

Endocrine-Resistant Breast Cancer: Mechanisms and Treatment

Andreas D. Hartkopf Eva-Maria Grischke Sara Y. Brucker

Department of Women's Health, University of Tübingen, Tübingen, Germany

Keywords

Breast cancer · Endocrine resistance · Endocrine treatment · Metastases

Abstract

Background: Endocrine treatment is one of the most effective therapies for estrogen receptor-positive breast cancer. However, most tumors will develop resistance to endocrine therapy as the cancer progresses. This review focuses on the mechanisms and markers of endocrine-resistant breast cancer. In addition, current and future strategies to overcome endocrine resistance are discussed. **Summary:** Several molecular mechanisms of endocrine resistance have been identified, including alterations in the ESR1 gene or in the PIK3CA/mTOR pathway. Meanwhile, CDK4/6, mTOR, and PI3K inhibition have shown to improve the efficacy of endocrine treatment and new promising approaches are being developed. **Key Message:** Overcoming primary or acquired resistance to endocrine treatment remains a major challenge. Since the molecular mechanisms of endocrine resistance are manifold, optimal combination and sequencing strategies will have to be developed in the future.

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Introduction

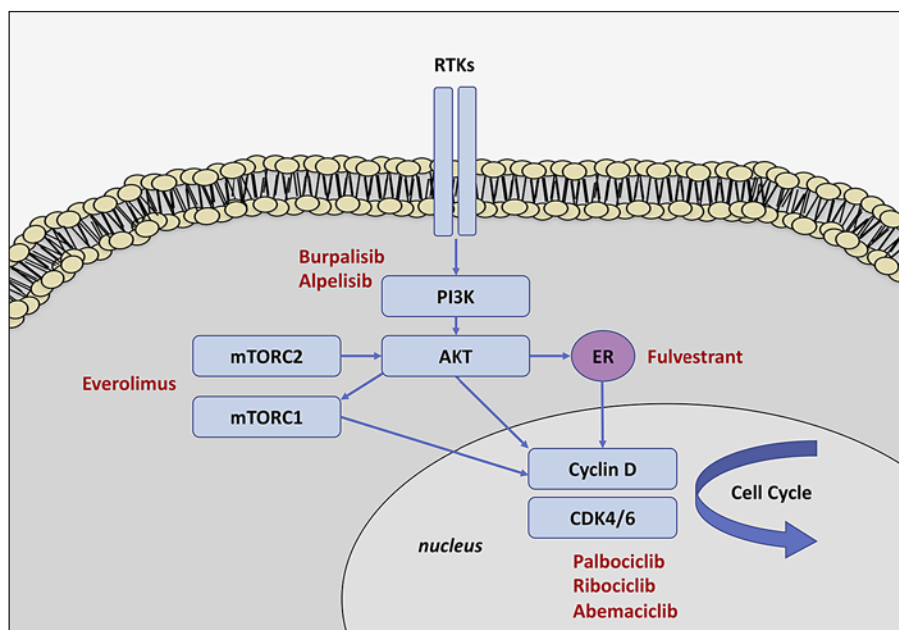
Breast cancer is the most common cancer disease among women. Approximately 70% of all tumors express the estrogen receptor (ER), a transcription factor that is activated by estrogen binding and that regulates the ex-

pression of various genes involved in tumor formation [1–3]. Two isoforms exist: ER α , which is predominantly expressed in breast cancer and the main target of endocrine therapies, and ER β , which seems to have an opposite effect to ER α and inhibits estrogen-dependent cell proliferation [3, 4]. Since the roles of ER α are well recognized in breast cancer, in this review, it will be referred as ER.

Endocrine therapy is one of the most effective treatment options for ER-positive breast cancer. In the metastatic setting, it is the therapy of choice, except in cases of immediately life-threatening disease, i.e., a visceral crisis [5, 6]. Classical endocrine therapies modulate the estrogen effect by blocking the ER (selective ER modulators, SERMs) or aim to reduce estrogen levels (e.g., the aromatase inhibitors [AIs] letrozole, anastrozole, and exemestane) [7]. Whereas SERMs, like tamoxifen, are effective in both premenopausal and postmenopausal women, AIs should only be used in the postmenopausal situation. For the use of AIs in premenopausal women, ovarian suppression must be performed, which today is usually induced by the administration of GnRH analogues.

A major challenge in treating ER-positive breast cancer is to overcome endocrine resistance [8]. Primary endocrine resistance is defined as a relapse within 2 years of adjuvant endocrine treatment or disease progression during the first 6 months of first-line endocrine therapy for advanced or metastatic breast cancer (MBC). Secondary resistance is defined in early breast cancer as a relapse that occurs after at least 2 years of endocrine therapy and during or within the first year of completing adjuvant endocrine therapy. In advanced breast cancer or MBC, sec-

Fig. 1. Simplified presentation of phosphoinositide 3-kinase (PI3K)/AKT/mTOR signaling in endocrine-resistant breast cancer. The PI3K/AKT pathway is activated by various receptor tyrosine kinases (RTKs). The mammalian target of rapamycin complex (mTORC) is an important downstream effector of PI3K/AKT. Activation of the PI3K/AKT/mTOR pathway promotes cell growth and proliferation. The estrogen receptor (ER) is a transcription factor that is activated by estrogen binding and that regulates various genes involved in tumor formation. Accumulation and binding of cyclin D to the cyclin-dependent kinases (CDK) 4 and 6 leads to cell cycle progression. Drugs to overcome endocrine resistance are displayed in red.



ondary resistance is defined as disease progression after more than 6 months of endocrine therapy [6].

This review aims to focus on mechanisms of and markers for endocrine resistance. We will moreover discuss current and future strategies to overcome endocrine resistance.

Mechanisms of Endocrine Resistance

Mechanisms of endocrine resistance include aberrations in the ER/PgR pathway (deregulation of ER expression, co-activators and co-repressors), genomic and epigenetic alterations of ESR1, expression of truncated ER-isoforms, post-translational modification, increased receptor tyrosine kinase signaling, and altered cell cycle regulation [9]. Moreover, genetic and/or epigenetic deregulations affect uptake, metabolism, and cellular responses of endocrine agents [10]. As efficacy of endocrine therapy relies on breast cancer cells that are dependent on ER activation for proliferation and differentiation, loss of the ER is one principal cause of de novo resistance to endocrine treatment [11, 12]. Several studies have shown that receptor expression may change during disease progression, and conversion from ER-positive to ER-negative breast cancer might occur in approximately 10–20% of the cases. This is why the ER status should be reevaluated from metastatic tissue whenever possible [6].

ESR1 Mutations

Mutations of the ESR1 gene, encoding for ER, are rare in primary breast cancer but have high prevalence (20–

40%) in patients with MBC who have previously received endocrine treatment [13–16]. Most mutations (D538G, Y537S, Y537N, Y537C, and E380) occur at hot spots in the ligand-binding domain of ER α resulting in constitutive ER activity [17, 18]. Analysis of circulating tumor DNA (ctDNA) from MBC patients of the BOLERO-2 trial (exemestane versus exemestane plus everolimus) revealed that the Y537S and D538G mutations are associated with a more aggressive disease biology [14]. Moreover, while the D538G mutation was associated with shorter progression-free survival (PFS) in patients treated with exemestane only, both the wild-type and mutant groups benefited from the addition of everolimus. Similarly, ctDNA analysis of plasma samples from MBC patients of the SoFEA (fulvestrant plus anastrozole versus fulvestrant versus exemestane) trial have shown that the detection of ESR1 mutations predicts resistance to exemestane while sensitivity to the selective estrogen receptor degrader (SERD) fulvestrant is partially maintained [19]. It must, however, be noted that ESR1 mutations also inhibit fulvestrant binding and that patients with ESR1 mutant cancers also had reduced PFS rates when treated with fulvestrant as compared to patients with wild-type tumors. Findings of these retrospective ctDNA investigations from prospective clinical trials indicate that ESR1 mutations can be acquired during endocrine therapy and may be used to monitor endocrine-resistant tumor cell clones and to guide endocrine treatment decisions.

Receptor Tyrosine Kinases

Receptor tyrosine kinases (RTKs) are a family of cell membrane-bound receptors whose intracellular do-

main contains a tyrosine kinase that phosphorylates tyrosine residues of target proteins [20]. RTKs (e.g., epidermal growth factor receptor [EGFR/ErbB family], insulin-like growth factor receptors [IGFR], vascular endothelial growth factor receptors [VEGFR], and fibroblast growth factor receptors [FGFR]) are activated upon ligand binding, which are mainly growth factors, cytokines, or hormones, and their activation/overexpression is associated with endocrine resistance [21–24]. Upon binding, intracellular signal transduction pathways are initiated, which include the mitogen activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/AKT pathways (Fig. 1) [2]. These pathways can activate the transcriptional activity of ER in the absence of estrogen signaling [25]. Additionally, RTKs can reduce estrogen dependence by decreasing the expression of ER [26].

PI3K/AKT signaling plays an important role in many cellular processes that regulate growth, survival, motility, and metabolism [27]. PI3Ks are a family of kinases necessary for normal cell growth and proliferation [28]. Mammalian class 1A PI3Ks are heterodimeric protein complexes and consist of a regulatory subunit (p85 α) and a catalytic subunit (p110) of which three isoforms exist: p110 α (encoded by PIK3CA), p110 β (encoded by PIK3CB) and p110 δ (encoded by PIK3CD). [29]. Somatic mutations in genes encoding for components of the PI3K/AKT occur in up to 70% of breast cancers and include mutations or amplification of the catalytic (p110) subunits of PI3K as well as mutations of PI3K modulators, such as the phosphatase and tensin homolog (PTEN), AKT, and mTOR [29, 30]. PIK3CA is mutated in up to 40% of human breast cancers and most alterations occur within the kinase (H1047R) and helical domains (E542K and E545K) of p110 α resulting in hyperactivation of PI3K [31, 32]. The prognostic impact of PI3CA mutations is still unclear: while in early ER-positive/HER2-negative breast cancer, an association with an increased disease-free survival has been reported, they seem to decrease prognosis in the advanced setting [33–35]. Importantly, the rate of PIK3CA mutations is not increased in MBC as compared to primary breast cancer and the concordance between matched primary and metastatic tissue samples is high [36]. An important downstream effector of the PI3K/AKT pathway is the mammalian target of rapamycin (mTOR) complex. [37]. The mTOR complex comprises two interdependent factors, mTORC1 and mTORC2, which are part of a positive feedback loop to the PI3K/AKT pathway. PI3K with subsequent AKT activation leads to increased mTORC1 kinase activity and promotes cell growth and proliferation. The tumor suppressor PTEN is a negative regulator of the mTOR loop and germline mutations of PTEN cause the PTEN hamartoma tumor syndrome, including the Cowden syn-

drome, which is associated with an increased risk of breast cancer [2, 38].

Cell Cycle Regulators

The cyclin D/cyclin-dependent kinases (CDK) 4/6/retinoblastoma (Rb) pathway controls cell cycle progression by regulating the G1-S checkpoint [39]. An important reason for the non-response or decreasing efficacy of endocrine therapy is the sustained activation of CDK4/6 [39]. The Rb is a tumor suppressor protein that prevents the cell from passing through the cell cycle from G1- to S-phase [40, 41]. Phosphorylation of Rb by the cyclin D1-CDK4/6 complex leads to its inactivation and allows the cell to enter into the cell cycle. Cyclin D1 amplification has been linked to tamoxifen resistance and occurs in 58% of luminal B cancers and 29% of luminal A breast cancers [13, 40, 42]. Additionally, *in vitro* data have shown activity of the CDK4/6 inhibitor palbociclib especially in ER-positive human breast cancer cell lines including those with estrogen resistance [43].

Strategies to Overcome Endocrine Resistance

Selective Estrogen Receptor Degraders

Many breast cancers being resistant to AI or tamoxifen treatment still depend on ER signaling [44]. SERDs destabilize the ER and, in contrast to SERMs, act as pure antagonists without any tissue tropism. Fulvestrant binds to the ER to block its dimerisation and nuclear localization. Moreover, as the fulvestrant-ER complex is unstable, its degradation is accelerated [45, 46]. Fulvestrant can bind to the ER even in the context of ESR1 mutations; however, higher doses are required to maintain clinical efficacy [19, 47].

In a preplanned combined analysis of two phase III trials, fulvestrant 250 mg every 4 weeks was compared to anastrozole (1 mg/day) in postmenopausal women who experienced progression after prior endocrine therapy [48]. No differences with respect to the median time to progression were found, which was 5.5 months in the fulvestrant group and 4.1 months in the anastrozole group. The same dose of fulvestrant was used in the phase III SoFEA trial that compared fulvestrant + AI versus fulvestrant versus AI. Again, no differences with respect to PFS, which was 4.4 months, 4.7 months, and 3.4 months, respectively, were found [49]. Interestingly, a retrospective analysis of the ESR1 mutation status in archival plasma ctDNA revealed that PFS was improved in patients with ESR1 mutant tumors receiving fulvestrant as compared to AI [19].

The phase III CONFIRM trial compared an increased dose of 500 mg fulvestrant (every 4 weeks) to 250 mg in patients who had previously progressed after receiving

endocrine treatment. The higher dose was associated with an improved PFS (hazard ratio [HR]: 0.80; 95% confidence interval [CI], 0.68–0.94; $p = 0.006$) and overall survival (OS) of 26.4 versus 22.3 months (HR: 0.81; 95% CI: 0.69–0.96; $p = 0.02$) [50, 51]. The phase II FIRST study confirmed these findings by comparing the higher 500 mg dose of fulvestrant with anastrozole. In this trial, however, the study population comprised of patients that had not received any endocrine treatment for MBC [52]. Patients treated with fulvestrant, had a significantly prolonged PFS (23.4 months vs. 13.1 months; HR: 0.66; 95% CI: 0.47–0.92; $p = 0.01$) and also seemed to have an increased OS. [53]. However, analysis of OS was not preplanned and not all patients participated in the additional follow-up [54].

The phase III FALCON trial randomly assigned patients to receive either anastrozole or fulvestrant (500 mg) as first-line treatment for hormone receptor (HR)-positive/HER2-negative MBC. Fulvestrant significantly improved PFS from 13.8 to 16.6 months (HR: 0.80; 95% CI: 0.64–1.00; $p = 0.486$) [55]. Due to the encouraging OS results of the FIRST study, long-term results of FALCON are eagerly awaited [56].

Inhibitors of the PI3K/AKT/mTOR Pathway

Several clinical trials have evaluated the combination of endocrine therapies with inhibitors of the PI3K/AKT/mTOR pathway to overcome endocrine resistance. In a neoadjuvant trial, adding the mTOR inhibitor RAD001 (everolimus) to letrozole resulted in reduced tumor cell proliferation and enhanced clinical efficacy to endocrine treatment [57]. The phase II TAMRAD trial investigated the efficacy of everolimus in combination with tamoxifen in patients with endocrine-resistant MBC. Everolimus increased PFS from 4.5 to 8.6 months (HR: 0.54; 95% CI: 0.36–0.81) and also prolonged OS (HR: 0.45; 95% CI: 0.24–0.81); however, the trial was not powered for OS analysis. The efficacy of everolimus was especially pronounced in patients with secondary as compared to primary endocrine resistance.

The phase III BOLERO-2 study compared everolimus and exemestane versus exemestane and placebo in patients with advanced HR-positive/HER2-negative breast cancer who suffered from disease recurrence or progression after/while receiving a nonsteroidal AI [58]. PFS was significantly longer with everolimus plus exemestane (7.8 versus 3.2 months; HR: 0.45; 95% CI: 0.38–0.54; $p < 0.001$) [59]. There was no statistically significant improvement in OS; however, the trial was not powered for this endpoint [59, 60]. Analysis of archival tumor tissue revealed that the efficacy of everolimus was independent from the PI3K mutational status while a potential lack of benefit was shown in patients with a Y537S mutation in the ESR1 gene as detected by ctDNA analysis [14, 61].

Buparlisib is a pan-PI3K inhibitor that targets each of the four catalytic isoforms of class I PI3Ks. The phase III BELLE-2 trial randomized HR-positive/HER2-negative MBC patients who had previously progressed under treatment with an AI to receive either fulvestrant alone or in combination with buparlisib. Buparlisib significantly increased PFS in the overall population (5.0 versus 6.9 months; HR: 0.78; 95% CI: 0.67–0.89; $p < 0.001$). In patients with PI3KCA mutations, as detected by ctDNA analysis, PFS was 3.2 versus 7.0 months (HR: 0.56; 95% CI: 0.39–0.80; $p < 0.001$). In the subsequent phase III BELLE-3 trial, which included HR-positive/HER2-negative MBC patients who had previously received endocrine therapy and an mTOR inhibitor, the addition of buparlisib to fulvestrant increased PFS from 1.8 to 3.9 months (HR: 0.67; 95% CI: 0.53–0.84; $p < 0.001$). Again, the PI3KCA mutational status, as assessed by analysis archival tumor tissue or plasma ctDNA, was predictive of efficacy.

Due to inactivation of different PI3K isoforms, various side effects can occur (e.g., hyperglycemia, rash, elevated liver enzymes, and mood disorders), resulting in low tolerability of buparlisib. The more specific PI3K inhibitor alpelisib, which selectively targets the p110 α isoform (encoded by PIK3CA), was evaluated in the clinical phase III SOLAR-1 study. HR-positive/HER2-negative patients with MBC who had been pretreated with endocrine therapy either received fulvestrant or a combination of fulvestrant and alpelisib. Again, hyperglycemia and rash were the two main adverse events that led to treatment discontinuation; however, safety profile was more favorable than with buparlisib. In patients with a PIK3CA mutated tumor, median PFS was 11.0 months in the alpelisib arm versus 5.7 months in the placebo group (HR: 0.65; 95% CI: 0.50–0.85; $p < 0.001$). In patients with wild-type PIK3CA tumors, alpelisib was not effective. Interestingly, patients with a PI3K mutation identified by ctDNA analysis seemed to have an even greater benefit of alpelisib as compared to the analysis of tumor tissue, which is in line with the results of a combined analysis from the BELLE-2 and BELLE-3 trials. Other PI3K inhibitors are talesilic, which was evaluated in the SANDPIPER trial, and pictilisib, assessed in the PEGGY and FERGY trials [62–64]. Because of modest PFS improvement at the cost of higher toxicities as compared to alpelisib, these compounds as well as buparlisib are currently not further developed for metastatic HR-positive/HER2-negative breast cancer.

CDK4/6 Inhibitors

Currently, three structurally similar selective CDK4/6 inhibitors are clinically used for the treatment of advanced ER-positive breast cancer: palbociclib (PD0332991), ribociclib (LEE011), and abemaciclib (LY2835219) [65]. All of these drugs show a similar im-

pressive activity in endocrine-naïve and endocrine-resistant breast cancer and are well tolerated. The most common side effect is neutropenia; nevertheless, febrile neutropenia is rare as compared to that induced by chemotherapy. As the risk of neutropenia is lower with abemaciclib, this is the only CDK4/6 inhibitor that is administered continuously, while palbociclib and ribociclib are used 3 weeks on, 1 week off.

In the phase II trial PALOMA-1, addition of palbociclib to letrozole increased median PF of HR-positive/HER2-negative MBC patients in the first-line setting from 10.2 to 20.2 months (HR: 0.49; 95% CI: 0.319–0.748; $p < 0.001$) [66]. These results were confirmed by the larger phase III trial, PALOMA-2 that yielded a median PFS of 14.5 versus 27.6 months (HR: 0.56; 95% CI: 0.46–0.72; $p < 0.001$) [67, 68]. Similarly, the phase III trial MONALEESA-2 revealed a median PFS of 16.0 months for letrozole alone as compared to 25.3 months for letrozole plus ribociclib (HR: 0.57; 95% CI 0.46–0.69; $p < 0.001$) [69, 70]. In MONALEESA-7, only premenopausal HR-positive/HER2-negative patients with MBC were included. All patients received the GnRH antagonist goserelin to induce ovarian function suppression. As alternative to treatment with an AI (letrozole or anastrozole) tamoxifen could be used. The addition of ribociclib to endocrine therapy yielded an increased PFS (13.0 vs. 28.8 months; HR: 0.55; 95% CI: 0.44–0.69; $p < 0.001$) and OS (HR: 0.71; 95% CI: 0.54–0.95; $p = 0.010$) [71, 72]. MONARCH-3 is a phase III trial that evaluated the combination of abemaciclib with anastrozole or letrozole in HR-positive/HER2-negative MBC patients who had no prior systemic therapy for MBC. Abemaciclib significantly enhanced median PFS from 14.8 to 28.18 months (HR: 0.54; 95% CI: 0.42–0.70; $p < 0.001$) [73, 74].

For the treatment of endocrine-resistant breast cancer, all three CDK4/6 inhibitors have been combined with fulvestrant (at the 500-mg dose). The addition of palbociclib to fulvestrant yielded a PFS benefit of 4.6 versus 9.5 months (PALOMA-3 trial; HR: 0.46; 95% CI: 9.2–11.0; $p < 0.001$), the addition of ribociclib a PFS benefit of 12.8 versus 20.5 months (MONALEESA-3 trial; HR: 0.59; 95% CI: 0.48–0.73; $p < 0.001$), and the addition of abemaciclib prolonged PFS from 9.3 to 16.4 months (MONARCH-2 trial; HR: 0.55; 95% CI: 0.45–0.68; $p < 0.001$) [75–77]. Although the HRs were similar, the absolute benefit differed in these trials, which is due to the different pretreatments of the study populations: whereas in MONALEESA-3, MBC patients were included in the first and second line, MONARCH-3 only included second-line patients, while in PALOMA, second- and higher-line patients could participate. Importantly, an OS benefit was observed in MONALEESA-3 (HR: 0.72; 95% CI: 0.57–0.92; $p = 0.005$) and MONARCH-2 (HR: 0.76; 95% CI: 0.61–0.95; $p = 0.01$) [78, 79].

Despite detailed knowledge about cell cycle regulation and the CDK4/6 pathway, no biomarker has yet been identified to predict efficacy of CDK4/6 inhibition. Although loss of RB, amplification of CCND, or low expression of p16 should theoretically result in a reduced probability of responding to CDK4/6 inhibitor treatment, none of these markers is clearly associated with treatment response [80–82]. The reason for these findings remains elusive but might be due to inadequate assays to reflect protein function as well as to tumor heterogeneity and the fact that most analyses have been done with archival tissue from primary tumors. Additionally, neither ESR1 mutations nor PI3CA mutations were found to be associated with efficacy of CDK4/6 treatment [83–85].

Perspectives

Even in endocrine-resistant breast cancer, the ER remains a promising target. This is why next-generation more selective SERDs with enhanced bioavailability are under investigation. AZD9496 is an orally available small molecule that downregulates ER with D538G, Y537S, Y537N, or Y537C alterations [86]. AZD9496 was found to block growth of ESR1-mutant breast tumors in pre-clinical models and was well tolerated in phase I clinical trials [87, 88]. Other SERDs currently being assessed are elacestrant (RAD1901) and GDC-0927 [88, 89].

Next to PI3K inhibitors, other strategies are under investigation to target the PI3K/AKT pathway. The AKT inhibitor capivasertib (AZD5363) leads to an increased dependency of tumor cells on ligand-dependent ER activation. This is why there is a strong rationale to combine AKT inhibition with endocrine therapy. The phase II FAKTION trial found that the combination of capivasertib with fulvestrant in ER-positive/Her2-negative MBC doubles PFS (4.8 vs. 10.3 months; HR: 0.58; 95% CI: 0.39–0.84; $p = 0.004$). Promisingly, there was a strong trend towards improved OS [90].

Crosstalk between PI3K/AKT/mTOR pathway provides a strong rationale to combine CDK4/6 with PI3K inhibitors. PI3K activation is a potential mechanism of resistance to CDK4/6 inhibitors [91]. Several trials that combine CDK4/6 inhibitors with various PI3K/AKT/mTOR inhibitors are underway (NCT03128619, NCT03006172, NCT02684032, NCT02732119, NCT02871791, NCT02599714).

Conclusion

Endocrine therapy is the therapy of choice in ER-positive breast cancer. It is of high clinical relevance to maintain endocrine-based treatment as long as possible and to

overcome or delay endocrine resistance. CDK4/6, mTOR, and PI3K inhibition have shown to enhance efficacy of endocrine treatment, and novel promising drugs that target further components of key pathways like the PI3K/AKT/mTOR pathway are currently being developed. As the molecular mechanism of endocrine resistance are manifold, optimal combination and sequencing strategies need to be developed. For this purpose, (circulating) biomarkers are promising to guide individual therapy decisions. Prospective cancer registries that prospectively collect various biomarkers at multiple timepoints during cancer progression and combine these with clinical data on prognosis, tolerability, and efficacy of different endocrine-based treatments are vital to face these challenges [92].

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Conflict of Interest Statement

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A.D.H., E.-M.G., and S.Y.B. wrote the manuscript.

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