary breast cancers. However, mutations in these genes, in particular *NF1*, are more frequent in MBC

(Table 1). NF1 negatively regulates RAS GTPase by functioning as a GTPase-activating protein (GAP), promoting the hydrolysis of RAS-GTP to RAS-GDP. Thus, loss of NF1 results in constitutive RAS activity. Loss-of-function NF1 alterations are associated with both intrinsic and acquired resistance to endocrine therapy (Bertucci et al., 2019; Griffith et al., 2018; Pearson et al., 2020; Razavi et al., 2018; Sokol et al., 2019). CRISPR-medicated knockout of NF1 in MCF7 cells induced MEK/ERK phosphorylation and promoted resistance to fulvestrant, which was reversed by the addition of an ERK inhibitor (Razavi et al., 2018). Depletion of NF1 in ER^+ breast cancer cells also promoted ER-independent cyclin D1 expression. Resistance to antiestrogens caused by NF1 loss was overcome by combining with CDK4/6i *in vitro* (Pearson et al., 2020). Razavi et al. also reported acquired hotspot alterations in *KRAS, BRAF*, and *MAP2K1* (the gene encoding MEK1) in post-treatment biopsies compared to matched pre-treatment tumors (Razavi et al., 2018). Furthermore, circulating tumor DNA (ctDNA) analysis of AI-resistant MBC revealed *KRAS*, *HRAS*, or *NRAS* mutations in >15% of patients, although mutations were often subclonal (Fribbens et al., 2018). Although RAS has traditionally been deemed "undruggable," recent successes in developing direct inhibitors of KRAS and blocking membrane localization of HRAS suggest that targeting RAS may be feasible in the near future (Ho et al., 2019; Kessler et al., 2019; Papke and Der, 2017). Finally, inhibitors of the MAPK pathway (BRAF, MEK, and ERK inhibitors) may overcome endocrine resistance mediated by *BRAF* and *MAP2K1* alterations (Flaherty et al., 2012; Lian et al., 2019; Sullivan et al., 2018).

Regulators of gene expression

Razavi et al. found enrichment of alterations in the transcriptional regulators *MYC, FOXA1, CTCF*, and *TBX3* in endocrine-resistant MBCs. These were mutually exclusive with alterations in *ESR1* or MAPK pathway components. Alterations in *MYC, FOXA1*, and *CTCF* were found to be either pre-existing or acquired following endocrine therapy (Razavi et al., 2018). A Myc activation signature was previously associated with endocrine resistance in long-term estrogen-deprived (LTED) cells and poor response to tamoxifen in patients (Miller et al., 2011b). CTCF is a transcriptional repressor of Myc (Filippova et al., 1996), suggesting CTCF loss-of-function mutations may lead to Myc upregulation. Decreasing Myc expression with BET inhibitors may be a potential strategy to overcome resistance in tumors with *MYC* or *CTCF* alterations (Chen et al., 2018; Delmore et al., 2011). Recent studies have demonstrated that direct targeting of Myc may also be possible (Beaulieu et al., 2019; Han et al., 2019). FOXA1 is a pioneering factor involved in chromatin remodeling and has been shown to cooperate with ER to induce gene expression (Toska et al., 2017). Thus, tumors with *FOXA1* mutations may still rely on ER protein expression and hence remain sensitive to SERDs. However, promoter hotspot mutations in *FOXA1* that increased FOXA1 expression were associated with reduced sensitivity to fulvestrant (Rheinbay et al., 2017).

Loss-of-function mutations or deletions in the SWI/SNF nucleosome remodeling components *ARID1A* and *ARID2* were also acquired following treatment with endocrine therapy (Razavi et al., 2018). Xu et al. recently reported that ARID1A knockout promoted resistance to fulvestrant in ER^+ breast cancer cells via impaired SWI/SNF recruitment to chromatin at luminal transcription factor loci, resulting in a luminal-to-basal transition and a

loss of dependency on ER (Xu et al., 2020). Similarly, Nagarajan et al. demonstrated that ARID1A is recruited to ER cis-regulatory elements in an ER-independent, but FOXA1-dependent manner wherein ARID1A represses expression of ER target genes. ARID1A loss led to increased enhancer-specific acetylation, recognized by the BET protein BRD4, which promoted the transcription of proliferation-associated genes (Nagarajan et al., 2020). This suggests that the lack of response to ER antagonists induced by *ARID1A* loss-of-function mutations could be potentially overcome by BET inhibitors.

DNA repair genes

High mutational load is associated with poor prognosis in ER^+ breast cancer (Haricharan et al., 2014). Haricharan et al. found that loss-of-function mutations and/or low expression of the mismatch repair (MMR) MutL genes (*MLH1/3, PMS1/2*) were associated with endocrine resistance by abolishing CHK2-mediated inhibition of CDK4. CDK4/6i remained effective in MutL-defective ER^+ breast cancer cells (Haricharan et al., 2017). Similarly, loss of nucleotide excision repair and base excision repair genes promoted endocrine resistance through dysregulation of the G1-S transition. Cells with loss of these genes were also sensitive to CDK4/6i (Anurag et al., 2018).

Epigenetic and non-genetic mechanisms

Epigenetic reprogramming

In concert with genomic evolution, epigenetic mechanisms shape tumor architecture by expanding the repertoire of tumor cell populations harboring distinct molecular profiles. The resulting heterogeneity increases the probability of the presence of clones expressing resistance-promoting transcriptional programs (Dagogo-Jack and Shaw, 2018). Epigenetic modifications alter chromatin accessibility through (i) post-translational modification of chromatin-bound histones by histone acetyltransferases, histone deacetylases and histone methyltransferases and (ii) through DNA methylation by DNA methyltransferases. Epigenetic modifications implicated in endocrine resistance can impact ER-regulated transcriptional programs, affect expression of ER coactivators or corepressors, or activate parallel signaling pathways that promote cell cycle progression or survival independently of estrogen or ER.

Structural variations and missense mutations in genes encoding enzymes that govern epigenetic regulation have been frequently implicated in breast cancer pathogenesis and resistance to endocrine therapies. An enrichment of somatic mutations in chromatin remodelers such as histone methyltransferases (*KMT2B, KMT2D, KMT2E*) and histone demethylases (*KDM4A, KDM5B, KDM5C, KDM6A*) have been noted particularly in the luminal subtype of breast cancer (Cancer Genome Atlas, 2012). Single nucleotide polymorphism (SNP) array analysis of breast tumors and cell lines revealed recurrent amplification and overexpression of the histone H3 lysine 4 (H3K4) demethylase *KDM5B* in luminal breast cancers (Yamamoto et al., 2014). KDM5B was shown to bind preferentially to promoter and enhancer regions of genes highly expressed in luminal cells. Notably, patients with ER^+ tumors with a high KDM5B activity score had a shorter disease-specific survival in response to endocrine treatment, compared to those with low KDM5B

activity. Mechanistically, KDM5 was shown to regulate transcriptomic heterogeneity in ER^+ cancers (Hinohara et al., 2019). Thus, higher KDM5 activity increases tumor cell heterogeneity and the likelihood of pre-existing clones with primary resistance to endocrine therapy. Along these lines, Patten et al. showed that under the selection pressure of hormonal therapies, epigenetic reprogramming promotes phenotypic heterogeneity and expansion of endocrine-resistant clones that were underrepresented at the time of treatment onset. The YY1 transcription factor was shown to act as a global co-activator of epigenetically-activated enhancers and stabilized ER binding to enhancers of genes involved in acquired endocrine resistance (Patten et al., 2018).

Deletion or loss-of-function mutations in H3K4 methyltransferase *KMT2C* occur frequently in ER^+ breast cancers and such alterations have also been associated with diminished response to AIs (Gala et al., 2018). This hormone-independent phenotype of KMT2C-depleted cells remains dependent on ER activity. Direct antagonists of ER may therefore represent an optimal therapeutic option for the treatment of ER^+ breast cancers with loss-of-function *KMT2C* alterations. On the other hand, endocrine resistance driven by loss of ER dependence would be refractory to all forms of endocrine treatment. Stone et al. identified hypermethylation of enhancers of ER-responsive genes as a potential mechanism of primary and acquired endocrine resistance. Enhancer hypermethylation occludes ER recruitment, which results in transcriptional reprogramming and ER independence (Stone et al., 2015). DNA methylome analysis could therefore serve as an effective tool to predict the responsiveness of ER^+ breast cancers to ER-targeting agents.

Aberrant co-factor activity

Jin et al. demonstrated that HOXB7 serves as an ER-activating co-factor and supports the transcription of *HER2, MYC* and other ER target genes in tamoxifen-resistant cells. Increased EGFR/HER2 signaling was shown to phosphorylate and stabilize MYC, which in turn suppressed the transcription of miR-196a, a repressor of HOXB7. Treatment with fulvestrant disengaged this feed-forward loop and induced complete regression of HOXB7-overexpressing MCF7 xenografts (Jin et al., 2015). Along these lines, Jeselsohn et al. reported continued dependence of tamoxifen-resistant cells on ER signaling and transcriptional activity. The ER cistrome of tamoxifen-resistant cells was vastly different from that of parental or LTED cells. The RUNX2 transcription factor was selectively upregulated in tamoxifen-resistant cells; RUNX2 interacted with ER to reprogram the ER cistrome and transcriptional activity. This transcriptional rewiring resulted in upregulation of gene expression programs associated with proliferation and metastasis (Jeselsohn et al., 2017).

The pioneer factor FOXA1 opens up densely packed chromatin to make it transcriptionally accessible to ER (Carroll et al., 2006) and other lineage-specific transcription factors. Amplification/overexpression of the *FOXA1* gene in ER^+ tumors is associated with inferior relapse-free survival in response to tamoxifen (Fu et al., 2016). FOXA1-driven tamoxifen resistance occurs in part through reprogramming of canonical FOXA1 cistrome to include new enhancers and enhanced transcriptional activity at established enhancers (Cocce et al., 2019). In line with these findings, Fu et al. demonstrated that the altered enhancer landscape

in FOXA1-high tamoxifen-resistant cells induces HIF-2α expression, which in turn initiates pro-metastatic transcriptional programs (Fu et al., 2019).

Additionally, breast cancer cells evade tamoxifen treatment by titrating the expression of ER co-regulators to restore ER transcriptional activity. For instance, overexpression of SRCs results in a switch of the antagonistic activity of tamoxifen-bound ER to an agonistic role (Osborne et al., 2003). Johmura and colleagues demonstrated that in ER^+ breast cancers, loss of F-box protein 22 (FBOX22) expression stabilizes KDM4B, facilitating SRC recruitment and ER transcriptional activity, even in the presence of SERMs (Johmura et al., 2018). Likewise, the ER corepressor NCoR is vital for tamoxifen to exert its antagonistic function. COPS5, which is amplified/overexpressed in >85% of tamoxifen-refractory tumors, causes proteasomal degradation of NCoR and switches tamoxifen into a potent ER agonist (Lu et al., 2016). Therefore, tamoxifen-resistant cells lacking NCoR remain ER-dependent and potentially sensitive to SERDs.

Compensatory crosstalk between signaling pathways

Upregulation of parallel oncogenic pathways can compensate for ER blockade (Figure 2). Using a genome-wide CRISPR/Cas9 screen on estrogen-deprived ER^+ cell lines, Xiao et al. identified C-terminal Src kinase (CSK) as one of the top tumor suppressors whose deletion restored cell growth in the absence of estrogen. The authors demonstrated that E2-bound ER activates the transcription of CSK to create a negative feedback loop that inhibits the oncogenic function of Src family tyrosine kinases (SFKs)/PAK2 via inhibitory phosphorylation. However, endocrine therapy disrupts this estrogen-induced negative feedback, leading to SFKs/PAK2 hyperactivation and worse clinical outcome. The combination of ER antagonists with a PAK2 inhibitor achieved durable suppression of ER^+ xenograft growth (Xiao et al., 2018).

Epithelial to mesenchymal transition (EMT)

Resistance to targeted therapies could be acquired through gain of novel resistance-promoting alterations or via clonal selection of rare, pre-existing drug resistant cells. Single cell transcriptomics revealed lack of such fully endocrine-resistant clones in a treatment-naïve cell population. Rather, a rare subpopulation of ‘pre-adapted’ cells has been described by Hong et al. This population harbors EMT and dormancy-related transcriptional features that support their survival through short-term endocrine therapy. Under the therapeutic stress of estrogen withdrawal, these pre-adapted cells underwent further transcriptional reprogramming and genomic alterations to achieve a fully endocrine-resistant phenotype (Hong et al., 2019). The frequency of this stepwise adaptation program in human tumors remains to be defined. ESR1 fusions (described above) upregulate the expression of EMT-related genes to support metastatic progression (Lei et al., 2018).

Lombardo et al. demonstrated that tamoxifen-resistant and LTED cells acquire an EMT phenotype via upregulation of Nicastrin and Notch4 (Lombardo et al., 2014). Likewise, DMXL2 expression is upregulated in endocrine-therapy resistant breast cancers, where it promotes an epithelial to mesenchymal switch via Notch signaling (Faronato et al., 2015). RNA sequencing of tamoxifen- and fulvestrant-resistant ER^+ breast cancer cells revealed

selective upregulation of SNAI2 expression, but not of other EMT-related transcription factors (Alves et al., 2018). SNAI2 overexpression was shown to be causally associated with EMT, metastatic traits, and an inferior survival benefit from endocrine therapy.

Cancer stem cells (CSCs)

Breast cancer stem-like cells have been frequently implicated in endocrine resistance, although whether they are sufficient to drive resistance is less clear. Several of the oncogenic alterations outlined above, including *ESR1* mutations, Notch signaling, AIB1 overexpression, and tumor microenvironmental factors have been shown to promote breast cancer stem-like cell expansion (Rodriguez et al., 2019). Residual tumors that survive endocrine therapy can be enriched with cancer cell populations exhibiting classical tumor-initiating features such as $CD44^{+}/CD24^{-/low}$ cell surface markers, high aldehyde dehydrogenase activity, and enhanced mammosphere formation (Creighton et al., 2009; Rodriguez et al., 2019). Gene expression profiling of tamoxifen- or fulvestrant-treated breast cancer patient-derived cells and PDXs revealed elevated expression of Notch target genes, which strongly correlated with high ALDH activity (Simoes et al., 2015). The upregulation of Notch signaling in tamoxifen- and fulvestrant-resistant cells was shown to be mediated by increased expression of Notch ligand JAG1. Pharmacological or genomic disruption of Notch 4 activity reversed tamoxifen and fulvestrant resistance and CSC activity, suggesting a causal relationship between a stem cell-like phenotype and endocrine resistance. Further, SRC3 overexpression, previously associated with tamoxifen resistance, induces a cancer stem cell-like phenotype by driving the expression of master EMT regulators and stemness-related markers (Rohira et al., 2017). Other stem cell-promoting factors implicated in endocrine resistance include SOX9 (Jeselsohn et al., 2017) and FOXM1 (Bergamaschi et al., 2014).

Metabolic reprogramming

ER^{+} breast cancers have been shown to evade endocrine therapy by switching to alternate metabolic processes. For example, the aggressive nature of *ESR1* LBD mutations was attributed to estrogen-independent metabolic rewiring. Compared to breast cancer cells expressing WT ESR1, which are mostly glucose dependent even upon estrogen stimulation, $ESR1^{Y537S}$-expressing cells exhibit elevated tricarboxylic acid cycle activity, glucose independence, and reliance on glutamine as an alternative carbon source (Zinger et al., 2019). Sansone et al. performed molecular profiling of pre- and on-treatment tumors from patients in a clinical trial of neoadjuvant letrozole, revealing an inverse correlation between ER and expression of the CSC marker CD133. Mechanistically, antiestrogens induced a metabolically-dormant, self-renewal-deficient state in which ER expression was suppressed. However, chronic exposure to fulvestrant increased paracrine expression of IL-6, which in turn elevated oxidative phosphorylation to restore growth in quiescent $CD133^{hi}/ER^{lo}/Mito^{lo}$ cells, in an ER-independent manner (Sansone et al., 2016).

Transcriptomic analysis of LTED cells revealed an augmentation of miR-23b-3p expression, which reprogrammed amino acid metabolism to promote endocrine resistance (Bacci et al., 2019). miR-23b-3p upregulation activated autophagy, suppressed SLC6A14 to limit the uptake of basic and neutral amino acids, and enhanced the expression of SLC1A2 to

increase the import of acidic amino acids such as aspartate and glutamate. The increased influx of acidic amino acids promoted endocrine resistance and metastatic aggressiveness (Bacci et al., 2019). Further, RNA-seq of LTED invasive lobular carcinoma cells lines identified activation of cholesterol and fatty acid metabolism as drivers of endocrine resistance (Du et al., 2018). Ligand-independent ER activation in LTED MCF7 cells was shown to upregulate miR-155 expression which conferred metabolic plasticity (Bacci et al., 2016). Compared to parental cells, endocrine-resistant cells were increasingly dependent on glycolysis. However, upon glycolytic pathway blockade, these cells promptly resorted to oxidative phosphorylation which made them impervious to metabolic targeting (Bacci et al., 2016). Tumors with high miR-155 levels are therefore likely to adapt rapidly and progress on aromatase inhibitors, but could be responsive to SERDs.

Endocrine sensitivity in lobular vs. ductal breast cancers

Invasive lobular carcinoma (ILC) comprises up to 15% of invasive breast cancers and is typically ER^+. ILC is characterized by loss of E-cadherin, leading to the discohesive phenotype associated with ILC (McCart Reed et al., 2015). Retrospective studies have suggested that tamoxifen is less effective than the AI letrozole in ILC (Metzger Filho et al., 2015). Preclinical studies have shown that tamoxifen acts as an ER agonist in ILC cell lines and that the ER-regulated transcriptome differs between ILC and ductal breast cancer cell lines (Sikora et al., 2014). Accordingly, mechanisms of endocrine resistance may be distinct in ILC compared to invasive ductal cancers. FGFR1, WNT4, and lipid metabolism have all been implicated in endocrine resistance specifically in ILC cell lines (Du et al., 2018; Sikora et al., 2014; Sikora et al., 2016), although clinical confirmation of these associations is lacking. Desmedt et al. showed that mutation rates in *PIK3CA, PTEN, AKT1, ERBB2*, *ARID1A*, and *FOXA1*, all implicated in endocrine resistance (discussed above), are higher in lobular vs ductal carcinomas. In this study, mutations in *ERBB2* and *AKT1* were associated with increased risk of early relapse (Desmedt et al., 2016). Finally, Sokol et al. reported that loss-of-function *NF1* alterations were enriched in endocrine-resistant metastatic ILC (Sokol et al., 2019).

Tumor microenvironment

Several components of the tumor microenvironment, including hypoxia, cancer-associated fibroblasts, extracellular matrix (ECM), exosomes, and inflammatory and immune cells have been implicated in endocrine resistance.

Hypoxia

Hypoxia is a critical microenvironmental factor that differentiates tumor and normal tissue and is associated with a poor response to endocrine therapy (Generali et al., 2006). Yang et al. found that ERα and the hypoxia-inducible factor HIF-1α coordinately regulate a subset of genes. HIF-1α overexpression in MCF-7 xenografts induced resistance to antiestrogen treatment and a hypoxia gene signature was associated with poor response to endocrine therapy in ER^+ breast cancers (Yang et al., 2015). Targeting the hypoxia-induced amino acid transporter SNAT2 may sensitize hypoxic breast cancer cells to antiestrogen treatment (Morotti et al., 2019).

Stromal factors

Cancer-associated fibroblasts (CAFs) play a key role in tumor progression via ECM remodeling and secretion of cytokines and growth factors that promote tumor cell proliferation and survival and modulation of immune cells (Houthuijzen and Jonkers, 2018). Breast CAFs can promote EMT in ER^+ breast cancer cells (Soon et al., 2013). CAFs can also secrete cytokines or growth factors that contribute to drug resistance. For example, Brechbuhl et al. found that conditioned media from the CD146-negative subset of CAFs reduces ER expression and tamoxifen sensitivity and activates RTKs in MCF7 cells. They further found that a $CD146^{neg}$ gene signature is associated with poor outcome in tamoxifen-treated patients (Brechbuhl et al., 2017).

Extracellular vesicles (EVs) can transfer proteins, DNA, and RNA between cells and promote cancer progression (Desrochers et al., 2016). Sansone et al. discovered CAF-derived EVs containing mitochondrial DNA in patients with endocrine-resistant MBC. Mechanistically, the authors showed that mtDNA-containing EVs promoted escape from metabolic quiescence in fulvestrant-treated cells via restoration of oxidative phosphorylation. These EVs also promoted self-renewal of cancer stem-like cells (discussed above), contributing to fulvestrant resistance (Sansone et al., 2017b). The same group showed that CAF-derived microvesicles transfer oncogenic miRNA miR-221 to tumor cells, promoting CSC generation and an ER^{low}/$Notch^{high}$ endocrine-resistant state in tumor cells. IL-6 blockade with tocilizumab inhibited the production of $miR\text{-}221^{hi}$ microvesicles by CAFs and subsequent development of CAF-CSC niches, and importantly, restored ER expression and fulvestrant sensitivity (Sansone et al., 2017a).

ECM components may also impact sensitivity to antiestrogen therapy. Elevated collagen I deposition increased ECM density/stiffness and promoted tamoxifen resistance in a mouse model of ER^+ breast cancer (Jallow et al., 2019).

Inflammatory and immune components

Recent studies have implicated inflammatory cytokines in endocrine resistance. Antiestrogen treatment induces the TGFβ cytokine in breast cancer cells, leading to antiestrogen resistance and immunosuppression (Joffroy et al., 2010). In a neoadjuvant study of 112 patients receiving an aromatase inhibitor, an inflammatory gene signature was the strongest correlate of poor anti-proliferative response (Dunbier et al., 2013). In fact, pro-inflammatory cytokines such as IL-1β and TNFα stimulate estrogen-independent ER transcriptional activation via IKKβ-dependent phosphorylation of ER Ser305, leading to endocrine resistance (Stender et al., 2017). Therefore, the tumor microenvironment directly signals to the ER and mediates ligand-independent ER activity. Despite these pioneering studies, the role of inflammatory cytokines in endocrine resistance remains an under-explored area of research.

ER^+ tumors have been considered to be immunologically “cold” due to low tumor-infiltrating lymphocyte (TIL) infiltration (Loi et al., 2013). Only ~20% of ER^+ breast cancer cells express the PD-L1 immune checkpoint protein and single-agent immune checkpoint inhibitors have shown limited efficacy in PD-L1-positive, ER^+ tumors (Rugo et al., 2018).

ERα has been shown to negatively regulate PD-L1 expression (Liu et al., 2018). Therefore, antiestrogen treatment may induce PD-L1 expression and synergize with ICIs. Clinical trials combining ICIs and antiestrogens in ER^+ MBC are ongoing.

Immune checkpoint inhibition may be particularly relevant in ER^+ tumors of the luminal B subtype that respond poorly to AIs. Anurag and colleagues demonstrated that high expression of the immune checkpoint components IDO1, LAG3, and PD1 was associated with AI-resistant proliferation in Luminal B tumors. IDO1 was also associated with poor prognosis in another cohort and was more highly expressed in Luminal B tumors (Anurag et al., 2019). However, more work is needed to determine If upregulation of these immune checkpoint components is causal to endocrine resistance. Functional studies with IDO1 inhibitors in preclinical models of luminal B tumors will be required to determine whether targeting IDO1 may reverse endocrine resistance in this subtype.

Conclusions and Future Directions

The determinants of sensitivity and resistance to endocrine therapy in ER^+ breast cancers mirror other hormone-dependent cancer types, including prostate cancer and endometrial cancer. Response to endocrine therapy in ER^+ endometrial cancer is generally low. Of note, many of the mechanisms of resistance listed above have also been implicated in endocrine-resistant endometrial cancers, including activation of the PI3K and cell cycle pathways, epigenetic deregulation, and the immune microenvironment (Jerzak et al., 2019). In prostate cancer, the androgen receptor (AR) functions much like the ER in breast cancer, and prostate cancer cells utilize many of the same mechanisms described herein to overcome androgen- and AR-targeted therapies. For example, genomic aberrations in AR and deregulation of AR cofactors and AR-mediated transcription represent major mechanisms of resistance (Attard and Antonarakis, 2016; Groner and Brown, 2017). Lineage plasticity can also promote antiandrogen resistance and AR-independent growth in a similar fashion to the luminal-to-basal transition mediated by *ARID1A* inactivation in endocrine-resistant breast cancers (Mu et al., 2017; Xu et al., 2020). Furthermore, some of the mechanisms of antiestrogen resistance described above are similar to mechanisms of resistance to targeted therapies in other cancer types, including *EGFR*- and *ALK*-altered lung cancers, *BRAF*-mutant melanoma, *NTRK*-rearranged tumors, and *HER2*-amplified or *HER2*-mutant breast cancer. These include 1) secondary mutations in the drug target that block drug-mediated target inhibition (ie, *ESR1, EGFR, ALK*, *NTRK, ERBB2*, etc) (Camidge et al., 2014; Hanker et al., 2017; Lin et al., 2017; Pao et al., 2005; Russo et al., 2016), 2) target-independent activation of downstream or bypass signaling pathways (ie, RTK, PI3K, and MAPK pathway deregulation) (Arteaga and Engelman, 2014; Cocco et al., 2019; Hazar-Rethinam et al., 2018; Shi et al., 2014), and 3) microenvironmental components that affect drug sensitivity (Hirata et al., 2015; Kalluri, 2016; Ruffell and Coussens, 2015; Sahai et al., 2020).

The explosion of studies from the past few years on multi-dimensional aspects of endocrine resistance in MBC suggest that there may be as yet unidentified factors that contribute to endocrine resistance. Indeed, Razavi et al. reported that 60% of endocrine-resistant MBC lacked known somatic drivers of resistance (Razavi et al., 2018). Thus far, studies of matched pre-treatment and post-progression biopsies of endocrine-resistance breast tumors

have been limited. For example, Razavi and colleagues performed whole-exome sequencing on 74 matched pairs. Larger numbers of patients with serial biopsies and more extended interrogation of tumor evolution as a function of time and treatment pressure (i.e., whole genome sequencing, single-cell RNA-sequencing, etc.) will be needed to more completely characterize the spectrum of somatic, epigenetic, and microenvironmental changes that drive endocrine resistance.

There is no doubt that CDK4/6i have transformed the treatment of advanced ER^+ breast cancers. The combination of a CDK4/6 inhibitor plus an AI or fulvestrant is currently the standard first-line treatment for metastatic ER^+ breast cancer. Therefore, a major focus of research should be on preventing or overcoming resistance to the combination of endocrine therapy and CDK4/6i. Some of the somatic alterations described above have also been shown to promote resistance to CDK4/6i, including *FGFR1* amplification, *PTEN* alterations, and *ERBB2* mutations (Costa et al., 2020; Formisano et al., 2019; Nayar et al., 2019). In contrast, *RB1* and *FAT1* alterations appear to be exclusively associated with resistance to CDK4/6 inhibitors and less to antiestrogens alone (Li et al., 2018; O'Leary et al., 2018). A companion review in this same issue focuses on de novo and acquired resistance to CDK4/6 antagonists.

Although the majority of early-stage ER^+ breast cancers are highly sensitive to endocrine therapies, the wide array of endocrine resistance mechanisms poses a barrier to curing clinically metastatic ER^+ breast cancer. Intra-tumor heterogeneity of resistance alterations represents a major challenge in treating endocrine-resistant MBC (Fribbens et al., 2018) and other drug-resistant cancers (Vasan et al., 2019). Potential strategies to improve the cure rates of ER^+ breast cancers include (i) treatment with the most effective upfront therapy/combinations to maximize tumor eradication (Vasan et al., 2019) (ie, endocrine therapy + CDK4/6i, PI3Kα inhibitors, etc., in early-stage tumors); (ii) tracking ctDNA to detect acquired resistance prior to frank clinical progression and targeting detected genomic alterations (Fribbens et al., 2018), and (iii) therapeutic targeting of dormant ER^+ breast cancer cells in order to eliminate recurrence (Gawrzak et al., 2018; Zhang et al., 2013).

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References

Aggelis V, and Johnston SRD (2019). Advances in Endocrine-Based Therapies for Estrogen Receptor-Positive Metastatic Breast Cancer. Drugs 79, 1849–1866. [PubMed: 31630379]

Alves CL, Elias D, Lyng MB, Bak M, and Ditzel HJ (2018). SNAI2 upregulation is associated with an aggressive phenotype in fulvestrant-resistant breast cancer cells and is an indicator of poor response to endocrine therapy in estrogen receptor-positive metastatic breast cancer. Breast Cancer Res 20, 60. [PubMed: 29921289]

Andre F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, Iwata H, Conte P, Mayer IA, Kaufman B, et al. (2019). Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med 380, 1929–1940. [PubMed: 31091374]

Andreano KJ, Wardell SE, Baker JG, Desautels TK, Baldi R, Chao CA, Heetderks KA, Bae Y, Xiong R, Tonetti DA, et al. (2020). G1T48, an oral selective estrogen receptor degrader, and the CDK4/6 inhibitor lerociclib inhibit tumor growth in animal models of endocrine-resistant breast cancer. Breast cancer research and treatment, 10.1007/s10549-10020-05575-10549.

Angus L, Smid M, Wilting SM, van Riet J, Van Hoeck A, Nguyen L, Nik-Zainal S, Steenbruggen TG, Tjan-Heijnen VCG, Labots M, et al. (2019). The genomic landscape of metastatic breast cancer highlights changes in mutation and signature frequencies. Nat Genet 51, 1450–1458. [PubMed: 31570896]

Anurag M, Punturi N, Hoog J, Bainbridge MN, Ellis MJ, and Haricharan S (2018). Comprehensive Profiling of DNA Repair Defects in Breast Cancer Identifies a Novel Class of Endocrine Therapy Resistance Drivers. Clin Cancer Res 24, 4887–4899. [PubMed: 29793947]

Anurag M, Zhu M, Huang C, Vasaikar S, Wang J, Hoog J, Burugu S, Gao D, Suman V, Zhang XH, et al. (2019). Immune Checkpoint Profiles in Luminal B Breast Cancer (Alliance). J Natl Cancer Inst, djz213.

Arteaga CL, and Engelman JA (2014). ERBB receptors: from oncogene discovery to basic science to mechanism-based cancer therapeutics. Cancer Cell 25, 282–303. [PubMed: 24651011]

Attard G, and Antonarakis ES (2016). Prostate cancer: AR aberrations and resistance to abiraterone or enzalutamide. Nat Rev Urol 13, 697–698. [PubMed: 27804988]

Bacci M, Giannoni E, Fearns A, Ribas R, Gao Q, Taddei ML, Pintus G, Dowsett M, Isacke CM, Martin LA, et al. (2016). miR-155 Drives Metabolic Reprogramming of ER+ Breast Cancer Cells Following Long-Term Estrogen Deprivation and Predicts Clinical Response to Aromatase Inhibitors. Cancer Res 76, 1615–1626. [PubMed: 26795347]

Bacci M, Lorito N, Ippolito L, Ramazzotti M, Luti S, Romagnoli S, Parri M, Bianchini F, Cappellesso F, Virga F, et al. (2019). Reprogramming of Amino Acid Transporters to Support Aspartate and Glutamate Dependency Sustains Endocrine Resistance in Breast Cancer. Cell reports 28, 104–118 e108. [PubMed: 31269432]

Baselga J, Campone M, Piccart M, Burris HA 3rd, Rugo HS, Sahmoud T, Noguchi S, Gnant M, Pritchard KI, Lebrun F, et al. (2012). Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 366, 520–529. [PubMed: 22149876]

Beaulieu ME, Jauset T, Masso-Valles D, Martinez-Martin S, Rahl P, Maltais L, Zacarias-Fluck MF, Casacuberta-Serra S, Serrano Del Pozo E, Fiore C, et al. (2019). Intrinsic cell-penetrating activity propels Omomyc from proof of concept to viable anti-MYC therapy. Sci Transl Med 11, eaar5012.

Benz CC, Scott GK, Sarup JC, Johnson RM, Tripathy D, Coronado E, Shepard HM, and Osborne CK (1992). Estrogen-dependent, tamoxifen-resistant tumorigenic growth of MCF-7 cells transfected with HER2/neu. Breast Cancer Res Treat 24, 85–95. [PubMed: 8095168]

Bergamaschi A, Madak-Erdogan Z, Kim YJ, Choi YL, Lu H, and Katzenellenbogen BS (2014). The forkhead transcription factor FOXM1 promotes endocrine resistance and invasiveness in estrogen receptor-positive breast cancer by expansion of stem-like cancer cells. Breast Cancer Res 16, 436. [PubMed: 25213081]

Bertucci F, Ng CKY, Patsouris A, Droin N, Piscuoglio S, Carbuccia N, Soria JC, Dien AT, Adnani Y, Kamal M, et al. (2019). Genomic characterization of metastatic breast cancers. Nature 569, 560–564. [PubMed: 31118521]

Bihani T, Patel HK, Arlt H, Tao N, Jiang H, Brown JL, Purandare DM, Hattersley G, and Garner F (2017). Elacestrant (RAD1901), a Selective Estrogen Receptor Degrader (SERD), Has Antitumor Activity in Multiple ER(+) Breast Cancer Patient-derived Xenograft Models. Clin Cancer Res 23, 4793–4804. [PubMed: 28473534]

Bocchinfuso WP, and Korach KS (1997). Mammary gland development and tumorigenesis in estrogen receptor knockout mice. J Mammary Gland Biol Neoplasia 2, 323–334. [PubMed: 10935020]

Borg A, Baldetorp B, Ferno M, Killander D, Olsson H, Ryden S, and Sigurdsson H (1994). ERBB2 amplification is associated with tamoxifen resistance in steroid-receptor positive breast cancer. Cancer Lett 81, 137–144. [PubMed: 7912163]

Brechbuhl HM, Finlay-Schultz J, Yamamoto TM, Gillen AE, Cittelly DM, Tan AC, Sams SB, Pillai MM, Elias AD, Robinson WA, et al. (2017). Fibroblast Subtypes Regulate Responsiveness of Luminal Breast Cancer to Estrogen. Clin Cancer Res 23, 1710–1721. [PubMed: 27702820]

Camidge DR, Pao W, and Sequist LV (2014). Acquired resistance to TKIs in solid tumours: learning from lung cancer. Nature reviews Clinical oncology 11, 473–481.

Cancer Genome Atlas N (2012). Comprehensive molecular portraits of human breast tumours. Nature 490, 61–70. [PubMed: 23000897]

Carroll JS, Meyer CA, Song J, Li W, Geistlinger TR, Eeckhoute J, Brodsky AS, Keeton EK, Fertuck KC, Hall GF, et al. (2006). Genome-wide analysis of estrogen receptor binding sites. Nat Genet 38, 1289–1297. [PubMed: 17013392]

Chen H, Liu H, and Qing G (2018). Targeting oncogenic Myc as a strategy for cancer treatment. Signal Transduct Target Ther 3, 5. [PubMed: 29527331]

Cocce KJ, Jasper JS, Desautels TK, Everett L, Wardell S, Westerling T, Baldi R, Wright TM, Tavares K, Yllanes A, et al. (2019). The Lineage Determining Factor GRHL2 Collaborates with FOXA1 to Establish a Targetable Pathway in Endocrine Therapy-Resistant Breast Cancer. Cell Rep 29, 889–903 e810. [PubMed: 31644911]

Cocco E, Schram AM, Kulick A, Misale S, Won HH, Yaeger R, Razavi P, Ptashkin R, Hechtman JF, Toska E, et al. (2019). Resistance to TRK inhibition mediated by convergent MAPK pathway activation. Nature medicine 25, 1422–1427.

Costa C, Wang Y, Ly A, Hosono Y, Murchie E, Walmsley CS, Huynh T, Healy C, Peterson R, Yanase S, et al. (2020). PTEN Loss Mediates Clinical Cross-Resistance to CDK4/6 and PI3Kalpha Inhibitors in Breast Cancer. Cancer discovery 10, 72–85. [PubMed: 31594766]

Couse JF, and Korach KS (1999). Estrogen receptor null mice: what have we learned and where will they lead us? Endocr Rev 20, 358–417. [PubMed: 10368776]

Creighton CJ, Li X, Landis M, Dixon JM, Neumeister VM, Sjolund A, Rimm DL, Wong H, Rodriguez A, Herschkowitz JI, et al. (2009). Residual breast cancers after conventional therapy display mesenchymal as well as tumor-initiating features. Proc Natl Acad Sci U S A 106, 13820–13825. [PubMed: 19666588]

Croessmann S, Formisano L, Kinch LN, Gonzalez-Ericsson PI, Sudhan DR, Nagy RJ, Mathew A, Bernicker EH, Cristofanilli M, He J, et al. (2019). Combined Blockade of Activating ERBB2 Mutations and ER Results in Synthetic Lethality of ER+/HER2 Mutant Breast Cancer. Clin Cancer Res 25, 277–289. [PubMed: 30314968]

Dagogo-Jack I, and Shaw AT (2018). Tumour heterogeneity and resistance to cancer therapies. Nat Rev Clin Oncol 15, 81–94. [PubMed: 29115304]

De Savi C, Bradbury RH, Rabow AA, Norman RA, de Almeida C, Andrews DM, Ballard P, Buttar D, Callis RJ, Currie GS, et al. (2015). Optimization of a Novel Binding Motif to (E)-3-(3,5-Difluoro-4-((1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)acrylic Acid (AZD9496), a Potent and Orally Bioavailable Selective Estrogen Receptor Downregulator and Antagonist. Journal of medicinal chemistry 58, 8128–8140. [PubMed: 26407012]

Dees EC, Aftimos PG, van Oordt CWMV, De Vries EGE, Neven P, Pegram MD, Iqbal R, Boers J, Xiao J, Sipes C, et al. (2019). Dose-escalation study of G1T48, an oral selective estrogen receptor degrader (SERD), in postmenopausal women with ER+/HER2-locally advanced or metastatic breast cancer (ABC). Annals of Oncology 30, 121–+.

Delmore JE, Issa GC, Lemieux ME, Rahl PB, Shi J, Jacobs HM, Kastritis E, Gilpatrick T, Paranal RM, Qi J, et al. (2011). BET bromodomain inhibition as a therapeutic strategy to target c-Myc. Cell 146, 904–917. [PubMed: 21889194]

DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, Jemal A, and Siegel RL (2019). Breast cancer statistics, 2019. CA Cancer J Clin 69, 438–451. [PubMed: 31577379]

Desmedt C, Zoppoli G, Gundem G, Pruneri G, Larsimont D, Fornili M, Fumagalli D, Brown D, Rothe F, Vincent D, et al. (2016). Genomic Characterization of Primary Invasive Lobular Breast Cancer. J Clin Oncol 34, 1872–1881. [PubMed: 26926684]

Desrochers LM, Antonyak MA, and Cerione RA (2016). Extracellular Vesicles: Satellites of Information Transfer in Cancer and Stem Cell Biology. Developmental cell 37, 301–309. [PubMed: 27219060]

Du T, Sikora MJ, Levine KM, Tasdemir N, Riggins RB, Wendell SG, Van Houten B, and Oesterreich S (2018). Key regulators of lipid metabolism drive endocrine resistance in invasive lobular breast cancer. Breast Cancer Res 20, 106. [PubMed: 30180878]

Dunbier AK, Ghazoui Z, Anderson H, Salter J, Nerurkar A, Osin P, A'Hern R, Miller WR, Smith IE, and Dowsett M (2013). Molecular profiling of aromatase inhibitor-treated postmenopausal breast tumors identifies immune-related correlates of resistance. Clin Cancer Res 19, 2775–2786. [PubMed: 23493347]

El-Ahmad Y, Tabart M, Halley F, Certal V, Thompson F, Filoche-Romme B, GrussLeleu F, Muller C, Brollo M, Fabien L, et al. (2020). Discovery of 6-(2,4-Dichlorophenyl)-5-[4-[(3S)-1-(3-fluoropropyl)pyrrolidin-3-yl]oxyphenyl]-8, 9-dihydro-7H-benzo[7]annulene-2-carboxylic acid (SAR439859), a Potent and Selective Estrogen Receptor Degrader (SERD) for the Treatment of Estrogen-Receptor-Positive Breast Cancer. J Med Chem 63, 512–528. [PubMed: 31721572]

Fanning SW, and Greene GL (2019). Next-Generation ERalpha Inhibitors for Endocrine-Resistant ER + Breast Cancer. Endocrinology 160, 759–769. [PubMed: 30753408]

Fanning SW, Jeselsohn R, Dharmarajan V, Mayne CG, Karimi M, Buchwalter G, Houtman R, Toy W, Fowler CE, Han R, et al. (2018). The SERM/SERD bazedoxifene disrupts ESR1 helix 12 to overcome acquired hormone resistance in breast cancer cells. eLife 7, e37161. [PubMed: 30489256]

Faronato M, Nguyen VT, Patten DK, Lombardo Y, Steel JH, Patel N, Woodley L, Shousha S, Pruneri G, Coombes RC, and Magnani L (2015). DMXL2 drives epithelial to mesenchymal transition in hormonal therapy resistant breast cancer through Notch hyperactivation. Oncotarget 6, 22467–22479. [PubMed: 26093085]

Filippova GN, Fagerlie S, Klenova EM, Myers C, Dehner Y, Goodwin G, Neiman PE, Collins SJ, and Lobanenkov VV (1996). An exceptionally conserved transcriptional repressor, CTCF, employs different combinations of zinc fingers to bind diverged promoter sequences of avian and mammalian c-myc oncogenes. Mol Cell Biol 16, 2802–2813. [PubMed: 8649389]

Flaherty KT, Robert C, Hersey P, Nathan P, Garbe C, Milhem M, Demidov LV, Hassel JC, Rutkowski P, Mohr P, et al. (2012). Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med 367, 107–114. [PubMed: 22663011]

Flanagan JJ, Qian Y, Gough SM, Andreoli M, Bookbinder M, Cadelina G, Bradley J, Rousseau E, Willard R, Pizzano J, et al. (2019). Abstract P5-04-18: ARV-471, an oral estrogen receptor PROTAC degrader for breast cancer. Cancer Research 79, P5-04-18.

Formisano L, Lu Y, Servetto A, Hanker AB, Jansen VM, Bauer JA, Sudhan DR, Guerrero-Zotano AL, Croessmann S, Guo Y, et al. (2019). Aberrant FGFR signaling mediates resistance to CDK4/6 inhibitors in ER+ breast cancer. Nat Commun 10, 1373. [PubMed: 30914635]

Formisano L, Stauffer KM, Young CD, Bhola NE, Guerrero-Zotano AL, Jansen VM, Estrada MM, Hutchinson KE, Giltnane JM, Schwarz LJ, et al. (2017). Association of FGFR1 with ERalpha Maintains Ligand-Independent ER Transcription and Mediates Resistance to Estrogen Deprivation in ER(+) Breast Cancer. Clin Cancer Res 23, 6138–6150. [PubMed: 28751448]

Fox EM, Miller TW, Balko JM, Kuba MG, Sanchez V, Smith RA, Liu S, Gonzalez-Angulo AM, Mills GB, Ye F, et al. (2011). A kinome-wide screen identifies the insulin/IGF-I receptor pathway as a mechanism of escape from hormone dependence in breast cancer. Cancer Res 71, 6773–6784. [PubMed: 21908557]

Fribbens C, Garcia Murillas I, Beaney M, Hrebien S, O'Leary B, Kilburn L, Howarth K, Epstein M, Green E, Rosenfeld N, et al. (2018). Tracking evolution of aromatase inhibitor resistance with circulating tumour DNA analysis in metastatic breast cancer. Ann Oncol 29, 145–153. [PubMed: 29045530]

Fribbens C, O'Leary B, Kilburn L, Hrebien S, Garcia-Murillas I, Beaney M, Cristofanilli M, Andre F, Loi S, Loibl S, et al. (2016). Plasma ESR1 Mutations and the Treatment of Estrogen Receptor-Positive Advanced Breast Cancer. J Clin Oncol 34, 2961–2968. [PubMed: 27269946]

Fu X, Creighton CJ, Biswal NC, Kumar V, Shea M, Herrera S, Contreras A, Gutierrez C, Wang T, Nanda S, et al. (2014). Overcoming endocrine resistance due to reduced PTEN levels in estrogen receptor-positive breast cancer by co-targeting mammalian target of rapamycin, protein kinase B, or mitogen-activated protein kinase kinase. Breast Cancer Res 16, 430. [PubMed: 25212826]

Fu X, Jeselsohn R, Pereira R, Hollingsworth EF, Creighton CJ, Li F, Shea M, Nardone A, De Angelis C, Heiser LM, et al. (2016). FOXA1 overexpression mediates endocrine resistance by altering the ER transcriptome and IL-8 expression in ER-positive breast cancer. Proc Natl Acad Sci U S A 113, E6600–E6609. [PubMed: 27791031]

Fu X, Pereira R, De Angelis C, Veeraraghavan J, Nanda S, Qin L, Cataldo ML, Sethunath V, Mehravaran S, Gutierrez C, et al. (2019). FOXA1 upregulation promotes enhancer and transcriptional reprogramming in endocrine-resistant breast cancer. Proc Natl Acad Sci U S A.

Gala K, Li Q, Sinha A, Razavi P, Dorso M, Sanchez-Vega F, Chung YR, Hendrickson R, Hsieh JJ, Berger M, et al. (2018). KMT2C mediates the estrogen dependence of breast cancer through regulation of ERalpha enhancer function. Oncogene 37, 4692–4710. [PubMed: 29755131]

Garner F, Shomali M, Paquin D, Lyttle CR, and Hattersley G (2015). RAD1901: a novel, orally bioavailable selective estrogen receptor degrader that demonstrates antitumor activity in breast cancer xenograft models. Anti-cancer drugs 26, 948–956. [PubMed: 26164151]

Gates LA, Gu G, Chen Y, Rohira AD, Lei JT, Hamilton RA, Yu Y, Lonard DM, Wang J, Wang SP, et al. (2018). Proteomic profiling identifies key coactivators utilized by mutant ERalpha proteins as potential new therapeutic targets. Oncogene 37, 4581–4598. [PubMed: 29748621]

Gawrzak S, Rinaldi L, Gregorio S, Arenas EJ, Salvador F, Urosevic J, Figueras-Puig C, Rojo F, Del Barco Barrantes I, Cejalvo JM, et al. (2018). MSK1 regulates luminal cell differentiation and metastatic dormancy in ER(+) breast cancer. Nat Cell Biol 20, 211–221. [PubMed: 29358704]

Generali D, Berruti A, Brizzi MP, Campo L, Bonardi S, Wigfield S, Bersiga A, Allevi G, Milani M, Aguggini S, et al. (2006). Hypoxia-inducible factor-1alpha expression predicts a poor response to primary chemoendocrine therapy and disease-free survival in primary human breast cancer. Clin Cancer Res 12, 4562–4568. [PubMed: 16899602]

Giltnane JM, Hutchinson KE, Stricker TP, Formisano L, Young CD, Estrada MV, Nixon MJ, Du L, Sanchez V, Ericsson PG, et al. (2017). Genomic profiling of ER(+) breast cancers after short-term estrogen suppression reveals alterations associated with endocrine resistance. Sci Transl Med 9.

Griffith OL, Spies NC, Anurag M, Griffith M, Luo J, Tu D, Yeo B, Kunisaki J, Miller CA, Krysiak K, et al. (2018). The prognostic effects of somatic mutations in ER-positive breast cancer. Nat Commun 9, 3476. [PubMed: 30181556]

Groner AC, and Brown M (2017). Role of steroid receptor and coregulator mutations in hormone-dependent cancers. The Journal of clinical investigation 127, 1126–1135. [PubMed: 28368289]

Guan J, Zhou W, Hafner M, Blake RA, Chalouni C, Chen IP, De Bruyn T, Giltnane JM, Hartman SJ, Heidersbach A, et al. (2019). Therapeutic Ligands Antagonize Estrogen Receptor Function by Impairing Its Mobility. Cell 178, 949–963 e918. [PubMed: 31353221]

Guerrero-Zotano AL, Stricker TP, Formisano L, Hutchinson KE, Stover DG, Lee KM, Schwarz LJ, Giltnane JM, Estrada MV, Jansen VM, et al. (2018). ER(+) Breast Cancers Resistant to Prolonged Neoadjuvant Letrozole Exhibit an E2F4 Transcriptional Program Sensitive to CDK4/6 Inhibitors. Clin Cancer Res 24, 2517–2529. [PubMed: 29581135]

Hamilton EP, Patel MR, Armstrong AC, Baird RD, Jhaveri K, Hoch M, Klinowska T, Lindemann JPO, Morgan SR, Schiavon G, et al. (2018). A First-in-Human Study of the New Oral Selective Estrogen Receptor Degrader AZD9496 for ER(+)/HER2(−) Advanced Breast Cancer. Clin Cancer Res 24, 3510–3518. [PubMed: 29440181]

Han H, Jain AD, Truica MI, Izquierdo-Ferrer J, Anker JF, Lysy B, Sagar V, Luan Y, Chalmers ZR, Unno K, et al. (2019). Small-Molecule MYC Inhibitors Suppress Tumor Growth and Enhance Immunotherapy. Cancer Cell 36, 483–497 e415. [PubMed: 31679823]

Hanker AB, Brewer MR, Sheehan JH, Koch JP, Sliwoski GR, Nagy R, Lanman R, Berger MF, Hyman DM, Solit DB, et al. (2017). An Acquired HER2(T798I) Gatekeeper Mutation Induces Resistance to Neratinib in a Patient with HER2 Mutant-Driven Breast Cancer. Cancer discovery 7, 575–585. [PubMed: 28274957]

Haricharan S, Bainbridge MN, Scheet P, and Brown PH (2014). Somatic mutation load of estrogen receptor-positive breast tumors predicts overall survival: an analysis of genome sequence data. Breast Cancer Res Treat 146, 211–220. [PubMed: 24839032]

Haricharan S, Punturi N, Singh P, Holloway KR, Anurag M, Schmelz J, Schmidt C, Lei JT, Suman V, Hunt K, et al. (2017). Loss of MutL Disrupts CHK2-Dependent Cell-Cycle Control through

CDK4/6 to Promote Intrinsic Endocrine Therapy Resistance in Primary Breast Cancer. Cancer discovery 7, 1168–1183. [PubMed: 28801307]

Hartmaier RJ, Trabucco SE, Priedigkeit N, Chung JH, Parachoniak CA, Vanden Borre P, Morley S, Rosenzweig M, Gay LM, Goldberg ME, et al. (2018). Recurrent hyperactive ESR1 fusion proteins in endocrine therapy-resistant breast cancer. Ann Oncol 29, 872–880. [PubMed: 29360925]

Hazar-Rethinam M, Kleyman M, Han GC, Liu D, Ahronian LG, Shahzade HA, Chen L, Parikh AR, Allen JN, Clark JW, et al. (2018). Convergent Therapeutic Strategies to Overcome the Heterogeneity of Acquired Resistance in BRAF(V600E) Colorectal Cancer. Cancer discovery 8, 417–427. [PubMed: 29431697]

Hinohara K, Wu HJ, Sebastien V, McDonald TO, Igarashi KJ, Yamamoto KN, Madsen T, Fassl A, Egri SB, Papanastasiou M, et al. (2019). KDM5 Histone Demethylase Activity Links Cellular Transcriptomic Heterogeneity to Therapeutic Resistance. Cancer Cell 35, 330–332. [PubMed: 30753830]

Hirata E, Girotti MR, Viros A, Hooper S, Spencer-Dene B, Matsuda M, Larkin J, Marais R, and Sahai E (2015). Intravital imaging reveals how BRAF inhibition generates drug-tolerant microenvironments with high integrin beta1/FAK signaling. Cancer Cell 27, 574–588. [PubMed: 25873177]

Ho A, Brana I, Haddad R, Bauman J, Bible K, Faugeras L, Oosting S, Wong DJ, Ahn M-J, Boni V, et al. (2019). Abstract PR08: Preliminary results from a phase 2 trial of tipifarnib in squamous cell carcinomas (SCCs) with HRAS mutations. Molecular Cancer Therapeutics 18, PR08.

Hong SP, Chan TE, Lombardo Y, Corleone G, Rotmensz N, Bravaccini S, Rocca A, Pruneri G, McEwen KR, Coombes RC, et al. (2019). Single-cell transcriptomics reveals multi-step adaptations to endocrine therapy. Nat Commun 10, 3840. [PubMed: 31477698]

Hortobagyi GN, Chen D, Piccart M, Rugo HS, Burris HA 3rd, Pritchard KI, Campone M, Noguchi S, Perez AT, Deleu I, et al. (2016a). Correlative Analysis of Genetic Alterations and Everolimus Benefit in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From BOLERO-2. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 34, 419–426. [PubMed: 26503204]

Hortobagyi GN, Stemmer SM, Burris HA, Yap Y-S, Sonke GS, Paluch-Shimon S, Campone M, Blackwell KL, André F, Winer EP, et al. (2016b). Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. The New England journal of medicine 375, 1738–1748. [PubMed: 27717303]

Houthuijzen JM, and Jonkers J (2018). Cancer-associated fibroblasts as key regulators of the breast cancer tumor microenvironment. Cancer Metastasis Rev 37, 577–597. [PubMed: 30465162]

Hyman DM, Smyth LM, Donoghue MTA, Westin SN, Bedard PL, Dean EJ, Bando H, El-Khoueiry AB, Perez-Fidalgo JA, Mita A, et al. (2017). AKT Inhibition in Solid Tumors With AKT1 Mutations. J Clin Oncol 35, 2251–2259. [PubMed: 28489509]

Jallow F, O'Leary KA, Rugowski DE, Guerrero JF, Ponik SM, and Schuler LA (2019). Dynamic interactions between the extracellular matrix and estrogen activity in progression of ER+ breast cancer. Oncogene 38, 6913–6925. [PubMed: 31406251]

Jerzak KJ, Duska L, and MacKay HJ (2019). Endocrine therapy in endometrial cancer: An old dog with new tricks. Gynecologic oncology 153, 175–183. [PubMed: 30616900]

Jeselsohn R, Bergholz JS, Pun M, Cornwell M, Liu W, Nardone A, Xiao T, Li W, Qiu X, Buchwalter G, et al. (2018). Allele-Specific Chromatin Recruitment and Therapeutic Vulnerabilities of ESR1 Activating Mutations. Cancer Cell 33, 173–186 e175. [PubMed: 29438694]

Jeselsohn R, Buchwalter G, De Angelis C, Brown M, and Schiff R (2015). ESR1 mutations-a mechanism for acquired endocrine resistance in breast cancer. Nat Rev Clin Oncol 12, 573–583. [PubMed: 26122181]

Jeselsohn R, Cornwell M, Pun M, Buchwalter G, Nguyen M, Bango C, Huang Y, Kuang Y, Paweletz C, Fu X, et al. (2017). Embryonic transcription factor SOX9 drives breast cancer endocrine resistance. Proc Natl Acad Sci U S A 114, E4482–E4491. [PubMed: 28507152]

Jeselsohn R, Yelensky R, Buchwalter G, Frampton G, Meric-Bernstam F, Gonzalez-Angulo AM, Ferrer-Lozano J, Perez-Fidalgo JA, Cristofanilli M, Gomez H, et al. (2014). Emergence of

constitutively active estrogen receptor-alpha mutations in pretreated advanced estrogen receptor-positive breast cancer. Clin Cancer Res 20, 1757–1767. [PubMed: 24398047]

Jhaveri K, Curigliano G, Yap YS, Cresta S, Duhoux FP, Terret C, Takahashi S, Ulaner GA, Kundamal N, Baldoni D, et al. (2019). Abstract PD1-08: Phase 1/1b study of novel oral selective estrogen receptor degrader (SERD) LSZ102 for estrogen receptor-positive (ER+) advanced breast cancer (ABC) with progression on endocrine therapy (ET). Cancer Research 79, PD1-08.

Jhaveri K, Winer EP, Lim E, Fidalgo JA, Bellet M, Mayer IA, Boni V, Patel JM, Bardia A, Garcia JM, et al. (2020). Abstract PD7-05: A first-in-human phase I study to evaluate the oral selective estrogen receptor degrader (SERD), GDC-9545, in postmenopausal women with estrogen receptor-positive (ER^+) HER2-negative ($HER2^-$) metastatic breast cancer. Cancer Research 80, PD7-05.

Jin K, Park S, Teo WW, Korangath P, Cho SS, Yoshida T, Gyorffy B, Goswami CP, Nakshatri H, Cruz LA, et al. (2015). HOXB7 Is an ERalpha Cofactor in the Activation of HER2 and Multiple ER Target Genes Leading to Endocrine Resistance. Cancer discovery 5, 944–959. [PubMed: 26180042]

Joffroy CM, Buck MB, Stope MB, Popp SL, Pfizenmaier K, and Knabbe C (2010). Antiestrogens induce transforming growth factor beta-mediated immunosuppression in breast cancer. Cancer Res 70, 1314–1322. [PubMed: 20145137]

Johmura Y, Maeda I, Suzuki N, Wu W, Goda A, Morita M, Yamaguchi K, Yamamoto M, Nagasawa S, Kojima Y, et al. (2018). Fbxo22-mediated KDM4B degradation determines selective estrogen receptor modulator activity in breast cancer. J Clin Invest 128, 5603–5619. [PubMed: 30418174]

Johnston S, Pippen J Jr., Pivot X, Lichinitser M, Sadeghi S, Dieras V, Gomez HL, Romieu G, Manikhas A, Kennedy MJ, et al. (2009). Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. J Clin Oncol 27, 5538–5546. [PubMed: 19786658]

Jones RH, Carucci M, Casbard AC, Butler R, Alchami F, Bale CJ, Bezecny P, Joffe J, Moon S, Twelves C, et al. (2019). Capivasertib (AZD5363) plus fulvestrant versus placebo plus fulvestrant after relapse or progression on an aromatase inhibitor in metastatic ER-positive breast cancer (FAKTION): A randomized, double-blind, placebo-controlled, phase II trial. Journal of Clinical Oncology 37, 1005–1005.

Joseph JD, Darimont B, Zhou W, Arrazate A, Young A, Ingalla E, Walter K, Blake RA, Nonomiya J, Guan Z, et al. (2016). The selective estrogen receptor downregulator GDC-0810 is efficacious in diverse models of ER+ breast cancer. eLife 5.

Juric D, Curigliano G, Cresta S, Yap YS, Terret C, Duhoux FP, Takahashi S, Kundamal N, Bhansali S, Liao S, et al. (2018). Phase I/Ib study of the SERD LSZ102 alone or in combination with ribociclib in ER plus breast cancer. Cancer Research 78, P5-21-04.

Kaklamani V, Bardia A, Wilks S, Weise A, Richards D, Harb W, Osborne C, Wesolowski R, Karuturi M, Conkling P, et al. (2020). Abstract PD7–07: Final analysis of phase 1 study of elacestrant (RAD1901), a novel selective estrogen receptor degrader (SERD), in estrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2−) advanced breast cancer. Cancer Research 80, PD7-07.

Kalinsky K, Jacks LM, Heguy A, Patil S, Drobnjak M, Bhanot UK, Hedvat CV, Traina TA, Solit D, Gerald W, and Moynahan ME (2009). PIK3CA Mutation Associates with Improved Outcome in Breast Cancer. Clinical Cancer Research 15, 5049. [PubMed: 19671852]

Kalluri R (2016). The biology and function of fibroblasts in cancer. Nature reviews Cancer 16, 582–598. [PubMed: 27550820]

Katzenellenbogen JA, Mayne CG, Katzenellenbogen BS, Greene GL, and Chandarlapaty S (2018). Structural underpinnings of oestrogen receptor mutations in endocrine therapy resistance. Nat Rev Cancer 18, 377–388. [PubMed: 29662238]

Kaufman B, Mackey JR, Clemens MR, Bapsy PP, Vaid A, Wardley A, Tjulandin S, Jahn M, Lehle M, Feyereislova A, et al. (2009). Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. J Clin Oncol 27, 5529–5537. [PubMed: 19786670]

Kessler D, Gmachl M, Mantoulidis A, Martin LJ, Zoephel A, Mayer M, Gollner A, Covini D, Fischer S, Gerstberger T, et al. (2019). Drugging an undruggable pocket on KRAS. Proc Natl Acad Sci U S A 116, 15823–15829. [PubMed: 31332011]

Kim RD, Sarker D, Meyer T, Yau T, Macarulla T, Park JW, Choo SP, Hollebecque A, Sung MW, Lim HY, et al. (2019). First-in-Human Phase I Study of Fisogatinib (BLU-554) Validates Aberrant FGF19 Signaling as a Driver Event in Hepatocellular Carcinoma. Cancer discovery 9, 1696–1707. [PubMed: 31575541]

Komm BS, Kharode YP, Bodine PVN, Harris HA, Miller CP, and Lyttle CR (2005). Bazedoxifene acetate: a selective estrogen receptor modulator with improved selectivity. Endocrinology 146, 3999–4008. [PubMed: 15961563]

Kurokawa H, Lenferink AE, Simpson JF, Pisacane PI, Sliwkowski MX, Forbes JT, and Arteaga CL (2000). Inhibition of HER2/neu (erbB-2) and mitogen-activated protein kinases enhances tamoxifen action against HER2-overexpressing, tamoxifen-resistant breast cancer cells. Cancer Res 60, 5887–5894. [PubMed: 11059787]

Laine M, Fanning SW, Greene M, Chang YF, Phung L, Tan TT, Hiipakka R, Komm B, and Greene G (2019). Lasofoxifene as a potential treatment for ER plus metastatic breast cancer. Journal of Clinical Oncology 37, 1056–1056.

Lauring J, Cosgrove DP, Fontana S, Gustin JP, Konishi H, Abukhdeir AM, Garay JP, Mohseni M, Wang GM, Higgins MJ, et al. (2010). Knock in of the AKT1 E17K mutation in human breast epithelial cells does not recapitulate oncogenic PIK3CA mutations. Oncogene 29, 2337–2345. [PubMed: 20101210]

Lee K. m., Guerrero-Zotano A, Hanker A, Servetto A, Sudhan D, Formisano L, Jansen V, González-Ericsson P, Sanders M, Stricker T, et al. (2020). Abstract GS6–06: A neoadjuvant trial with letrozole identifies *PRR11* in the 17q23 amplicon as a mechanism of resistance to endocrine therapy in ER-positive breast cancer. Cancer Research 80, GS6–06.

Lei JT, Gou X, Seker S, and Ellis MJ (2019). ESR1 alterations and metastasis in estrogen receptor positive breast cancer. Journal of cancer metastasis and treatment 5.

Lei JT, Shao J, Zhang J, Iglesia M, Chan DW, Cao J, Anurag M, Singh P, He X, Kosaka Y, et al. (2018). Functional Annotation of ESR1 Gene Fusions in Estrogen Receptor-Positive Breast Cancer. Cell reports 24, 1434–1444 e1437. [PubMed: 30089255]

Levine KM, Priedigkeit N, Basudan A, Tasdemir N, Sikora MJ, Sokol ES, Hartmaier RJ, Ding K, Ahmad NZ, Watters RJ, et al. (2019). FGFR4 overexpression and hotspot mutations in metastatic ER+ breast cancer are enriched in the lobular subtype. NPJ breast cancer 5, 19. [PubMed: 31263748]

Li S, Shen D, Shao J, Crowder R, Liu W, Prat A, He X, Liu S, Hoog J, Lu C, et al. (2013). Endocrine-therapy-resistant ESR1 variants revealed by genomic characterization of breast-cancer-derived xenografts. Cell reports 4, 1116–1130. [PubMed: 24055055]

Li Z, Razavi P, Li Q, Toy W, Liu B, Ping C, Hsieh W, Sanchez-Vega F, Brown DN, Da Cruz Paula AF, et al. (2018). Loss of the FAT1 Tumor Suppressor Promotes Resistance to CDK4/6 Inhibitors via the Hippo Pathway. Cancer Cell 34, 893–905 e898. [PubMed: 30537512]

Lian T, Li C, and Wang H (2019). Trametinib in the treatment of multiple malignancies harboring MEK1 mutations. Cancer Treat Rev 81, 101907. [PubMed: 31715422]

Lin JJ, Riely GJ, and Shaw AT (2017). Targeting ALK: Precision Medicine Takes on Drug Resistance. Cancer discovery 7, 137–155. [PubMed: 28122866]

Lin NU, and Winer EP (2008). Advances in adjuvant endocrine therapy for postmenopausal women. J Clin Oncol 26, 798–805. [PubMed: 18258989]

Liu L, Shen Y, Zhu X, Lv R, Li S, Zhang Z, Shi YG, and Tan L (2018). ERalpha is a negative regulator of PD-L1 gene transcription in breast cancer. Biochem Biophys Res Commun 505, 157–161. [PubMed: 30241942]

Loi S, Haibe-Kains B, Majjaj S, Lallemand F, Durbecq V, Larsimont D, Gonzalez-Angulo AM, Pusztai L, Symmans WF, Bardelli A, et al. (2010). PIK3CA mutations associated with gene signature of low mTORC1 signaling and better outcomes in estrogen receptor-positive breast cancer. Proc Natl Acad Sci U S A 107, 10208–10213. [PubMed: 20479250]

Loi S, Sirtaine N, Piette F, Salgado R, Viale G, Van Eenoo F, Rouas G, Francis P, Crown JP, Hitre E, et al. (2013). Prognostic and predictive value of tumor-infiltrating lymphocytes in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02–98. J Clin Oncol 31, 860–867. [PubMed: 23341518]

Lombardo Y, Faronato M, Filipovic A, Vircillo V, Magnani L, and Coombes RC (2014). Nicastrin and Notch4 drive endocrine therapy resistance and epithelial to mesenchymal transition in MCF7 breast cancer cells. Breast Cancer Res 16, R62. [PubMed: 24919951]

Lu R, Hu X, Zhou J, Sun J, Zhu AZ, Xu X, Zheng H, Gao X, Wang X, Jin H, et al. (2016). COPS5 amplification and overexpression confers tamoxifen-resistance in ERalpha-positive breast cancer by degradation of NCoR. Nat Commun 7, 12044. [PubMed: 27375289]

Ma CX, Reinert T, Chmielewska I, and Ellis MJ (2015). Mechanisms of aromatase inhibitor resistance. Nat Rev Cancer 15, 261–275. [PubMed: 25907219]

Magnani L, Frige G, Gadaleta RM, Corleone G, Fabris S, Kempe MH, Verschure PJ, Barozzi I, Vircillo V, Hong SP, et al. (2017). Acquired CYP19A1 amplification is an early specific mechanism of aromatase inhibitor resistance in ERalpha metastatic breast cancer. Nat Genet 49, 444–450. [PubMed: 28112739]

McCart Reed AE, Kutasovic JR, Lakhani SR, and Simpson PT (2015). Invasive lobular carcinoma of the breast: morphology, biomarkers and ‘omics. Breast Cancer Res 17, 12. [PubMed: 25849106]

Merenbakh-Lamin K, Ben-Baruch N, Yeheskel A, Dvir A, Soussan-Gutman L, Jeselsohn R, Yelensky R, Brown M, Miller VA, Sarid D, et al. (2013). D538G mutation in estrogen receptor-alpha: A novel mechanism for acquired endocrine resistance in breast cancer. Cancer Res 73, 6856–6864. [PubMed: 24217577]

Metzger Filho O, Giobbie-Hurder A, Mallon E, Gusterson B, Viale G, Winer EP, Thurlimann B, Gelber RD, Colleoni M, Ejlertsen B, et al. (2015). Relative Effectiveness of Letrozole Compared With Tamoxifen for Patients With Lobular Carcinoma in the BIG 1–98 Trial. J Clin Oncol 33, 2772–2779. [PubMed: 26215945]

Miller TW, Balko JM, Fox EM, Ghazoui Z, Dunbier A, Anderson H, Dowsett M, Jiang A, Smith RA, Maira SM, et al. (2011a). ERalpha-dependent E2F transcription can mediate resistance to estrogen deprivation in human breast cancer. Cancer discovery 1, 338–351. [PubMed: 22049316]

Miller TW, Balko JM, Ghazoui Z, Dunbier A, Anderson H, Dowsett M, Gonzalez-Angulo AM, Mills GB, Miller WR, Wu H, et al. (2011b). A gene expression signature from human breast cancer cells with acquired hormone independence identifies MYC as a mediator of antiestrogen resistance. Clin Cancer Res 17, 2024–2034. [PubMed: 21346144]

Miller TW, Hennessy BT, Gonzalez-Angulo AM, Fox EM, Mills GB, Chen H, Higham C, Garcia-Echeverria C, Shyr Y, and Arteaga CL (2010). Hyperactivation of phosphatidylinositol-3 kinase promotes escape from hormone dependence in estrogen receptor-positive human breast cancer. J Clin Invest 120, 2406–2413. [PubMed: 20530877]

Morotti M, Bridges E, Valli A, Choudhry H, Sheldon H, Wigfield S, Gray N, Zois CE, Grimm F, Jones D, et al. (2019). Hypoxia-induced switch in SNAT2/SLC38A2 regulation generates endocrine resistance in breast cancer. Proc Natl Acad Sci U S A 116, 12452–12461. [PubMed: 31152137]

Mu P, Zhang Z, Benelli M, Karthaus WR, Hoover E, Chen C-C, Wongvipat J, Ku S-Y, Gao D, Cao Z, et al. (2017). SOX2 promotes lineage plasticity and antiandrogen resistance in TP53- and RB1-deficient prostate cancer. Science (New York, NY) 355, 84–88.

Nagarajan S, Rao SV, Sutton J, Cheeseman D, Dunn S, Papachristou EK, Prada JG, Couturier DL, Kumar S, Kishore K, et al. (2020). ARID1A influences HDAC1/BRD4 activity, intrinsic proliferative capacity and breast cancer treatment response. Nat Genet.

Nayar U, Cohen O, Kapstad C, Cuoco MS, Waks AG, Wander SA, Painter C, Freeman S, Persky NS, Marini L, et al. (2019). Acquired HER2 mutations in ER(+) metastatic breast cancer confer resistance to estrogen receptor-directed therapies. Nat Genet 51, 207–216. [PubMed: 30531871]

Newby JC, Johnston SR, Smith IE, and Dowsett M (1997). Expression of epidermal growth factor receptor and c-erbB2 during the development of tamoxifen resistance in human breast cancer. Clin Cancer Res 3, 1643–1651. [PubMed: 9815855]

Nilsson S, Makela S, Treuter E, Tujague M, Thomsen J, Andersson G, Enmark E, Pettersson K, Warner M, and Gustafsson JA (2001). Mechanisms of estrogen action. Physiol Rev 81, 1535–1565. [PubMed: 11581496]

O'Leary B, Cutts RJ, Liu Y, Hrebien S, Huang X, Fenwick K, Andre F, Loibl S, Loi S, Garcia-Murillas I, et al. (2018). The Genetic Landscape and Clonal Evolution of Breast Cancer Resistance to Palbociclib plus Fulvestrant in the PALOMA-3 Trial. Cancer discovery 8, 1390–1403. [PubMed: 30206110]

Osborne CK, Bardou V, Hopp TA, Chamness GC, Hilsenbeck SG, Fuqua SA, Wong J, Allred DC, Clark GM, and Schiff R (2003). Role of the estrogen receptor coactivator AIB1 (SRC-3) and HER-2/neu in tamoxifen resistance in breast cancer. J Natl Cancer Inst 95, 353–361. [PubMed: 12618500]

Pan H, Gray R, Braybrooke J, Davies C, Taylor C, McGale P, Peto R, Pritchard KI, Bergh J, Dowsett M, et al. (2017). 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. N Engl J Med 377, 1836–1846. [PubMed: 29117498]

Pao W, Miller VA, Politi KA, Riely GJ, Somwar R, Zakowski MF, Kris MG, and Varmus H (2005). Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. PLoS Med 2, e73. [PubMed: 15737014]

Paoletti C, Schiavon G, Dolce EM, Darga EP, Carr TH, Geradts J, Hoch M, Klinowska T, Lindemann J, Marshall G, et al. (2018). Circulating Biomarkers and Resistance to Endocrine Therapy in Metastatic Breast Cancers: Correlative Results from AZD9496 Oral SERD Phase I Trial. Clin Cancer Res 24, 5860–5872. [PubMed: 30082476]

Papke B, and Der CJ (2017). Drugging RAS: Know the enemy. Science 355, 1158–1163. [PubMed: 28302824]

Patten DK, Corleone G, Gyorffy B, Perone Y, Slaven N, Barozzi I, Erdos E, Saiakhova A, Goddard K, Vingiani A, et al. (2018). Enhancer mapping uncovers phenotypic heterogeneity and evolution in patients with luminal breast cancer. Nat Med 24, 1469–1480. [PubMed: 30038216]

Pearson A, Proszek P, Pascual J, Fribbens C, Shamsher MK, Kingston B, O'Leary B, Herrera-Abreu MT, Cutts RJ, Garcia-Murillas I, et al. (2020). Inactivating NF1 Mutations Are Enriched in Advanced Breast Cancer and Contribute to Endocrine Therapy Resistance. Clin Cancer Res 26, 608–622. [PubMed: 31591187]

Prall OW, Rogan EM, Musgrove EA, Watts CK, and Sutherland RL (1998). c-Myc or cyclin D1 mimics estrogen effects on cyclin E-Cdk2 activation and cell cycle reentry. Mol Cell Biol 18, 4499–4508. [PubMed: 9671459]

Puyang X, Furman C, Zheng GZ, Wu ZJ, Banka D, Aithal K, Agoulnik S, Bolduc DM, Buonamici S, Caleb B, et al. (2018). Discovery of Selective Estrogen Receptor Covalent Antagonists for the Treatment of ERalpha(WT) and ERalpha(MUT) Breast Cancer. Cancer discovery 8, 1176–1193. [PubMed: 29991605]

Razavi P, Chang MT, Xu G, Bandlamudi C, Ross DS, Vasan N, Cai Y, Bielski CM, Donoghue MTA, Jonsson P, et al. (2018). The Genomic Landscape of Endocrine-Resistant Advanced Breast Cancers. Cancer Cell 34, 427–438 e426. [PubMed: 30205045]

Rheinbay E, Parasuraman P, Grimsby J, Tiao G, Engreitz JM, Kim J, Lawrence MS, Taylor-Weiner A, Rodriguez-Cuevas S, Rosenberg M, et al. (2017). Recurrent and functional regulatory mutations in breast cancer. Nature 547, 55–60. [PubMed: 28658208]

Robinson DR, Wu YM, Vats P, Su F, Lonigro RJ, Cao X, Kalyana-Sundaram S, Wang R, Ning Y, Hodges L, et al. (2013). Activating ESR1 mutations in hormone-resistant metastatic breast cancer. Nat Genet 45, 1446–1451. [PubMed: 24185510]

Rodriguez D, Ramkairsingh M, Lin X, Kapoor A, Major P, and Tang D (2019). The Central Contributions of Breast Cancer Stem Cells in Developing Resistance to Endocrine Therapy in Estrogen Receptor (ER)-Positive Breast Cancer. Cancers (Basel) 11.

Rohira AD, Yan F, Wang L, Wang J, Zhou S, Lu A, Yu Y, Xu J, Lonard DM, and O'Malley BW (2017). Targeting SRC Coactivators Blocks the Tumor-Initiating Capacity of Cancer Stem-like Cells. Cancer Res 77, 4293–4304. [PubMed: 28611048]

Rosati RL, Da Silva Jardine P, Cameron KO, Thompson DD, Ke HZ, Toler SM, Brown TA, Pan LC, Ebbinghaus CF, Reinhold AR, et al. (1998). Discovery and preclinical pharmacology of a novel,

potent, nonsteroidal estrogen receptor agonist/antagonist, CP-336156, a diaryltetrahydronaphthalene. Journal of medicinal chemistry 41, 2928–2931. [PubMed: 9685230]

Rueda OM, Sammut SJ, Seoane JA, Chin SF, Caswell-Jin JL, Callari M, Batra R, Pereira B, Bruna A, Ali HR, et al. (2019). Dynamics of breast-cancer relapse reveal late-recurring ER-positive genomic subgroups. Nature 567, 399–404. [PubMed: 30867590]

Ruffell B, and Coussens LM (2015). Macrophages and therapeutic resistance in cancer. Cancer cell 27, 462–472. [PubMed: 25858805]

Rugo HS, Delord JP, Im SA, Ott PA, Piha-Paul SA, Bedard PL, Sachdev J, Tourneau CL, van Brummelen EMJ, Varga A, et al. (2018). Safety and Antitumor Activity of Pembrolizumab in Patients with Estrogen Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer. Clin Cancer Res 24, 2804–2811. [PubMed: 29559561]

Russo M, Misale S, Wei G, Siravegna G, Crisafulli G, Lazzari L, Corti G, Rospo G, Novara L, Mussolin B, et al. (2016). Acquired Resistance to the TRK Inhibitor Entrectinib in Colorectal Cancer. Cancer discovery 6, 36–44. [PubMed: 26546295]

Sahai E, Astsaturov I, Cukierman E, DeNardo DG, Egeblad M, Evans RM, Fearon D, Greten FR, Hingorani SR, Hunter T, et al. (2020). A framework for advancing our understanding of cancer-associated fibroblasts. Nature reviews Cancer 20, 174–186. [PubMed: 31980749]

Sanchez CG, Ma CX, Crowder RJ, Guintoli T, Phommaly C, Gao F, Lin L, and Ellis MJ (2011). Preclinical modeling of combined phosphatidylinositol-3-kinase inhibition with endocrine therapy for estrogen receptor-positive breast cancer. Breast Cancer Res 13, R21. [PubMed: 21362200]

Sansone P, Berishaj M, Rajasekhar VK, Ceccarelli C, Chang Q, Strillacci A, Savini C, Shapiro L, Bowman RL, Mastroleo C, et al. (2017a). Evolution of Cancer Stem-like Cells in Endocrine-Resistant Metastatic Breast Cancers Is Mediated by Stromal Microvesicles. Cancer Res 77, 1927–1941. [PubMed: 28202520]

Sansone P, Ceccarelli C, Berishaj M, Chang Q, Rajasekhar VK, Perna F, Bowman RL, Vidone M, Daly L, Nnoli J, et al. (2016). Self-renewal of CD133(hi) cells by IL6/Notch3 signalling regulates endocrine resistance in metastatic breast cancer. Nat Commun 7, 10442. [PubMed: 26858125]

Sansone P, Savini C, Kurelac I, Chang Q, Amato LB, Strillacci A, Stepanova A, Iommarini L, Mastroleo C, Daly L, et al. (2017b). Packaging and transfer of mitochondrial DNA via exosomes regulate escape from dormancy in hormonal therapy-resistant breast cancer. Proc Natl Acad Sci U S A 114, E9066–E9075. [PubMed: 29073103]

Schiavon G, Hrebien S, Garcia-Murillas I, Cutts RJ, Pearson A, Tarazona N, Fenwick K, Kozarewa I, Lopez-Knowles E, Ribas R, et al. (2015). Analysis of ESR1 mutation in circulating tumor DNA demonstrates evolution during therapy for metastatic breast cancer. Sci Transl Med 7, 313ra182.

Shi H, Hugo W, Kong X, Hong A, Koya RC, Moriceau G, Chodon T, Guo R, Johnson DB, Dahlman KB, et al. (2014). Acquired resistance and clonal evolution in melanoma during BRAF inhibitor therapy. Cancer discovery 4, 80–93. [PubMed: 24265155]

Shiino S, Kinoshita T, Yoshida M, Jimbo K, Asaga S, Takayama S, and Tsuda H (2016). Prognostic Impact of Discordance in Hormone Receptor Status Between Primary and Recurrent Sites in Patients With Recurrent Breast Cancer. Clin Breast Cancer 16, e133–140. [PubMed: 27268749]

Shomali M, Cheng J, Koundinya M, Weinstein M, Malkova N, Sun F, Hebert A, Cindachao M, Hoffman D, McManus J, et al. (2017). Abstract P3-04-05: Identification of SAR439859, an orally bioavailable selective estrogen receptor degrader (SERD) that has strong antitumor activity in wild-type and mutant ER+ breast cancer models. Cancer Research 77, P3-04-05.

Siegel RL, Miller KD, and Jemal A (2020). Cancer statistics, 2020. CA Cancer J Clin 70, 7–30. [PubMed: 31912902]

Sikora MJ, Cooper KL, Bahreini A, Luthra S, Wang G, Chandran UR, Davidson NE, Dabbs DJ, Welm AL, and Oesterreich S (2014). Invasive lobular carcinoma cell lines are characterized by unique estrogen-mediated gene expression patterns and altered tamoxifen response. Cancer Res 74, 1463–1474. [PubMed: 24425047]

Sikora MJ, Jacobsen BM, Levine K, Chen J, Davidson NE, Lee AV, Alexander CM, and Oesterreich S (2016). WNT4 mediates estrogen receptor signaling and endocrine resistance in invasive lobular carcinoma cell lines. Breast Cancer Res 18, 92. [PubMed: 27650553]

Simoes BM, O'Brien CS, Eyre R, Silva A, Yu L, Sarmiento-Castro A, Alferez DG, Spence K, Santiago-Gomez A, Chemi F, et al. (2015). Anti-estrogen Resistance in Human Breast Tumors Is Driven by JAG1-NOTCH4-Dependent Cancer Stem Cell Activity. Cell reports 12, 1968–1977. [PubMed: 26387946]

Smyth LM, Piha-Paul SA, Won HH, Schram AM, Saura C, Loi S, Lu J, Shapiro GI, Juric D, Mayer IA, et al. (2020). Efficacy and Determinants of Response to HER Kinase Inhibition in HER2-Mutant Metastatic Breast Cancer. Cancer discovery 10, 198–213. [PubMed: 31806627]

Sokol ES, Feng YX, Jin DX, Basudan A, Lee AV, Atkinson JM, Chen J, Stephens PJ, Frampton GM, Gupta PB, et al. (2019). Loss of function of NF1 is a mechanism of acquired resistance to endocrine therapy in lobular breast cancer. Ann Oncol 30, 115–123. [PubMed: 30423024]

Soon PS, Kim E, Pon CK, Gill AJ, Moore K, Spillane AJ, Benn DE, and Baxter RC (2013). Breast cancer-associated fibroblasts induce epithelial-to-mesenchymal transition in breast cancer cells. Endocr Relat Cancer 20, 1–12. [PubMed: 23111755]

Stender JD, Nwachukwu JC, Kastrati I, Kim Y, Strid T, Yakir M, Srinivasan S, Nowak J, Izard T, Rangarajan ES, et al. (2017). Structural and Molecular Mechanisms of Cytokine-Mediated Endocrine Resistance in Human Breast Cancer Cells. Mol Cell 65, 1122–1135 e1125. [PubMed: 28306507]

Stone A, Zotenko E, Locke WJ, Korbie D, Millar EK, Pidsley R, Stirzaker C, Graham P, Trau M, Musgrove EA, et al. (2015). DNA methylation of oestrogen-regulated enhancers defines endocrine sensitivity in breast cancer. Nat Commun 6, 7758. [PubMed: 26169690]

Sullivan RJ, Infante JR, Janku F, Wong DJL, Sosman JA, Keedy V, Patel MR, Shapiro GI, Mier JW, Tolcher AW, et al. (2018). First-in-Class ERK1/2 Inhibitor Ulixertinib (BVD-523) in Patients with MAPK Mutant Advanced Solid Tumors: Results of a Phase I Dose-Escalation and Expansion Study. Cancer discovery 8, 184–195. [PubMed: 29247021]

Toska E, Osmanbeyoglu HU, Castel P, Chan C, Hendrickson RC, Elkabets M, Dickler MN, Scaltriti M, Leslie CS, Armstrong SA, and Baselga J (2017). PI3K pathway regulates ER-dependent transcription in breast cancer through the epigenetic regulator KMT2D. Science 355, 1324–1330. [PubMed: 28336670]

Toy W, Shen Y, Won H, Green B, Sakr RA, Will M, Li Z, Gala K, Fanning S, King TA, et al. (2013). ESR1 ligand-binding domain mutations in hormone-resistant breast cancer. Nat Genet 45, 1439–1445. [PubMed: 24185512]

Toy W, Weir H, Razavi P, Lawson M, Goeppert AU, Mazzola AM, Smith A, Wilson J, Morrow C, Wong WL, et al. (2017). Activating ESR1 Mutations Differentially Affect the Efficacy of ER Antagonists. Cancer discovery 7, 277–287. [PubMed: 27986707]

Tria GS, Abrams T, Baird J, Burks HE, Firestone B, Gaither LA, Hamann LG, He G, Kirby CA, Kim S, et al. (2018). Discovery of LSZ102, a Potent, Orally Bioavailable Selective Estrogen Receptor Degrader (SERD) for the Treatment of Estrogen Receptor Positive Breast Cancer. Journal of medicinal chemistry 61, 2837–2864. [PubMed: 29562737]

Turner N, Kingston B, Kilburn L, Kernaghan S, Wardley AM, Macpherson I, Baird RD, Roylance R, Stephens P, Oikonomidou O, et al. (2020). Abstract GS3–06: Results from the plasmaMATCH trial: A multiple parallel cohort, multi-centre clinical trial of circulating tumour DNA testing to direct targeted therapies in patients with advanced breast cancer (CRUK/15/010). Cancer Research 80, GS3–06.

Turner N, Pearson A, Sharpe R, Lambros M, Geyer F, Lopez-Garcia MA, Natrajan R, Marchio C, Iorns E, Mackay A, et al. (2010). FGFR1 amplification drives endocrine therapy resistance and is a therapeutic target in breast cancer. Cancer Res 70, 2085–2094. [PubMed: 20179196]

Turner NC, Ro J, André F, Loi S, Verma S, Iwata H, Harbeck N, Loibl S, Huang Bartlett C, Zhang K, et al. (2015). Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. The New England journal of medicine 373, 209–219. [PubMed: 26030518]

Vasan N, Baselga J, and Hyman DM (2019). A view on drug resistance in cancer. Nature 575, 299–309. [PubMed: 31723286]

Wang Y, Shi Z, Jiang Y, and Dai X (2018). Abstract 5776: Pharmacologic and PK/PD study of D-0502: An orally bioavailable SERD with potent antitumor activity in ER-positive breast cancer cell lines and xenograft models. Cancer Research 78, 5776.

Wardell SE, Ellis MJ, Alley HM, Eisele K, VanArsdale T, Dann SG, Arndt KT, Primeau T, Griffin E, Shao J, et al. (2015a). Efficacy of SERD/SERM Hybrid-CDK4/6 Inhibitor Combinations in Models of Endocrine Therapy-Resistant Breast Cancer. Clin Cancer Res 21, 5121–5130. [PubMed: 25991817]

Wardell SE, Marks JR, and McDonnell DP (2011). The turnover of estrogen receptor alpha by the selective estrogen receptor degrader (SERD) fulvestrant is a saturable process that is not required for antagonist efficacy. Biochem Pharmacol 82, 122–130. [PubMed: 21501600]

Wardell SE, Nelson ER, Chao CA, Alley HM, and McDonnell DP (2015b). Evaluation of the pharmacological activities of RAD1901, a selective estrogen receptor degrader. Endocr Relat Cancer 22, 713–724. [PubMed: 26162914]

Wardell SE, Yllanes AP, Baker JG, Baldi RM, Krebs TK, Sorrentino J, Bisi J, Strum J, and Norris JD (2017). Abstract 5641: Effects of G1T48, a novel orally bioavailable selective estrogen receptor degrader (SERD), and the CDK4/6 inhibitor, G1T38, on tumor growth in animal models of endocrine resistant breast cancer. Cancer Research 77, 5641.

Weir HM, Bradbury RH, Lawson M, Rabow AA, Buttar D, Callis RJ, Curwen JO, de Almeida C, Ballard P, Hulse M, et al. (2016). AZD9496: An Oral Estrogen Receptor Inhibitor That Blocks the Growth of ER-Positive and ESR1-Mutant Breast Tumors in Preclinical Models. Cancer Res 76, 3307–3318. [PubMed: 27020862]

Wittmann BM, Sherk A, and McDonnell DP (2007). Definition of functionally important mechanistic differences among selective estrogen receptor down-regulators. Cancer Res 67, 9549–9560. [PubMed: 17909066]

Xiao T, Li W, Wang X, Xu H, Yang J, Wu Q, Huang Y, Geradts J, Jiang P, Fei T, et al. (2018). Estrogen-regulated feedback loop limits the efficacy of estrogen receptor-targeted breast cancer therapy. Proc Natl Acad Sci U S A 115, 7869–7878. [PubMed: 29987050]

Xu G, Chhangawala S, Cocco E, Razavi P, Cai Y, Otto JE, Ferrando L, Selenica P, Ladewig E, Chan C, et al. (2020). ARID1A determines luminal identity and therapeutic response in estrogen-receptor-positive breast cancer. Nat Genet 52, 198–207. [PubMed: 31932695]

Yamamoto S, Wu Z, Russnes HG, Takagi S, Peluffo G, Vaske C, Zhao X, Moen Vollan HK, Maruyama R, Ekram MB, et al. (2014). JARID1B is a luminal lineage-driving oncogene in breast cancer. Cancer Cell 25, 762–777. [PubMed: 24937458]

Yang J, AlTahan A, Jones DT, Buffa FM, Bridges E, Interiano RB, Qu C, Vogt N, Li JL, Baban D, et al. (2015). Estrogen receptor-alpha directly regulates the hypoxia-inducible factor 1 pathway associated with antiestrogen response in breast cancer. Proc Natl Acad Sci U S A 112, 15172–15177. [PubMed: 26598706]

Zhang QX, Borg A, Wolf DM, Oesterreich S, and Fuqua SA (1997). An estrogen receptor mutant with strong hormone-independent activity from a metastatic breast cancer. Cancer Res 57, 1244–1249. [PubMed: 9102207]

Zhang XH, Giuliano M, Trivedi MV, Schiff R, and Osborne CK (2013). Metastasis dormancy in estrogen receptor-positive breast cancer. Clin Cancer Res 19, 6389–6397. [PubMed: 24298069]

Zinger L, Merenbakh-Lamin K, Klein A, Elazar A, Journo S, Boldes T, Pasmanik-Chor M, Spitzer A, Rubinek T, and Wolf I (2019). Ligand-binding Domain-activating Mutations of ESR1 Rewire Cellular Metabolism of Breast Cancer Cells. Clin Cancer Res 25, 2900–2914. [PubMed: 30733228]

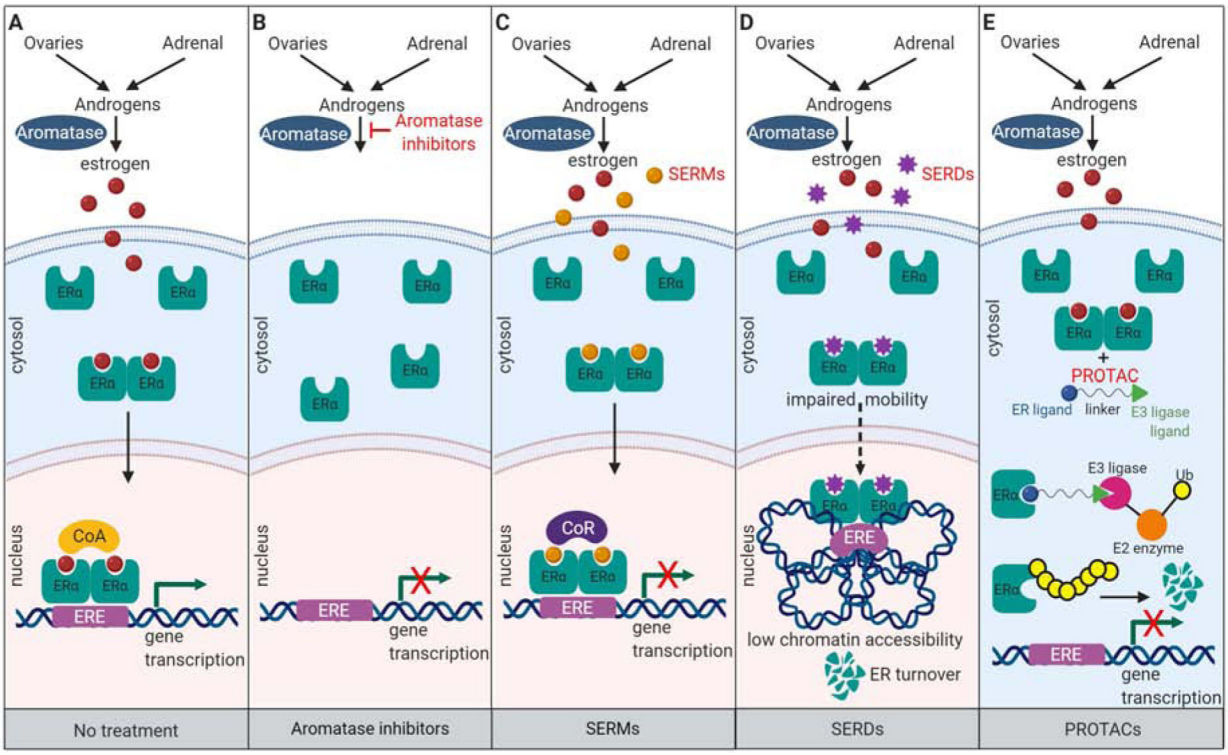

Figure 1:

Mechanism of action of endocrine therapies. (A) Ovaries, adrenal glands, adipose tissue, breast, and other tissues produce androgens which are converted to estrogens by aromatase. Upon binding to estrogen, the estrogen receptor (ER) dimerizes and translocates to the nucleus, where ER dimers bind coactivators (CoA) to form a transcriptionally active ER complex. (B) Non-steroidal, reversible aromatase inhibitors (AI) such as letrozole or anastrozole, or steroidal, irreversible AIs such as exemestane, block estrogen production by inhibiting the aromatization of androgens to estrogens. (C) Selective estrogen receptor modulators (SERMs) such as tamoxifen and raloxifene competitively inhibit the binding of estrogen to ER. SERM-bound ER dimers interact with the chromatin at estrogen response elements (ERE). However, SERM-bound ER dimers associate with co-repressors (CoR), which inhibit ER transcriptional activity in the breast. (D) Selective estrogen receptor downregulators (SERDs) such as fulvestrant are considered to be pure ER-antagonists. The inhibitory effect of SERDs was recently attributed to reduced ability of SERD-bound ER to translocate to the nucleus. Further, the ER-SERD complex is unable to establish an open chromatin conformation to facilitate transcription of ER-regulated genes. SERD-bound ER undergoes degradation as a consequence of impaired mobility. (E) Proteolysis targeting chimeras (PROTACs) are heterobifunctional molecules that consist of a ligand for ER and another ligand which serves as a substrate for the E3 ubiquitin ligase complex. Upon binding to ER, PROTACs recruit the E3 ubiquitin ligase complex which polyubiquitilate ER and mark it for proteasomal degradation.

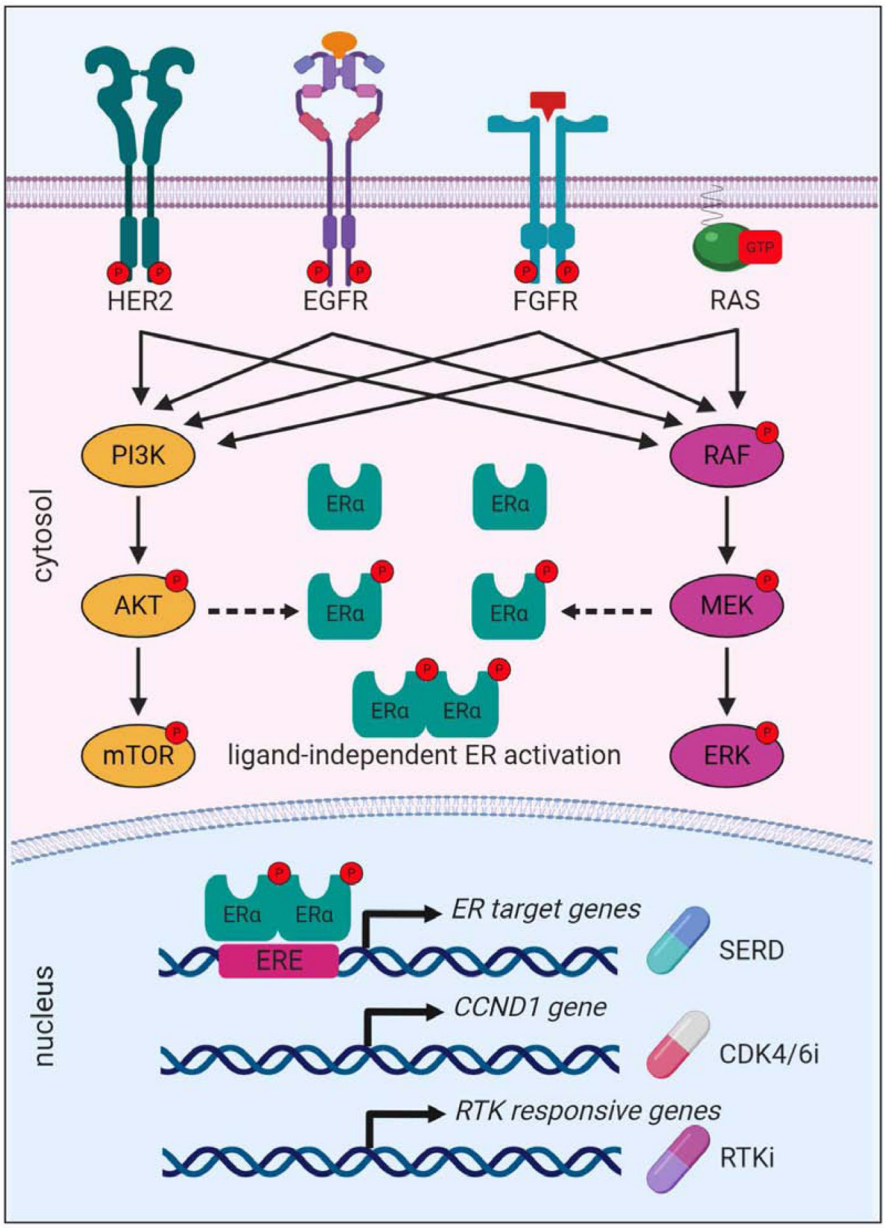

Figure 2:

Activation of HER2, EGFR, FGFR, and other RTKs promotes endocrine resistance. Aberrant activation of RTKs (most commonly by mutation or amplification) augment PI3K and MAPK signaling, which induce ER phosphorylation and promote ligand-independent ER activation. Loss-of-function mutations in *NF1* constitutively activates Ras, which can further activate PI3K and MAPK pathways. Phosphorylation of ER promotes transcription of ER-regulated genes in a ligand-independent manner. *CCND1*, the gene encoding for cyclin D1, is a major target of both ER and oncogenic RTK signaling. In addition to ER, RTKs activate other transcription factors that promote ER-independent survival. RTK-mediated endocrine resistance could be potentially overcome by the combination of an ER antagonist and corresponding RTK inhibitor ± CDK4/6 inhibitor.

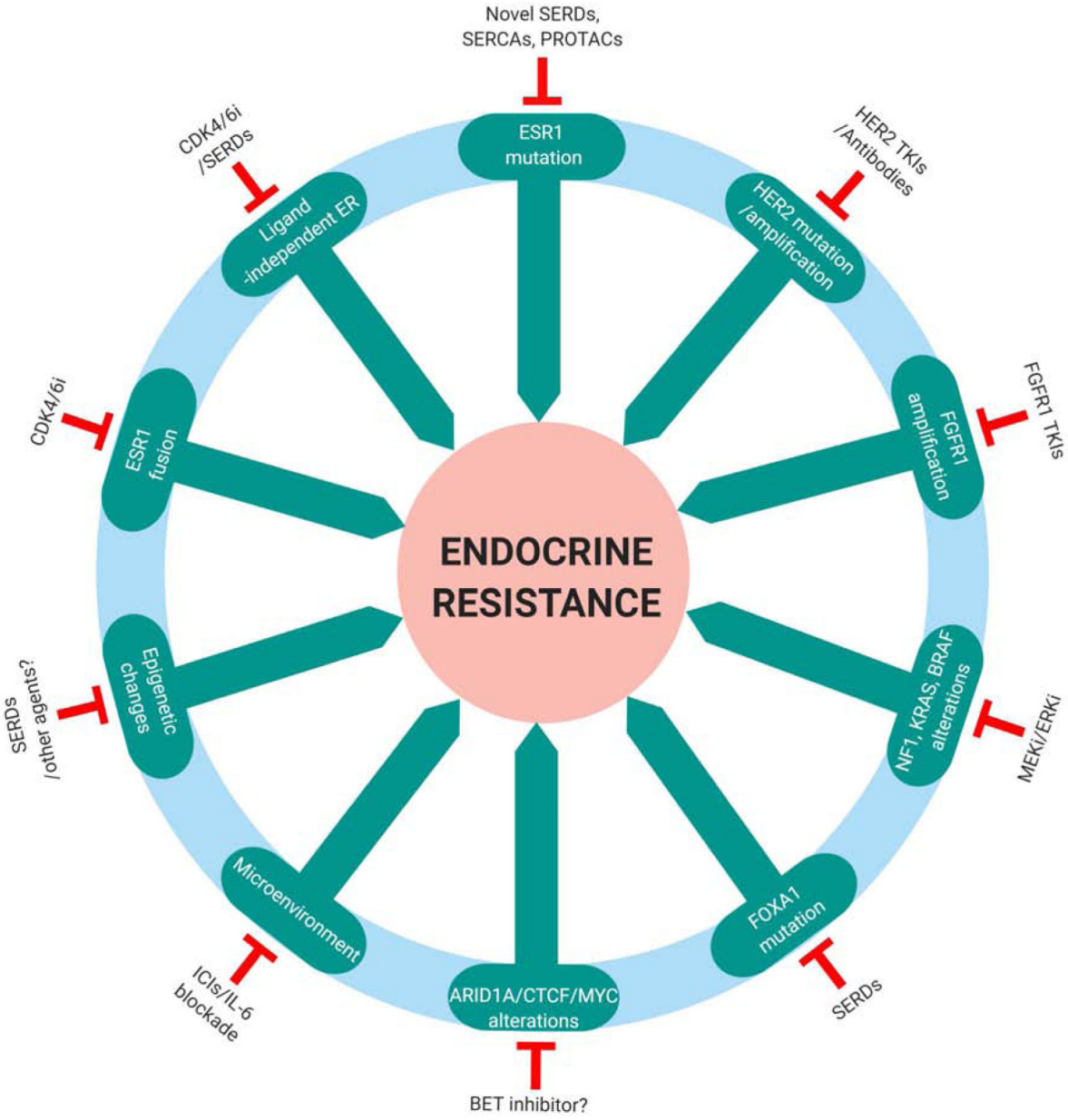

Figure 3:

Mechanisms of endocrine resistance and potential therapeutic strategies to combat resistance. SERD, selective estrogen receptor downregulator; SERCA, selective estrogen receptor covalent antagonist; PROTAC, proteolysis targeting chimera; TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor

Table 1.

Somatic alterations associated with endocrine resistance

Gene	Alteration	Frequency in primary (%)	Frequency in metastatic (%)	Sufficient to drive endocrine resistance? (preclinical)	Clinical association	Targeted therapies	Stage of development
ESR1	Mutation	1.8	16.3	Yes (Jeselsohn et al., 2014; Toy et al., 2013)	Yes (Jeselsohn et al., 2014; O'Leary et al., 2018; Toy et al., 2013)	Next-generation SERMs, SERDs, PROTACs; CDK7 inhibitor	Phase I-approved
ESR1	Fusion *	Very rare	>1 (Hartmaier et al., 2018)	Yes (Hartmaier et al., 2018; Lei et al., 2018)	Yes (Hartmaier et al., 2018; Lei et al., 2018)	CDK4/6 inhibitor	Approved
ERBB2 (HER2)	Amplification	0.8	2.1	Yes (tamoxifen) (Benz et al., 1992)	Yes (Johnston et al., 2009; Kaufman et al., 2009)	HER2-targeting antibodies or antibody-drug conjugates	Approved
ERBB2 (HER2)	Mutation	2.4	6.7	Yes (Croessmann et al., 2019; Nayar et al., 2019)	Yes (Croessmann et al., 2019; Nayar et al., 2019; Razavi et al., 2018; Smyth et al., 2020)	HER2 TKIs	Phase II (HER2-mutant)
EGFR	Amplification	0.7	1.4	Yes (Razavi et al., 2018)	Yes (Razavi et al., 2018)	EGFR antibodies or TKIs	Approved (other cancer types)
FGFR1	Amplification	10.2	14.9	Yes (Formisano et al., 2019; Turner et al., 2010)	Yes (Giltnane et al., 2017)	FGFR TKIs	Phase II
PIK3CA	Mutation	43.7	38.1	ND	Yes (Andre et al., 2019)	PI3Ka inhibitor; mTOR inhibitor	Approved
PTEN	Mutation/deletion	9.3	9.6	Yes (PTEN knockdown) (Fu et al., 2014)	ND	AKT inhibitor	Phase III (TNBC)
AKT1	Mutation	5.5	6.6	No (Lauring et al., 2010)	Yes (Turner et al., 2020)	AKT inhibitor; mTOR inhibitor	Phase III (TNBC); approved
NF1	Mutation/deletion	2.7	6.4	Yes (NF1 knockdown) (Pearson et al., 2020; Razavi et al., 2018; Sokol et al., 2019)	Yes (Griffith et al., 2018; Pearson et al., 2020; Razavi et al., 2018; Sokol et al., 2019)	MEK or ERK inhibitor; CDK4/6 inhibitor	Phase II-approved
KRAS	Mutation	0.3	0.9	ND	Yes (Fribbens et al., 2018; Razavi et al., 2018)	KRAS inhibitor or PROTAC	Preclinical
BRAF	Mutation	0.7	0.5	ND	Yes (Razavi et al., 2018)	BRAF+MEK inhibitor	Approved (other cancer types)
MAP2K1	Mutation	0.5	0.2	ND	Yes (Razavi et al., 2018)	MEK inhibitor	Approved (other cancer types)
MYC	Amplification	4.7	8.7	ND	Yes (Miller et al., 2011b; Razavi et al., 2018)	Myc inhibitor; BET/BRD4 inhibitor	Preclinical-Phase II
FOXA1	Mutation	3.3	5	ND	Yes (Razavi et al., 2018)	SERDs	Approved

Gene	Alteration	Frequency in primary (%)	Frequency in metastatic (%)	Sufficient to drive endocrine resistance? (preclinical)	Clinical association	Targeted therapies	Stage of development
CTCF	Mutation	1.5	2.3	ND	Yes (Razavi et al., 2018)	BET/BRD4 inhibitor?	Phase II
ARID1A	Mutation/deletion	4.6	7.1	Yes (Nagarajan et al., 2020; Xu et al., 2020)	Yes (Razavi et al., 2018; Xu et al., 2020)	BET/BRD4 inhibitor	Phase II
ARID2	Mutation/deletion	0.5	3.8	ND	Yes (Razavi et al., 2018)	BET/BRD4 inhibitor?	Phase II

Select somatic alterations associated with endocrine resistance are shown. Unless otherwise indicated, frequencies in primary (n=615) and metastatic (n=564) ER^+/HER2− breast cancers were retrieved from www.cBioPortal.org (selected study: MSK, Cancer Cell 2018). ER^+/HER2− status was based on the primary tumor. Preclinical evidence for sufficiency includes overexpression (for amplification), knockdown (for gene deletion/loss-of-function mutations), or ectopic or knock-in expression of gene mutations being sufficient to drive increased growth under estrogen deprivation, tamoxifen treatment, or fulvestrant treatment. Clinical association includes 1) acquired alterations following treatment with tamoxifen, AIs, or fulvestrant in matched patient samples; 2) alteration is associated with poor response to endocrine therapy in clinical studies; or 3) evidence that targeting the alteration restores endocrine sensitivity in clinical trials.

[*] *ESR1* fusions were not reported in the MSK study

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Table 2.

Next-generation ER-targeting agents in clinical trials

Drug	Type of inhibitor	Source	Stage of Development	Clinical Trial Identifier (ER + MBC)	References
Bazedoxifene	SERM/SERD hybrid (oral)	Pfizer	Approved (osteoporosis)	NCT02448771	(Fanning et al., 2018; Komm et al., 2005; Wardell et al., 2015a)
Lasofoxifene	SERM (oral)	Sermonix	Phase III (osteoporosis)	NCT03781063	(Laine et al., 2019; Rosati et al., 1998)
Elacestrant (RAD1901)	SERM/SERD hybrid (oral)	Radius Health	Phase III	NCT03778931	(Bihani et al., 2017; Garner et al., 2015; Kaklamani et al., 2020; Wardell et al., 2015b)
SAR439859	SERD (oral)	Sanofi	Phase II	NCT04059484; NCT03284957 (with palbociclib)	(El-Ahmad et al., 2020; Shomali et al., 2017)
Rintodestrant (G1T48)	SERD (oral)	G1 Therapeutics	Phase I/II	NCT03455270	(Andreano et al., 2020; Dees et al., 2019; Wardell et al., 2017)
LSZ102	SERD (oral)		Phase I	NCT02734615 (single agent or with ribociclib or alpelisib)	(Jhaveri et al., 2019; Juric et al., 2018; Tria et al., 2018)
GDC-9545	SERD (oral)	Genentech	Phase I	NCT03332797	(Jhaveri et al., 2020)
AZD9496	SERD (oral)	Astra Zeneca	Phase I	NCT03236974	(De Savi et al., 2015; Hamilton et al., 2018; Weir et al., 2016)
ZN-c5	SERD (oral)	Zeno Alpha	Phase I/II	NCT03560531	
D-0502	SERD (oral)	InventisBio	Phase I	NCT03471663	(Wang et al., 2018)
SHR9549	SERD (oral)	Jiangsu Hengrui Medicine	Phase I	NCT03596658	
LY3484356	SERD (oral)	Eli Lilly	Phase I	NCT04188548	
H3B-6545	Selective estrogen receptor covalent antagonist (SERCA; oral)	H3 Biomedicine	Phase I/II	NCT03250676	(Puyang et al., 2018)
ARV-471	PROTAC (oral)	Arvinas	Phase I	NCT04072952	(Flanagan et al., 2019)

Next-generation ER-targeting agents currently in clinical trials for advanced/metastatic ER^+ breast cancer (www.ClinicalTrials.gov).