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Endocrine Resistance in Breast Cancer: Focus on the Phosphatidylinositol 3-Kinase/Akt/ Mammalian Target of Rapamycin Signaling Pathway

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Keywords
Hormone receptor-positive breast cancer · Estrogen receptor · Endocrine resistance · PI3K/mTOR pathway

Summary
Breast cancer is the most common cancer among women. Up to 75% of breast cancers express the estrogen receptor (ER)α and/or the progesterone receptor (PR). Patients with hormone receptor-positive metastatic breast cancer are typically treated with endocrine therapy. Yet, not all patients with metastatic breast cancer respond to endocrine treatments and are considered to have primary (de novo) resistance. Furthermore, all patients who initially respond to endocrine treatment will eventually develop acquired resistance. Several mechanisms have been linked to the development of endocrine resistance, including reduced expression of ERα, altered regulation of the ER pathway, and activation of various growth factor signaling pathways, among them the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway. This pathway is involved in critical processes including cell survival, proliferation, and angiogenesis, and plays a central role in breast cancer development. Recent laboratory and clinical data implicate this pathway as mediating endocrine resistance, and agents directed against critical components of this pathway are either already approved for clinical use in breast cancer patients or are currently being tested in clinical trials. In this review, we describe the interaction between the PI3K/Akt/mTOR pathway and the ER cascade, its role in mediating endocrine resistance, and the clinical implications of this interaction.

Schlüsselwörter
Hormonrezeptor-positiver Brustkrebs · Östrogenrezeptor · Endokrine Resistenz · PI3K/mTOR-Signalweg

Zusammenfassung
Brustkrebs ist bei Frauen die am häufigsten auftretende Krebsart. Bis zu 75% der Mammakarzinome exprimieren den Östrogenrezeptor (ER)α und/oder den Progesteronrezeptor (PR). Patienten mit Hormonrezeptor-positivem metastatischem Brustkrebs werden typischerweise mit einer endokrinen Therapie behandelt. Jedoch sprechen nicht alle Patienten mit metastatischem Brustkrebs auf die endokrine Therapie an und man geht davon aus, dass sie eine primäre (De-novo-)Resistenz aufweisen. Außerdem entwickeln alle Patienten, die zunächst auf eine endokrine Therapie ansprechen, schließlich eine erworbene Resistenz. Verschiedene Mechanismen sind mit der Entwicklung der endokrinen Resistenz in Verbindung gebracht worden, dazu gehören eine reduzierte Expression des ERα, eine veränderte Regulation des ER-Signalwegs und die Aktivierung verschiedener Wachstumsfaktor-Signalwege wie z.B. der Phosphatidylinositol-3-Kinase (PI3K)/Akt/mammalian Target of Rapamycin (mTOR)-Signalweg. Dieser Signalweg ist an wichtigen Prozessen wie dem Überleben und der Proliferation von Zellen sowie der Angiogenese beteiligt und spielt bei der Entstehung von Brustkrebs eine zentrale Rolle. Neueste Labor- und klinische Daten legen nahe, dass dieser Signalweg die endokrine Resistenz vermittelt. Gegen ausschlaggebende Komponenten dieses Signalweges gerichtete Wirkstoffe sind entweder schon für die klinische Anwendung bei Brustkrebspatientinnen zugelassen oder werden gerade in klinischen Studien getestet. In diesem Übersichtsartikel beschreiben wir die Interaktion zwischen dem PI3K/Akt/mTOR-Signalweg und der ER-Kaskade, ihre Rolle bei der Vermittlung der endokrinen Resistenz und die klinische Bedeutung dieser Interaktion.

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Introduction

Breast cancer is the most common cancer among women worldwide [1]. Up to 75% of all breast cancers express the estrogen receptor (ER)α and/or the progesterone receptor (PR). Patients with hormone receptor (HR)-positive metastatic breast cancer are typically treated with endocrine therapy. Yet, not all patients with metastatic breast cancer respond to endocrine treatments and are considered to have primary (de novo) resistance. Furthermore, all patients who initially respond to endocrine treatment will eventually develop acquired resistance. Several mechanisms have been linked to the development of endocrine resistance, including reduced expression of ERα, altered regulation of co-activators of the ER and activation of various growth factor signaling pathways; among them are the epidermal growth factor (EGF), insulin-like growth factor (IGF)-1 and the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathways [2]. The PI3K/Akt/mTOR signaling pathway is involved in critical processes including cell survival, proliferation and angiogenesis, and plays a central role in the development of breast cancer [3, 4]. Recent laboratory and clinical data implicate this pathway as mediating endocrine resistance, and agents directed against critical components of this pathway are either approved for clinical use in breast cancer patients or are currently being tested in clinical trials. In this review, we will describe the interaction between the PI3K/Akt/mTOR pathway and the ER signaling cascade, its role in mediating endocrine resistance, and the clinical implications of this interaction.

Mechanism of Endocrine Resistance in Breast Cancer

Estrogen is a steroid hormone that controls many aspects of human physiology, including development, reproduction and homeostasis. Two ERs have been identified: ERα and ERβ. However, only ERα is closely associated with carcinogenesis and serves as the target for endocrine treatments. The ERs belong to the superfamily of nuclear HRs that function as ligand-activated transcription factors [5, 6]. Upon binding of estrogen to the ligand-binding domain of the ER, the receptor dimerizes, attracts a host of co-activators and co-repressors and binds to specific estrogen response elements residing in the promoter of estrogen-regulated genes. Binding of the ER can either activate or repress gene expression. The ER can also bind to other transcription factors such as activator protein-1 (AP-1) and specificity protein-1 (SP-1) at their specific sites on the DNA, thereby functioning as a co-regulator. The ERs may also exert non-genomic activities outside the nucleus, at the membrane, in the cytoplasm, or even in the mitochondria [7]. Blockade of the estrogen action is the mainstay of treatment of ER-expressing breast cancer. Pharmacologic endocrine therapies include direct inhibition of the receptor by selective estrogen receptor modulators (SERM; e.g. tamoxifen), selective estrogen receptor down-regulators (SERD; e.g. fulvestrant), or inhibition of estrogen production using aromatase inhibitor antagonists [8–11].

Multiple mechanisms responsible for endocrine resistance have been proposed and can be divided into 3 conceptual categories [2, 12]:

- Deregulation of components of the ER pathway itself, including loss of expression of ERα, expression of truncated isoforms of ERα, and post-translational modifications and altered activity of co-activators and co-repressors in tumor cells.
- Alterations in cell cycle and cell survival signaling molecules, due to yet undefined factors; e.g., up-regulation of positive regulators of the cell cycle (e.g. Myc and cyclins E1 and D1) controlling G1 phase progression and down-regulation of negative regulators of the cell cycle as p21 and p27.
- Activation of signaling pathways that can provide alternative proliferation and survival stimuli to the tumors in the presence of effective inhibition of the ER pathway. Many of these pathways can emerge as ER-independent drivers of tumor growth and survival, thus conferring resistance to all types of endocrine therapy. Among these pathways are the EGF, the insulin/IGF-1 and the PI3K/Akt/mTOR pathways.

The PI3K/Akt/mTOR Pathway

Multiple players participate in the activation and prompt regulation of the PI3K/Akt/mTOR pathway; many of them are kinases (i.e. enzymes that transfer phosphate from ATP to a specific substrate) and others regulate the localization of their downstream targets, mostly by promoting attachment to the inner side of the cell membrane. We describe here the classic chain of events occurring upon activation of the PI3K/Akt/mTOR pathway (fig. 1) [13].

Step 1: Activation of a receptor. Classic activation starts with binding of an extracellular growth factor, e.g. EGF, IGF-1, or insulin, to the cognate cell surface tyrosine kinase receptor. Upon binding, the receptor dimerizes, becomes autophosphorylated and recruits adaptor proteins, e.g. the insulin receptor substrate (IRS)1 and IRS2.

Step 2: Activation of PI3K and generation of phosphatidylinositol-3,4,5-trisphosphate (PIP3). The PI3Ks constitute a large family of kinases involved in multiple physiological aspects. The PI3K class mostly implicated in cancer is the class IA. PI3KIA contains a catalytic subunit (p110) encoded by PIK3CA and a regulatory subunit (p85), and is recruited to the phosphorylated receptor tyrosine kinase and activated by it. Interestingly, PI3K can also be activated directly by the Ras protein. The substrate of PI3K is phosphatidylinositol

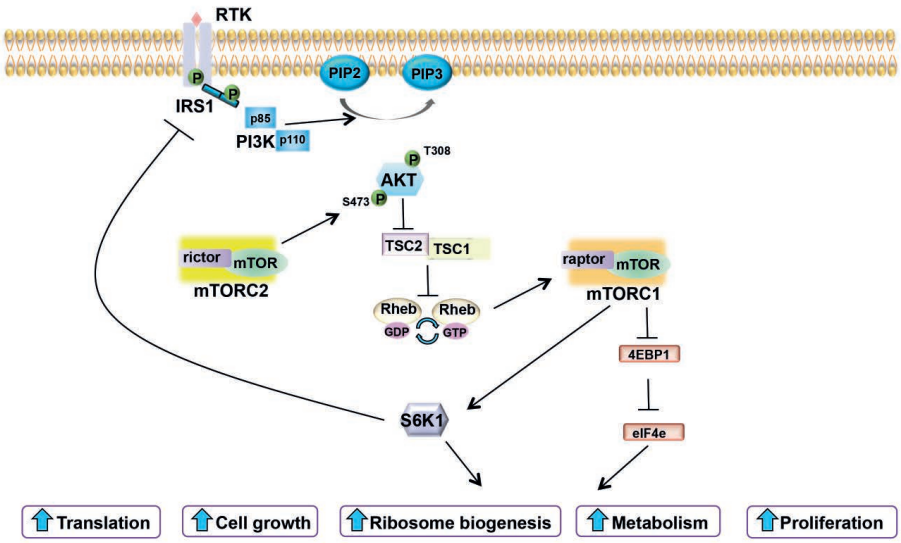

Fig. 1. Overview of the PI3K/Akt/mTOR pathway. RTK = Receptor tyrosine kinase, P = phosphate, IRS1 = insulin receptor substrate 1, PIP2 = phosphatidylinositol 4.5-bisphosphate, PIP3 = phosphatidylinositol 3.4.5-trisphosphate, PI3K = phosphatidylinositol 3-kinase, AKT = activated protein kinase B, mTOR = mammalian target of rapamycin, rictor = rapamycin-insensitive companion of mTOR, raptor = regulatory-associated protein of mTOR, TSC = tuberous sclerosis complex, Rheb = Ras homolog enriched in brain, GDP = guanosindiphosphate, GTP = guanosintriphosphate, S6K1 = ribosomal S6 kinase 1, 4EBP1 = 4E-binding protein 1, eIF4e = eukaryotic translation initiation factor 4E.

4,5-bisphosphate (PIP2 or PI(4,5)P2). PI3K phosphorylates PIP2 to generate PIP3 (or PI(3,4,5)P3). PIP3 is a second messenger that promotes the translocation of Akt to the cell membrane. Important negative regulators of this step are phosphatase and tensin homolog (PTEN) and inositol polyphosphate-4-phosphatase, type II (INPP4B), which dephosphorylate PIP3 and PIP2, respectively [14], thus reducing the levels of PIP3.

Step 3: Activation of Akt. Akt (also known as protein kinase B or PKB), is a serine/threonine protein kinase. Akt contains a specific domain (pleckstrin homology (PH) domain) that binds to PIP3 generated by PI3K. Binding of PIP3 to Akt triggers its translocation to the membrane and induces a conformational change enabling Akt phosphorylation and thus its activation by another kinase, phosphoinositide-dependent kinase 1 (Pdk1). While Pdk1 phosphorylates Akt on threonine at position 308 (Thr308), full activation of Akt occurs only following an additional phosphorylation, on serine at position 473 (Ser473). Interestingly, this second phosphorylation is mediated by the downstream complex mTORC2 (see below). Thus, full activation of Akt is unique and requires the activity of both upstream (PI3K) and downstream (mTORC2) components of the pathway. Upon activation, Akt dissociates from the membrane and translocates to the cytoplasm and the nucleus, where it phosphorylates multiple proteins involved in translation, metabolism, proliferation, survival, and angiogenesis. One of these proteins is tuberous sclerosis complex 2 (TSC2).

Step 4: Phosphorylation of TSC2 and activation of mTOR. TCS2 inactivates the small G protein Rheb. Upon phosphorylation of TSC2, its activity on Rheb is inhibited, resulting in the accumulation of active GTP-bound Rheb and activation of its downstream target mTOR.

Step 5: Formation of active mTOR complexes. mTOR is a serine/threonine kinase which serves as the catalytic subunit of one of two complexes. When mTOR is complexed with regulatory-associated protein of mTOR (RAPTOR), it forms the mTOR complex 1 (mTORC1). The two major downstream effectors of mTORC1 are 4E-BP1 and S6K1 (ribosomal S6 kinase 1), which enhance the translation of proteins associated with proliferation and survival [15]. When mTOR is complexed with rapamycin-insensitive companion of mTOR (rictor), it forms the complex mTORC2 (mTOR-rictor complex 2). As mentioned above, an important target of mTORC2 is Akt. Thus, phosphorylation of Akt by mTORC2 is required for full activation of Akt.

Negative feedback loops in the PI3K/Akt/mTOR pathway: Another layer of complexity is a negative feedback loop formed by inhibition of the pathway through the activation of mTORC1 [16]. The activated S6K1 inhibits the upstream component of the IRS-1 pathway, thus leading to inhibition of the pathway. Direct inhibition of mTORC1 may therefore relieve this negative feedback loop and lead to a paradoxical activation of Akt. Furthermore, inhibition of mTORC1 may also lead to the activation of the mitogen-activated protein kinase (MAPK) pathway [17]. Recent data indicate that direct inhibition of Akt may also release the negative feedback and induce the expression of multiple receptor tyrosine kinases, including the human epidermal growth factor receptor (HER)3 and IGF-1R [18]. The existence of these negative feedback loops carries important clinical implications and suggests that targeting a single component of the pathway may lead to a paradoxical activation of other components and of alternative pathways.

PI3K/Akt/mTOR Signaling in Breast Cancer

Signaling through the PI3K/Akt/mTOR pathway promotes breast cancer tumorigenesis through multiple cellular pro-

cesses including increased cell growth, proliferation and motility, a shift to glycolytic metabolism, increased cell migration, and deregulated apoptosis [19]. Mutations of the PI3K pathway are the most common genetic alterations in HR-positive breast cancer and occur in over 70% of these cancers [14]. A recent comprehensive analysis identified activating mutations of PI3K in 45% of luminal A and 29% of luminal B breast cancers [20, 21]. The prognostic role of PIK3CA mutations is not clear and their presence may actually be associated with improved survival [22]. Typical markers of PI3K pathway activation (pAKT, pS6 and p4EBP1) were not elevated in PIK3CA-mutated luminal A cancers, therefore obstructing their prognostic importance in HR-positive breast cancer [21]. On the other hand, PIK3CA-gene signature (GS) has a potential to identify those ER-positive breast cancer patients who may benefit from the addition of everolimus to letrozole. Therefore, further evaluation of the PIK3CA-GS as a predictive biomarker is warranted [54]. Down-regulation of PTEN is another frequent event and has been identified in up to 44% of breast cancers [14].

The PI3K/Akt/mTOR Pathway and Endocrine Resistance

Ample preclinical data indicate crosstalk between the ER and the PI3K/Akt/mTOR signaling pathways. Studies in breast cancer cell lines noted an association between the activity of the Akt pathway and hormone resistance. Thus, while Akt activity induces tamoxifen resistance in these cells, inhibition of Akt or mTOR can restore the sensitivity to tamoxifen as well as to aromatase inhibitors and fulvestrant [23–27]. A unique model for studying mechanisms associated with endocrine resistance consists of ER-positive breast cancer cells grown for prolonged periods of time in the absence of estrogen (long-term estrogen deprivation, LTED). These LTED cells show hyperactivation of the PI3K/Akt/mTOR pathway and inhibition of PI3K and mTOR induced their apoptosis [28]. Taken together, these data suggest that, upon adaptation to hormone deprivation, breast cancer cells heavily rely on PI3K signaling. However, the mechanisms of crosstalk between the PI3K/Akt/mTOR pathway and the ER pathway are not well characterized. Interestingly, Akt and PI3K may directly phosphorylate the ER, induce estrogen-independent activation and induce the expression of ER targets [23].

Clinical data further support the association between the activity of the PI3K/Akt/mTOR pathway and resistance to hormonal treatment. Thus, activation of Akt [29–32] and reduced PTEN expression [33] were associated with either resistance to hormonal treatment in metastatic breast cancer or with relapse in breast cancer patients treated with tamoxifen.

Inhibition of the PI3K/Akt/mTOR Pathway: A Novel Strategy to Restore Hormone Sensitivity

Preclinical studies indicated that inhibition of critical components of the PI3K/Akt/mTOR pathway can restore hormone sensitivity [23–26]. The inhibitors can be divided into several groups:

Allosteric inhibitors of mTOR: The first compound identified in this group is rapamycin, which was isolated from a soil sample on Easter Island (Rapa Nui) in 1975 [34]. The target of rapamycin, mTOR, was identified only in 1991. The mechanisms of action of rapamycin are complex and involve binding to the cytoplasmic receptor protein FKBP12. The complex then binds to a specific domain on mTORC1 and inhibits its activity allosterically [35]. As this domain is found only in mTOR, rapamycin is considered to be highly specific. However, recent data suggest that rapamycin may also modulate rictor phosphorylation and that prolonged rapamycin treatment may reduce the mTORC2 levels in some cell lines [36]. While rapamycin has been shown to inhibit the growth of different cancer cell lines and xenografts [37, 38], its poor aqueous solubility and chemical stability limited its clinical development and led to the development of synthetic rapamycin analogs (rapalogs) with more favorable pharmacological characteristics. Currently, 3 analogs of rapamycin have been developed: everolimus (RAD001), temsirolimus, and deforolimus. Ample preclinical studies indicate that the rapalogs can restore hormone sensitivity (e.g. [27, 39, 40]).

Following the development of the rapalogs, inhibitors of other components of the pathway have been developed and include allosteric Akt inhibitors (e.g. MK-2206), kinase inhibitors of Akt (e.g., AZD5363), and kinase inhibitors of PI3K (e.g., BMK120, XL147). As mentioned above, inhibition of mTOR may lead to a paradoxical activation of PI3K. In order to overcome this, dual kinase inhibitors targeting both mTOR and PI3K have also been developed (e.g., BYL719, XL765). Treatments with compounds belonging to each of these groups have been associated with restoring endocrine sensitivity [28, 41, 42]. The differential activities of a rapalog (RAD001), a PI3K inhibitor (BMK120), and a dual PI3K/mTOR inhibitor (BGT226) have been tested in breast cancer cells grown under LTED. Apoptosis was most highly induced by the dual PI3K/mTOR inhibitor, followed by the PI3K catalytic subunit inhibitor, and then the mTOR inhibitor [43].

Clinical Studies

While compounds of each of these groups are currently being tested in clinical trials for the treatment of HR-positive breast cancer, only phase 2 and 3 studies involving the rapalogs everolimus and temsirolimus have been published to date (described below). As the data regarding everolimus and temsirolimus is contradicting, each drug will be described

Table 1. Phase 2 and 3 clinical trials with everolimus and temsirolimus in HR-positive breast cancer

Study	Study design	Patients	Treatment	Response rate	PFS
Everolimus					
Baselga et al. [45]	phase 2 randomized	postmenopausal, neoadjuvant (n = 272)	letrozole + everolimus vs. letrozole + placebo	68% vs. 59%	not evaluated
TAMRAD, Bachelot et al. [46]	phase 2 randomized	metastatic breast cancer (n = 111)	tamoxifen + everolimus vs. tamoxifen	61% vs. 42% (p = 0.045)	8.6 months vs. 4.5 months (p = 0.002)
BOLERO-II, Baselga et al. [48]	phase 3 randomized	postmenopausal advanced breast cancer, failure of non-steroidal aromatase inhibitors (n = 724)	exemestane + everolimus vs. exemestane + placebo	9.5% vs. 0.4% (p < 0.0001)	6.9 months vs. 2.8 months (p < 0.001)
Temsirolimus					
Carpenter et al. [51]	phase 2 randomized	advanced breast cancer (n = 92)	letrozole + temsirolimus (10 mg/day) vs. letrozole + temsirolimus (30 mg/day for 5 days q2w) vs. letrozole	n = 9, 9, and 12, respectively	PFS at 1 year: 69% vs. 62% vs. 48%
HORIZON, Wolff et al. [52]	phase 3 randomized	postmenopausal advanced breast cancer (n = 1,112)	letrozole + temsirolimus (30 mg/day for 5 days q2w) vs. letrozole	27% vs. 27%	8.8 vs. 8.9 months

separately. A summary of the major clinical trials is presented in table 1.

Everolimus

The first study to demonstrate the activity of everolimus in breast cancer was the National Cancer Institute of Canada (NCIC) study, a phase 2 trial that included 49 patients and evaluated the safety and efficacy of oral everolimus, as a single agent, in minimally pretreated patients with metastatic breast cancer. The patients were randomized to receive either 10 mg daily or 70 mg weekly doses of everolimus. While no responses were noted for the weekly therapy, a 12% response rate was noted with the daily therapy. The most important side effect noted in this trial was pneumonitis, which occurred in 11 of 33 patients in the daily dosage group [44].

The efficacy of everolimus was next tested in the neoadjuvant setting in HR-positive patients, in combination with the aromatase inhibitor letrozole [45]. In this randomized phase 2 trial, 272 newly diagnosed postmenopausal patients with operable HR-positive breast cancer received 4 months of neoadjuvant letrozole combined with either everolimus or placebo. The response rate, as estimated by clinical palpation, was higher in the everolimus arm compared with letrozole alone (68.1% vs. 59.1%, respectively; p = 0.062), and a reduction in proliferation, as estimated by Ki-67 staining, was noted in 57% of the patients in the everolimus arm compared to 30% in the placebo arm. More patients experienced a grade 3 or 4 adverse event (AE) in the everolimus group compared to the placebo group (22.6% vs. 3.8%), and a dose reduction or interruption in treatment due to an AE occurred in over half of the patients in the everolimus group. The most common grade 3 or 4 AE was pneumonitis, which resolved shortly after discontinuing everolimus.

The TAMRAD (tamoxifen and RAD001) trial was a randomized phase 2 study involving 111 postmenopausal women with HR-positive advanced breast cancer, randomized to receive tamoxifen alone or tamoxifen in combination with everolimus 10 mg daily [46]. The clinical benefit rate, which was the primary endpoint, was significantly improved in patients receiving tamoxifen plus everolimus versus tamoxifen alone (61% vs. 42%, respectively; p = 0.045). The time to progression (TTP) was also significantly improved in patients treated with tamoxifen and everolimus compared with tamoxifen alone (8.6 vs. 4.5 months, respectively). Preliminary analysis demonstrated that the risk of death was also reduced by 55% with everolimus. Importantly, patients with secondary resistance seemed to benefit more from the addition of everolimus to tamoxifen than patients with primary resistance. An open-label, multicenter, phase 2 study evaluated treatment with everolimus plus letrozole in postmenopausal women with HR-positive metastatic breast cancer after recurrence or progression on one or more endocrine treatments. The study enrolled 69 patients in 7 institutions in Israel. Preliminary findings were presented in an abstract form [47]. Patients had received a median of 2 previous lines (range, 5–1 lines) of hormonal therapy for advanced breast cancer. The overall response rate was 17.7%, the clinical benefit rate was 75.8%, and the progression-free survival (PFS) was 8.7 months. These data indicate the ability of everolimus to reverse endocrine resistance following multiple lines of treatments, and even following re-introduction of hormonal treatments that have already failed. The landmark study that led to the approval of everolimus for the treatment of breast cancer patients was the BOLERO-II trial (Breast cancer trials of OraL EveROlimus) [48]. In this trial, 724 postmenopausal women (median age, 62 years) with HR-positive, HER2-negative, locally advanced or metastatic breast cancer who were refractory to non-steroidal aromatase inhibitors and had documented disease recurrence or progression were randomized to receive exemestane with either everolimus or placebo. The study was stopped

early after a preplanned interim analysis had indicated significantly better PFS for the combined therapy group compared with the exemestane-only group (median 6.9 months vs. 2.8 months, hazard ratio (HR) 0.43, 95% confidence interval (CI) 0.35–0.54; $p < 0.001$). The overall response rates were also improved in the combination group (9.5% vs. 0.4%; $p < 0.0001$). The most common grade 3 or 4 AEs associated with everolimus were stomatitis, anemia, dyspnea, hyperglycemia, fatigue, and pneumonitis. Following these results, the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) authorized everolimus in combination with exemestane for the treatment of postmenopausal women with advanced HR-positive, HER2-negative breast cancer after failure of treatment with letrozole or anastrozole. The addition of everolimus to exemestane was also specifically tested in Asian patients and showed similar efficacy to that observed in non-Asian patients [49]. Taken together, these studies suggest that everolimus adds to the anticancer activity of endocrine therapy in a variety of clinical settings and with different classes of endocrine agents.

Temsirolimus

Temsirolimus was first evaluated as a single agent in 109 heavily pretreated patients with metastatic breast cancer [50]. The patients were randomized to receive either 75 or 250 mg of temsirolimus once a week. An objective response was observed in 9.2% of the patients. A phase 2, 3-arm study evaluated temsirolimus in combination with letrozole in postmenopausal women with HR-positive metastatic breast cancer. The addition of temsirolimus did not increase the response rate but increased the number of patients with PFS at 1 year. However, data were presented only in an abstract form and no statistical analyses are currently available [51]. A subsequent phase 3 study (the HORIZON study) randomized 1,112 postmenopausal women with locally advanced or metastatic breast cancer to receive letrozole alone or letrozole plus oral temsirolimus as a first-line endocrine treatment [52]. The study was terminated prematurely, as the combination yielded no clinical benefit. In an exploratory analysis, improved PFS was shown in letrozole/temsirolimus-treated patients at ages ≤ 65 years (9.0 vs. 5.6 months, HR 0.75, 95% CI 0.60–0.93; $p = 0.009$) [52]. A possible explanation for the failure of the HORIZON study compared to the positive results of the BOLERO-II trial is the previous use of aromatase inhibitors. All patients in the BOLERO-II trial failed on aromatase inhibitors. Indeed, the response rate in the control groups receiving only aromatase inhibitors was 0.4% in the BOLERO-II and 27% in the HORIZON trial. Thus, mTOR inhibition may be active only after the development of endocrine resistance. An alternative explanation for the difference between the trials may be the dosing or schedule of administration of temsirolimus. The temsirolimus dose selected for the HORIZON trial (30 mg/day for 5 days every 2 weeks) showed somewhat reduced efficacy in a phase 2 trial compared to daily administration of 10 mg/day [51].

Rapamycin (Sirolimus)

A recent trial evaluated the addition of tamoxifen to sirolumus in HR-positive metastatic breast cancer. The study was done in 2 groups including 400 patients: (1) prior exposure to aromatase inhibitors or failed on tamoxifen within 6 months and (2) no prior exposure to aromatase inhibitors. In group 1, the addition of sirolimus to tamoxifen increased the response rate from 4% to 39% ($p = 0.00018$) and the TTP from 3.3 to 11.7 months (HR 0.43; $p = 0.0023$). For group 2, the response rate was 33% versus 76% ($p = 0.0043$) and the TTP was 9.0 versus 16.0 months (HR = 0.48; $p = 0.0028$). This study concluded that the combination of sirolimus and tamoxifen was effective and well tolerated [53].

Concluding Remarks

The development of resistance to hormonal agents represents a major challenge in treating HR-positive advanced breast cancer. Complicated mechanisms involving several signaling pathways, among them the PI3K/Akt/mTOR pathway, contribute to the development of endocrine resistance. While recent clinical data support the addition of everolimus to hormonal therapy in previously treated patients with advanced or metastatic breast cancer, the role of mTOR inhibitors in the first line of treatment in advanced disease, in the neoadjuvant, or in the adjuvant setting is not yet established. Studies evaluating the role of everolimus in the adjuvant setting are currently underway as well as an SWOG-NSABP trial in the USA (SWOG-NSABP S1207) and a UNICANCER trial in France (UNIRAD). Results are expected within the next 5 years. Following the negative results of the HORIZON trial, the use of temsirolimus in breast cancer is currently not recommended. Results of ongoing trials may indicate inhibitors of other components of the PI3K/Akt/mTOR pathway as novel therapies for HR-positive breast cancer.

Currently, no biomarkers can predict the response to mTOR inhibitors in breast cancer. The development of such biomarkers is essential in order to enhance the efficacy and to minimize unnecessary AEs. Correlative analyses based on the recent phase 3 trials may allow the discovery of new biomarkers and are currently underway.

Disclosure Statement

The authors report no conflict of interest in this work.

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