ER-α36: a novel biomarker and potential therapeutic target in breast cancer

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Abstract: Estrogen receptor-alpha36 (ER-α36) is a 36-kDa variant of estrogen receptor-alpha (ER-α) firstly identified and cloned by Wang et al in 2005. It lacks both transactivation domains (activation function 1 and activation function 2) and has different biological characteristics compared to traditional ER-α (ER-α66). ER-α36 primarily locates on plasma membrane and cytoplasm and functions as a mediator in the rapid membrane-initiated non-genomic signaling pathway. Additionally, it inhibits the traditional genomic signaling pathway mediated by ER-α66 in a dominant-negative pattern. Accumulating evidence has demonstrated that ER-α36 regulates the physiological function of various tissues. Thus, dysregulation of ER-α36 is closely associated with plenty of diseases including cancers. ER-α36 is recognized as a molecular abnormality which solidly correlates to carcinogenesis, aggressiveness, and therapeutic response of breast cancer. Additionally, special attention has been paid to the role of ER-α36 in endocrine therapy resistance. Therefore, ER-α36 provides a novel biomarker of great value for diagnosis, prognosis, and treatment of breast cancer. It may also be a potential therapeutic target for breast cancer patients, especially for those who are resistant to endocrine therapy. In this review, we will overview and update the biological characteristics, underlying mechanism, and function of ER-α36, focusing on its biological function in breast cancer and endocrine therapy resistance. We will evaluate its application value in clinical practice.

Keywords: ER, ER-α36, breast cancer, endocrine therapy resistance

Introduction

Estrogen is essential to the development and physiology of target organs, such as uterus, ovary, and breast. Dysregulation of estrogen results in pathological processes including osteoporosis, breast cancer, and endometrial cancer.1 These pleiotropic effects of estrogen are related to estrogen receptors (ERs) which are generally regarded as ligand-activated transcription factors belonging to the nuclear receptor superfamily.1,3 Two different forms of ER have been discovered, ER-α and ER-β.3,4 They share similar architecture composed of three independent but interactional function domains.5,6 The N-terminal A/B domains possess a ligand-independent transactivation domain (activation function 1 [AF-1]) interacting with co-activators and activating transcription of target genes.6 The C or DNA-binding domain contains two zinc finger-like structures, allowing dimerization of receptors and then binding to target DNA sequences.6 The C-terminal D/E/F domains or ligand-binding domains mediate ligand binding, receptor dimerization, and nuclear localization and have a ligand-dependent activation domain (activation function 2 [AF-2]) (Figure 1B).6

ER-α36 is a 36-kDa variant of ER-α generating from full length ER-α by alternative splicing or different usage of promoters.6–9 Compared to ER-α66, ER-α36 retains...
DNA-binding, partial dimerization, and ligand-binding domains but lacks both transactivation domains (AF-1 and AF-2).\textsuperscript{3,14,15} ER-α36 mainly locates on plasma membrane and cytoplasm mediating non-genomic estrogen signaling.\textsuperscript{5,10,11} Additionally, it inhibits traditional genomic estrogen signaling mediated by ER-α66 in a dominant-negative pattern.\textsuperscript{10} Accumulating evidence has demonstrated that ER-α36 participates in the development and physiological function of many tissues. Therefore, it is related to diseases such as postmenopausal osteoporosis,\textsuperscript{12} airway hyperresponsiveness,\textsuperscript{13} and even malignancies including gastric,\textsuperscript{14-16} hepatic,\textsuperscript{17} endometrial,\textsuperscript{18} and breast cancers.\textsuperscript{19} ER-α36 is crucial in the carcinogenesis and aggressiveness of breast cancer; in addition, it explains why antiestrogen therapy loses efficacy in ER-positive breast cancer patients.\textsuperscript{20-22} These achievements imply that ER-α36 is a promising biomarker for diagnosis, prognosis, and treatment of various diseases, especially breast cancer.\textsuperscript{23-25} What’s more, it provides a novel pharmaceutical approach to individualized treatment of breast cancer.

This review will overview and update the biological characteristics, molecular mechanism, and biological role of ER-α36, focusing on its function in carcinogenesis, progression, and endocrine therapy resistance of breast cancer and its potential application value in clinical practice.

**Basic characteristics of ER-α36**

Transcription of ER-α36 initiates from a previously unidentified promoter in the first intron of ER-α66, which continues from exon 2 to exon 6 and skips the final exon 7 and exon 8 of ER-α66 (Figure 1A).\textsuperscript{3,6,10,14,15} As a result, ER-α36 lacks both transactivation domains (AF-1 and AF-2) and retains DNA-binding, partial dimerization, and ligand-binding domains of ER-α66 (Figure 1B). The last 138 amino acids encoded by the final exon 7 and exon 8 are replaced by an extra, unique 27-amino-acid sequence at C-terminus. This extra sequence may broaden the ligand-binding spectrum of ER-α36 so that it is able to interact with more factors other than estrogen.\textsuperscript{10} ER-α36 primarily locates on plasma membrane (50%) and cytoplasm (40%) rather than nucleus.\textsuperscript{10,19,26-28} Because it has three potential myristoylation sites near N-terminus instead of the nuclear-location signals of ER-α66, ER-α36 may be modified by palmitoylation posttranslationally and then locate on plasma membrane and cytoplasm just like ER-α46, another variant of ER-α66.\textsuperscript{6,10,11} Therefore, ER-α36 is a potential regulator of membrane-initiated mitogenic signaling pathways responding to E2α, E2β, E3, E4, and even tamoxifen, an estrogen antagonist.\textsuperscript{6,10,24}

Though ER-α36 exists in both ER-α66-positive and ER-α66-negative breast cancer cells,\textsuperscript{10,28} it is highly expressed in the majority of ER-α66-negative breast cancer.\textsuperscript{19,29} Furthermore, overexpression of ER-α36 is usually accompanied with a decrease of ER-α66,\textsuperscript{10,24,28,30} indicating that ER-α66 and ER-α36 are mutually regulated and inversely associated.\textsuperscript{10,20,24,27-30} Wilms’ tumor suppressor WT1 is one of the coordinators which activates promoters of ER-α66 but suppresses ER-α36 promoter activity.\textsuperscript{31} Another coordinator
is synuclein γ (SNCG), which binds to ER-α66 or ER-α36 depending on E2 concentration. In addition, ER-α66 can negatively regulate the promoter activity of ER-α36. Deng et al found that proteasome inhibitors dramatically increased the steady level of ER-α66, indicating that the proteasome system took part in the expression regulation of ER-α36 and ER-α66. With the dynamic regulation of ER-α66 and ER-α36, genomic and non-genomic estrogen signaling pathways are also coordinated to maintain a balance. Although the explicit mechanism needs further investigation, it is obvious that an imbalance of ER-α66 and ER-α36 may result in abnormal proliferation and differentiation, finally leading to diseases including breast cancer.

Molecular mechanism underlying ER-α36 action

Under normal conditions, ERs bind to estrogen and then transfer to the nucleus, subsequently binding to specific estrogen response elements and regulating transcription of downstream DNA (Figure 2). Other than the traditional genomic pathway, ERs mediate the non-genomic pathway by membrane-associated receptors. The non-genomic pathway controls more genes than the genomic pathway, regulating cellular growth, survival, motility, invasion, and apotosis. What’s more, non-physiologic estrogen also activates the non-genomic pathway, which is important to so-called “nontarget” tissue such as the cardiovascular system. The unique structure and intracellular location of ER-α36 decide its molecular mechanism. Lacking both transcriptional activation domains, ER-α36 binds to the same target DNA sequence as ER-α66 does, but possesses no intrinsic transcriptional activity. Thus, ER-α36 functions as a powerful competitor of the genomic signaling pathway mediated by ER-α66. Additionally, ER-α36 mediates rapid membrane-initiated estrogen signaling cascades, which regulate various biological functions and are associated with tumorigenesis, aggressive phenotype, and treatment sensitivity of carcinomas (Figure 2).

ER-α36 and downstream kinases

The mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway is the most popular mitogenic signaling in cancers, which can be rapidly activated by E2. Research has demonstrated that membrane-initiated signaling pathways mediated by ER-α36 could stimulate the transcription of ELK1 in the nucleus. Tong et al found that ER-α36 also activated ERK1/2 through the protein kinase C delta signaling pathway and then elevated expression of cyclin D1/cyclin-dependent kinase 4, a transcriptional coregulator that regulates cell cycle progression. The MAPK/ERK signaling pathway mediated by ER-α36 contributes to the potential invasion and metastasis of cancer.

**Figure 2** Genomic and non-genomic activities mediated by ERs.

**Notes:** ER-α66 binds to estrogen and then transfers to the nucleus to interact with specific EREs and induce transcription of target genes. ER-α36 has a broader ligand-binding spectrum than ER-α66 so that it can respond to E2α, E2β, E3, E4, and even tamoxifen. ER-α36 can mediate rapid MIES such as MAPK/ERK, PI3K/Akt, and PKC δ to regulate biological functions of cells.

**Abbreviations:** Akt, protein kinase B; BCSCs, breast cancer stem cells; cdk 4, cyclin-dependent kinase 4; ER-α36, estrogen receptor-alpha36; ER-α66, estrogen receptor-alpha66; EREs, estrogen response elements; ERK, extracellular signal-regulated kinase; ERs, estrogen receptors; GSK3 β, glycogen synthase kinase 3 beta; JNKs, c-Jun N-terminal kinases; MAPK, mitogen-activated protein kinases; MIES, membrane-initiated estrogen signaling; PKC δ, protein kinase C delta; PI3K, phosphatidylinositide 3-kinase.
cells.\textsuperscript{23,24,44} What’s more, it induces paclitaxel resistance through c-Jun N-terminal kinases (JNKs), an important component of the MAPK family mediating paclitaxel-induced apoptosis and death (Figure 2).\textsuperscript{23,24,44}

Phosphatidylinositide 3-kinase/protein kinase B (PI3K/Akt) is another classical pathway associated with malignant cancers.\textsuperscript{49–51} Rapid phosphorylation of Akt, which is induced by E2, testosterone, and tamoxifen, can be blocked by a PI3K inhibitor or knockdown of ER-\textalpha\textsubscript{36}, suggesting that the PI3K/Akt pathway is one of the non-genomic pathways mediated by ER-\textalpha\textsubscript{36} (Figure 2).\textsuperscript{26,47}

\textbf{ER-\textalpha\textsubscript{36} associated proteins}

Several proteins are involved in the stability and function of ER-\textalpha\textsubscript{36}, thus promoting mitogenic estrogen signaling mediated by ER-\textalpha\textsubscript{36}. Glucose-regulated protein 94, an endoplasmic reticulum chaperone, is a potential downstream effector of the ER-\textalpha\textsubscript{36}-mediated pathway in gastric cancer.\textsuperscript{15} SNCG, previously regarded as breast cancer-specific gene BCSG1,\textsuperscript{52} binds to ER-\textalpha\textsubscript{36} without heat shock protein 90 to prevent degradation of ER-\textalpha\textsubscript{36} and significantly strengthen ER-\textalpha\textsubscript{36}-mediated mitogenic estrogen signaling pathways.\textsuperscript{33}

Many investigators discovered a significant co-expression of ER-\textalpha\textsubscript{36} and epidermal growth factor receptor (EGFR) in primary breast cancers, indicating that ER-\textalpha\textsubscript{36} took part in EGFR-related carcinogenesis.\textsuperscript{19} Further studies elucidated that epidermal growth factor (EGF) induced phosphorylation of ERK1/2 via ER-\textalpha\textsubscript{36} in a time- and dose-dependent pattern.\textsuperscript{18} A positive feedback loop was confirmed that EGFR signaling activated transcription of ER-\textalpha\textsubscript{36} through an activator-protein-1-binding site in the promoter of ER-\textalpha\textsubscript{36}. In turn, ER-\textalpha\textsubscript{36} interacted with the EGFR/Src/Shc complex to strengthen the EGFR signaling pathway and stabilize EGFR protein (Figure 3).\textsuperscript{20} A similar feedback loop between ER-\textalpha\textsubscript{36} and human epidermal growth factor receptor 2 (HER-2), a member of the EGFR family, was reported.\textsuperscript{23} Interestingly, our previous study found that HER-2 expression didn’t increase in tamoxifen-resistant cells, which overexpressed ER-\textalpha\textsubscript{36} and EGFR.\textsuperscript{23} In the Src/EGFR/signal transducer and activator of transcription 5 (STAT5) pathway mediated by ER-\textalpha\textsubscript{36}, Src functions as a switch to adjust phosphorylation of EGFR and then recruits STAT5 as a downstream effector, which regulates activation of the MAPK/ERK signaling pathway and expression of cyclin D1 (Figure 3).\textsuperscript{16,20,54} Therefore, the positive feedback loops between ER-\textalpha\textsubscript{36} and growth factor receptors are important for cellular function, although the definite mechanism has not been clarified.

\textbf{Biological roles of ER-\textalpha\textsubscript{36}}

ER-\textalpha\textsubscript{36} participates in the development and function of target tissues. For example, expression and subcellular localization of ER-\textalpha\textsubscript{36} are necessary for folliculogenesis,

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{feedback_loop.png}
\caption{Positive feedback loop between EGFR and ER-\textalpha\textsubscript{36}.}
\textbf{Notes:} A positive feedback loop has been confirmed that EGFR signaling activates transcription of ER-\textalpha\textsubscript{36} through an AP-1-binding site in the promoter region of ER-\textalpha\textsubscript{36}. In turn, ER-\textalpha\textsubscript{36} is able to stabilize EGFR protein and mediate MAPK/ERK and Src/EGFR/STAT5 pathways. In the Src/EGFR/STAT5 pathway, Src functions as a switch by phosphorylation to enhance proliferation and malignant properties of cancer.
\textbf{Abbreviations:} AP-1, activator protein 1; EGFR, epidermal growth factor receptor; ER-\textalpha\textsubscript{36}, estrogen receptor-alpha36; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinases; STAT5, signal transducer and activator of transcription 5.
\end{figure}
oocyte meiotic maturation, ovulation, and luteinization of the postnatal ovary, thus facilitating maturation of the female reproductive system. Additionally, ER-α36 maintains the bone density of postmenopausal women. However, dysregulation of ER-α36 leads to various dysfunctions and diseases, such as osteoporosis, airway hyperresponsiveness, and even cancers. Since the mammary gland is estrogen-dependent, ER-α36 plays a particularly vital role in breast cancer. Therefore, we will focus on its role in breast cancer and endocrine therapy resistance and its potential application value in clinical practice.

**Biological function of ER-α36 in breast cancer**

In order to investigate the biological function of ER-α36 in breast cancer, Zhang et al established ER-α36-knockdown MDA-MB-231 cell lines in which expression of ER-α36 decreased obviously. They found knockdown of ER-α36 suppressed proliferation, migration, and invasion and increased sensitivity to paclitaxel in MDA-MB-231 cells. Chaudhri et al got similar results that ER-α36 was able to enhance cellular proliferation and metastasis and protect against apoptosis. Recently, Yu et al studied the relationship between ER-α36 and chemotherapy response in 120 breast cancer patients and found that ER-α36-negative patients had better response to anthracycline and/or paclitaxel than ER-α36-positive patients.

**ER-α36 and breast cancer stem cells (BCSCs)**

BCSCs, a subpopulation of stem/progenitor cells that possesses the ability to self-renew, play a key role in occurrence, recurrence, metastasis, and chemotherapy resistance of breast cancer. CD44+/CD24−/low and aldehyde dehydrogenase 1 (ALDH1) were identified as markers of BCSCs. Kang et al found that ER-α36 was highly expressed in ALDH1-positive SK-BR-3 cells. Additionally, the depletion of ER-α36 reduced the growth rate and proportion of ALDH1high cells, indicating that ER-α36 contributed to the proliferation and maintenance of stem-like cells. Deng et al observed that estrogen significantly increased the population of CD44+/CD24−/low cells in MCF-7 and T47D breast cancer cells, but failed to do so after knocking down ER-α36, suggesting that estrogen positively regulated BCSCs through the ER-α36-mediated signaling pathway. Furthermore, they found that overexpression of ER-α36 tended to promote self-renewal and tumor-seeding efficiency of BCSCs through the PI3K/AKT/glycogen synthase kinase 3 beta/β-catenin signaling pathway (Figure 2).

**ER-α36 and endocrine therapy resistance**

Endocrine therapy is a dominant anticancer method for ER-positive breast cancer patients. Although aromatase inhibitors are increasingly applied in postmenopausal women, antiestrogens are still used as first-line therapy, especially when aromatase inhibitors are ineffective. However, less or no response after long-term treatment is the major obstacle in antiestrogen treatment.

**Tamoxifen**

Tamoxifen is a competitive antagonist of ER-α, effectively blocking traditional genomic signaling pathway mediated by ER-α. However, it can activate different kinase cascades and produce second messengers, thus acting as an agonist that is equal to estrogen. For example, tamoxifen strongly activates the MAPK/ERK signaling pathway to stimulate cell growth; additionally, it activates the p38/MAPK and SAPK/JNK pathways to induce apoptosis. In recent years, a large number of explorations have concentrated on the association between ER-α36 and tamoxifen resistance. Due to the unique 27-amino-acid domain, ER-α36 has a broader ligand-binding spectrum than ER-α66 so that it can respond to tamoxifen. Usually, ER-α36 is highly expressed in ER-α66-negative breast cancer, which is insensitive to endocrine therapy. Clinical research demonstrated that high expression of ER-α36 was associated with decreased tamoxifen sensitivity and poorer survival in ER-α66-positive breast cancer patients who received tamoxifen as adjuvant therapy. Additionally, laboratory studies revealed that the tamoxifen-resistant MCF-7 cell line (MCF-7/TAM) highly expressed ER-α36. However, knocking down ER-α36 in MCF-7/TAM cells could not restore their sensitivity to tamoxifen completely. This may be because the expression level of ER-α36 in MCF-7/TAM cells is too high to be completely blocked; besides, biological reprogramming during development of tamoxifen resistance is much more complicated than upregulation of ER-α36. Furthermore, proteins maintaining the stability and function of ER-α36 such as SNCG can strengthen tamoxifen resistance mediated by ER-α36. Therefore, ER-α36 is an underlying cause of tamoxifen resistance in breast cancer patients.

Previous explorations have demonstrated that ER-α36 is a potent mediator of membrane-initiated signaling pathways associated with agonist effects of tamoxifen, which leads to...
tamoxifen resistance.\textsuperscript{10,24} For example, the MAPK/ERK and PI3K/AKT signaling pathways that are mediated by ER-\textgreek{a}36 induce the expression of protooncogene c-Myc, which has profound mitogenic effects (Figure 4).\textsuperscript{10,44} ER-\textgreek{a}36 also mediates the Src/EGFR/STAT5 pathway regulating activity of the MAPK/ERK signaling pathway and expression of the growth-promoting cyclin D1 (Figure 4).\textsuperscript{66} However, it is still unknown whether other non-genomic pathways, such as protein kinase C, protein kinase A, and calcium channels are involved in tamoxifen resistance.

Further research has revealed that overexpression of EGFR with downregulation of ER-\textgreek{a}66 is responsible for tamoxifen resistance.\textsuperscript{67-69} Li et al established a tamoxifen-resistant MCF-7 cell line (MCF-7/TAM) that had an accelerated proliferation rate as well as enhanced migratory and invasive ability. In MCF-7/TAM cells, ER-\textgreek{a}36 upregulated EGFR expression and downregulated ER-\textgreek{a}66 expression, switching growth status from estrogen-dependent to growth-factor-dependent, which was a critical step in the development of tamoxifen resistance (Figure 4).\textsuperscript{23}

ICI 182,780 (Fulvestrant, Faslodex\textsuperscript{®})

ICI 182,780 (Fulvestrant, Faslodex), a ‘pure’ antiestrogen, not only accelerates degradation but also impairs dimerization and nuclear localization of ER-\textgreek{a}66.\textsuperscript{70,71} However, several studies reported that ICI 182,780 failed to induce degradation of ER-\textgreek{a}36,\textsuperscript{6,72} presumably because ER-\textgreek{a}36 has a truncated ligand-binding domain lacking the last four helices (helix 9–12) of ER-\textgreek{a}66, which are essential for protein degradation induced by ICI 182,780.\textsuperscript{6,73} Therefore, failure of ER-\textgreek{a}36 degradation is a highly possible reason for ICI 182,780 resistance.

**Application value of ER-\textgreek{a}36**

Metastasis and recurrence are the most intractable issues in the management of cancer; thus, using molecular alteration to assess tumor degree and prognosis is of great significance. A large number of studies have confirmed that ER-\textgreek{a}36-positive breast cancers tend to have more lymph node metastasis, advanced degree, less sensitivity to chemotherapy or endocrine therapy, and poorer outcome than ER-\textgreek{a}36-negative breast cancer. Therefore, ER-\textgreek{a}36 is a promising biomarker for malignant behavior, therapeutic response, and outcome of breast cancer, guiding clinical decisions in early diagnosis, prognosis estimation, and personalized treatment. For example, we can combine the expression of ER-\textgreek{a}66 and ER-\textgreek{a}36 to predict whether endocrine therapy is suitable and effective for breast cancer patients.

Given its important role in carcinogenesis, progression, and therapeutic response of breast cancer, ER-\textgreek{a}36 is emerging as a potential therapeutic target for breast cancer. The surface localization of ER-\textgreek{a}36 makes it possible to generate

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**Figure 4** ER-\textgreek{a}36 and tamoxifen resistance.

**Notes:** ER-\textgreek{a}36 is an important cause of tamoxifen resistance. On the one hand, it activates membrane-initiated signaling pathways, such as MAPK/ERK, PI3K/AKT, and Src/EGFR/STAT5 pathways, causing the agonist effect of tamoxifen. On the other hand, ER-\textgreek{a}36 upregulates EGFR and downregulates ER-\textgreek{a}66 switching growth status from estrogen-dependent to growth-factor-dependent. Therefore, ER-\textgreek{a}36 leads to tamoxifen resistance.

**Abbreviations:** Akt, protein kinase B; EGFR, epidermal growth factor receptor; ER-\textgreek{a}36, estrogen receptor-alpha36; ER-\textgreek{a}66, estrogen receptor-alpha66; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinases; MCF-7/TAM, tamoxifen-resistant MCF-7 cell line; PI3K, phosphatidylinositol 3-kinase; STAT5, signal transducer and activator of transcription 5.
specific surface epitopes for treatment intervention with small molecules or biologics which directly down-modulate the ER-α36 protein or indirectly block its downstream signaling pathways, such as biological antagonists, monoclonal antibodies, and small kinase inhibitors. Inhibition of ER-α36 can suppress tumor growth and progression, benefitting breast cancer patients, especially those who are resistant to endocrine therapy. Though few studies have focused on the therapeutic application of ER-α36 and no clinical trials currently, a targeted agent suitable for clinical testing will be available in the near future. Broussoflavonol B, a flavonoid purified from the bark of Broussonetia papyrifera (Moraceae), exhibits a more potent growth inhibition effect than tamoxifen in ER-negative breast cancer. It decreases the steady level of ER-α36 and EGFR and restricts growth of stem-like cells in MDA-MB-231 cells.

**Conclusion**

ER-α36 is a variant of ER-α with different characteristics and functions than ER-α66. It locates on plasma membrane and cytoplasm. Therefore, ER-α36 mediates the non-genomic signaling pathway and suppresses the traditional genomic signaling pathway. ER-α36 plays a key role in breast cancer, leading to an accelerated proliferation rate together with enhanced migratory and invasive ability. Additionally, it mediates the agonist action of tamoxifen and switches the growth status of breast cancer cells from estrogen-dependent to growth-factor-dependent, both of which can be the molecular mechanisms of tamoxifen resistance. Furthermore, failure of ER-α36 degradation is a possible reason for Fulvestrant resistance. Therefore, ER-α36 is a promising biomarker for tumor behavior and therapeutic response, being a new indicator to select optimal candidates for therapeutic strategies. Additionally, it is a potential therapeutic target to improve survival of breast cancer patients.

These achievements make the heterogeneity of the estrogen effect more clear and put a new insight into the properties of ER-α36. Additionally, studies of ER-α36 deepen our knowledge of the carcinogenesis and progression of breast cancer and provide an alternative explanation for endocrine therapy resistance. However, there are still many challenges in the future. More research is needed to clarify the biological function and deep mechanism of ER-α36. Additionally, developing an effective and specific inhibitor of ER-α36 is a difficult work. Before the inhibitor is widely used, the inhibitory consequences should be validated regarding proliferation, invasion, migration, and survival of tumor cells and clinical trials with large sample sizes and long-term observation are also needed.

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**Disclosure**

The authors declare no conflicts of interest in this work.

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