

# Resistance to endocrine therapy in breast cancer: exploiting estrogen receptor/growth factor signaling crosstalk

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## Abstract

Targeting the estrogen receptor (ER) is the oldest form of molecular targeted therapy, and the widespread use of the selective estrogen receptor modulator tamoxifen in breast cancer is responsible for major improvements in cure rates, quality of life, and disease prevention in the last 25 years. Newer forms of endocrine therapy now available for the management of endocrine responsive breast cancer include a new generation of aromatase inhibitors, which lower the estrogen ligand for ER, and pure ER antagonists which destroy the receptor. Despite these recent clinical advances, intrinsic and acquired resistance to these endocrine therapies is still a common feature that limits the success of this therapeutic strategy. Recent research into the molecular biology of ER signaling has revealed a remarkably complex interactive signaling with other growth factor signaling pathways in breast cancer cells, potentially explaining some of the reasons behind endocrine therapy action as well as resistance. This view of a more complex ER signaling system has uncovered new molecular targets which, if present in a cancer cell, might be additionally targeted using various signal transduction inhibitors to overcome or prevent resistance to endocrine therapy. In addition, the dynamic inverse relationship between the expression of ER and growth factor receptors brings more excitement to the potential of restoring ER expression in apparently ER-negative cells by inhibition of growth factor signaling. Ongoing clinical trials of endocrine therapy combined with growth factor pathway inhibitors or their downstream signaling elements promise to further improve the present care for breast cancer patients.

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## Introduction

Breast cancer is a classical hormone-dependent tumor, and estrogen is well known to play a major role in the development and progression of the disease. Knowing that nearly 70% of breast tumors express the receptor for estrogen (ER) and/or the progesterone receptor (PgR), an ER-dependent gene product, targeting of the ER using antiestrogen therapy has been a reliable therapeutic modality for all stages of the disease. Although estrogen deprivation, by means of bilateral ovariectomy, was the first endocrine therapeutic modality described for breast

cancer (Beatson 1896), the selective estrogen receptor modulator (SERM) tamoxifen has been the mainstay endocrine therapy of breast cancer for the last 25 years. Tamoxifen is responsible for improved survival in early breast cancer (EBCTCG 1998) as well as improved quality of life for patients with metastatic disease (Jaiyesimi *et al.* 1995). Tamoxifen has also been shown to be effective in reducing the incidence of breast cancer in patients at risk for developing the disease (Fisher *et al.* 1998) and in women with ductal carcinoma-*in situ* (Fisher *et al.* 1999). Over the past decade, therapeutic options against ER-positive breast cancer have expanded tremendously with the addition of several new endocrine agents which either lower the estrogen ligand for the ER (aromatase inhibitors; Osborne 1999) or degrade the ER itself using fulvestrant (Howell *et al.* 2000). These agents, which can lead to a more effective inhibition of

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ER signaling, have been proven clinically successful and are now an integral part of our treatment strategy for breast cancer (Buzdar 2003). These recent therapeutic advances have improved our ability to improve breast cancer outcome with the relatively inexpensive and nontoxic modality of endocrine therapy.

Despite the documented benefits of ER-targeted therapy in breast cancer, it is known that not all patients who have ER or PgR expressing tumors respond to endocrine manipulation (*de novo* resistance) and a substantial number of patients who do respond will develop disease progression or recurrence while on therapy (acquired resistance). While some of the predictors of endocrine therapy failure are clinical factors, such as poor performance status and other indicators of bulky disease, molecular features other than the ER itself must play a role in determining the degree of benefit from endocrine therapy. In support of this, endocrine therapy failures and disease relapses still occur even in clinically disease-free patients in the adjuvant setting who have excellent performance status. Recent years have witnessed tremendous advances in our understanding of ER biology and revealed an increasingly complex process of ER signaling that includes an elaborate interdependence and interaction with other growth factor signaling pathways in the cancer cell (Schiff *et al.* 2003). The recognition of this molecular crosstalk between ER and other growth factor signaling pathways is beginning to help us better understand the causes of endocrine resistance, and to develop new therapeutic strategies to overcome it in breast cancer patients.

### ER functions and crosstalk with growth factor receptor pathways

Estrogen exerts most of its effects through direct activation of ER-regulated gene expression – this is called the genomic action of ER (also known as nuclear-initiated steroid signaling, or NISS) (Nemere *et al.* 2003). Binding of the estrogen ligand to the ER in the nucleus results in receptor phosphorylation, dimerization, and the recruitment of specific coregulator proteins, termed coactivators, which enhance binding of the receptor complex to promoter regions of target genes known as the estrogen response elements (EREs) and augment the receptor's transcriptional activity (Osborne *et al.* 2001, Schiff *et al.* 2005). Subsequent translation leads to the synthesis of crucial proteins which orchestrate cell growth, division, differentiation, and survival, and which promote breast cancer progression. On the other hand, binding of an

antiestrogen to the ER alters the molecular conformation of the receptor and leads to a preferential recruitment of corepressor proteins. As a result, the transcriptional activation function of the receptor complex is inhibited and gene transcription is impeded. Importantly, however, the recruitment of the coregulatory proteins to the receptor complex is a dynamic process that is influenced by the relative accessibility of the various coactivators and corepressors in a given tumor cell. Thus, the agonist versus antagonist effects of SERMs like tamoxifen, which possess mixed agonist/antagonist properties, may be modified by the absolute and relative levels of ER coregulator proteins, and changes in levels of ER coactivator and corepressor proteins have indeed been associated with *de novo* and acquired resistance to endocrine therapy (Schiff *et al.* 2003). Our study of the ER coactivator amplified in breast cancer 1 (AIB1), which is gene-amplified and/or overexpressed in about half of breast cancers, has shown that high tumor levels of this protein may reduce the effectiveness of adjuvant tamoxifen (Osborne *et al.* 2003). Additionally, signaling from multiple kinase pathways, which can phosphorylate ER and its accessory proteins and thereby modify their activity (Font de Mora & Brown 2000) can also augment ER genomic action including in the presence of SERMs (Shou *et al.* 2004). Interestingly, our clinical study mentioned above showed that patients whose tumors expressed high levels of both AIB1 and human epidermal receptor 2 (HER2) had worse outcomes with tamoxifen therapy than all other patients combined (Osborne *et al.* 2003).

In addition to this classic ER genomic action, associated with its nuclear location, a smaller portion of ER may reside in the cell membrane or cytoplasm and initiate more rapid cellular signaling by direct interaction with a variety of signaling pathways (Cato *et al.* 2002, Losel *et al.* 2003). This so-called nongenomic ER action (also referred to as membrane-initiated steroid signaling or MISS) (Nemere *et al.* 2003) has been described in many tissues and target organs as the crucial activity for mediating many estrogen responses (Dhandapani & Brann 2002, Ho & Liao 2002, Kousteni *et al.* 2002, Simoncini *et al.* 2002). Recently, a role for nongenomic ER activity in mediating estrogen-induced growth and survival effects has also been described in breast cancer cells, and the existence of membrane ER has now been established by numerous biochemical, immunohistological, and genetic methods (Levin 2002, Pedram *et al.* 2002, Razandi *et al.* 2003b). This membrane ER can potentially interact with and activate via phosphorylation several membrane tyrosine kinases in

breast cancer cells. A physical association between ER and the insulin-like growth factor receptor (IGFR), for example, has been described and leads to activation of IGFR downstream signaling which is stimulated by tamoxifen, but can be completely blocked by either the pure antiestrogen fulvestrant (Huynh & Pollak 1993) or inhibitors of mitogen activated protein kinase (MAPK) kinase (Kahlert *et al.* 2000). ER can also directly interact with HER2 in the membrane, and this interaction has been shown to be crucial for protecting HER2-overexpressing breast cancer cells from tamoxifen-induced apoptosis (Chung *et al.* 2002). Estrogen-activated membrane ER can also phosphorylate and activate the epidermal growth factor receptor (EGFR) in a process that involves activation of G-proteins, c-Src, and MMPs (Razandi *et al.* 2003a). ER also directly associates with a plethora of other key signaling molecules such as c-Src (Migliaccio *et al.* 2002, Wong *et al.* 2002), Shc (Song *et al.* 2002), and the p85 $\alpha$  regulatory subunit of PI3K (Sun *et al.* 2001, Migliaccio *et al.* 2002). Many of these interactions lead to the activation of key secondary signaling messengers and downstream kinase pathways, such as the p21Ras/p42/44 MAPK and AKT, leading to the activation of various cellular processes such as proliferation, growth, and survival. In addition to activating their known sets of downstream transcription regulators, these kinase signals can also activate nuclear ER activity as well as other components in ER's transcriptional machinery and thus promote ER-dependent transcription (ER genomic activity) (Sun *et al.* 2001, Shou *et al.* 2002, Stoica *et al.* 2003). This loop of pathway interdependence, or bidirectional crosstalk, augments signaling of both ER and growth factor receptor pathways and enhances propagation and survivability of a breast cancer cell by the shared contribution of multiple pathways. More importantly, this crosstalk makes a breast cancer cell potentially more resistant to single forms of molecular therapy, such as ER-targeted therapy, and thus simultaneous inhibition of the ER and other pathways may be necessary to overcome cancer growth.

Clearly, ER actions are involved in an intricate network of crosstalk with other growth factor pathways, and ER nongenomic activity, at least in preclinical models, is highly dependent on growth factor signaling (Fig. 1A). Indeed, overexpression of growth factor receptors such as EGFR/HER2 may augment both genomic and nongenomic ER actions in breast cancer experimental systems (Chung *et al.* 2002, Kumar *et al.* 2002, Stoica *et al.* 2003, Shou *et al.* 2004) and may lead to tamoxifen resistance (Benz *et al.* 1992, Miller *et al.* 1994) (Fig. 1B). Our recent work suggests

that MCF-7 xenografts become growth-stimulated by tamoxifen when HER2 is overexpressed in the originating cell line (Shou *et al.* 2004), perhaps, in part, due to tamoxifen activation of the nongenomic activities of ER. Interestingly, these *de novo* tamoxifen-resistant HER2 overexpressing tumors continue to be sensitive to estrogen deprivation and to the pure ER antagonist fulvestrant (Massarweh *et al.* 2002a), indicating the continued dependence of these cancer cells on a functional ER. Thus, removal of the ligand for ER or downregulation of the ER itself may offer a more complete blockade of both genomic and nongenomic ER activities, and thus may lessen the crosstalk between the ER and the EGFR/HER2 pathway resulting in a lower probability for *de novo* therapeutic resistance (Fig. 1B).

In addition to the role of EGFR/HER2 in *de novo* resistance to endocrine therapies, there is increasing experimental evidence that such growth factor receptor pathways may play an important role in acquired resistance to endocrine therapy as well (Knowlden *et al.* 2003, Nicholson *et al.* 2003). In particular, a few recent provocative clinical studies suggest that acquired resistance to tamoxifen may also be associated with an increase in *HER2* gene amplification and/or expression in patients with breast cancer (Meng *et al.* 2004, Gutierrez *et al.* 2005, Lipton *et al.* 2005).

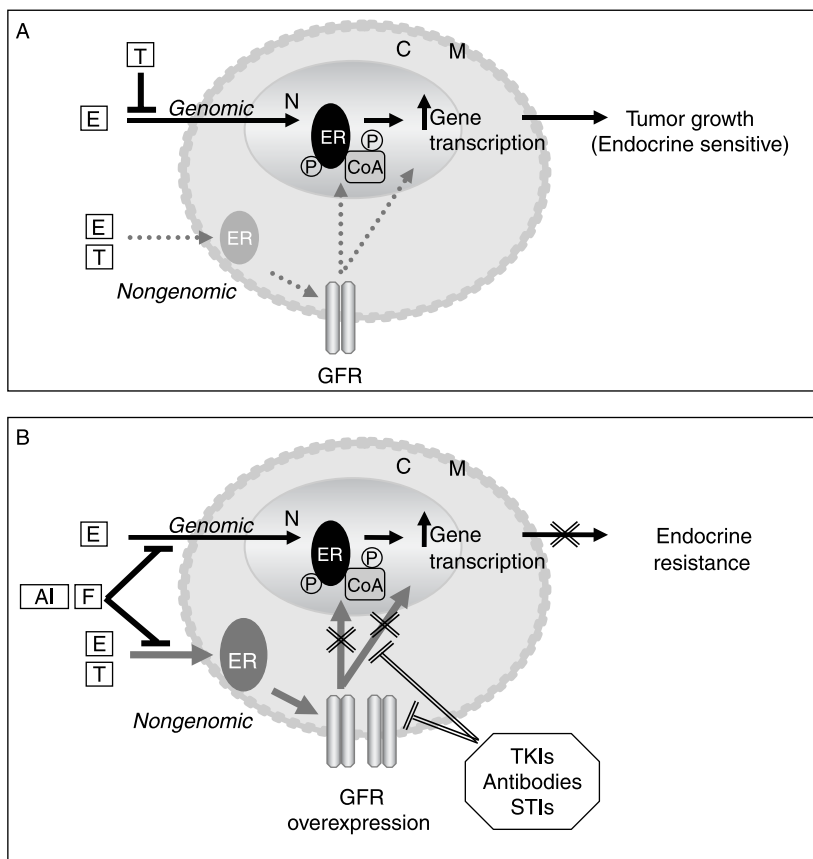
In experimental systems, when MCF-7 cells are treated long-term with tamoxifen *in vitro*, they eventually become resistant and show increased expression of EGFR, which contributes to regulating cancer cell growth under the condition of continuing tamoxifen treatment. Similarly, when fulvestrant-treated MCF-7 cells eventually become resistant to this form of endocrine therapy in culture systems, there is an elevated expression of EGFR and downstream MAPK levels, suggesting a role for this growth factor receptor pathway in acquired resistance to fulvestrant as well (McClelland *et al.* 2001). Data from our *in vivo* xenograft breast cancer model confirm that the levels of EGFR expression do increase markedly in MCF-7 tumors that develop acquired resistance to tamoxifen (Massarweh *et al.* 2002b), and this acquired resistance actually manifests in tumors as tamoxifen-stimulated growth (Osborne *et al.* 1994). From a molecular perspective, it is intriguing how a breast tumor that continues to express ER now becomes stimulated by tamoxifen through overexpression of EGFR/HER2. Since these tumors continue to express ER and remain sensitive to subsequent ER-targeted therapy such as fulvestrant (Osborne *et al.* 1995), this form of resistance cannot be purely growth factor-dependent but has to be, to some extent, mediated by ER signaling

as well. Although the molecular details about the relative contribution of the genomic and nongenomic actions of ER to this form of tamoxifen resistance and the nature of their crosstalk with the growth factor pathways are still under investigation, the above studies can help explain why endocrine therapy alone might not be adequate treatment for some patients with breast cancer (Fig. 1).

### Clinical relevance of ER crosstalk with growth factor signaling pathways

Clinically, some data suggest that breast cancers with higher growth factor receptor expression, in particular EGFR and HER2, are indeed more likely to be resistant

to endocrine therapy (Wright *et al.* 1992, Borg *et al.* 1994, Leitzel *et al.* 1995, Yamauchi *et al.* 1997, Houston *et al.* 1999, De Placido *et al.* 2003, Arpino *et al.* 2005, De Laurentiis *et al.* 2005). However, other studies did not confirm this association (Elledge *et al.* 1998, Berry *et al.* 2000). This discrepancy is possibly related to the heterogeneity in patient populations studied and the treatments given, to retrospective and subset analyses, and to varying methodologies used to measure ER and HER2 among the different studies (Yamauchi *et al.* 2001). More recently, clinical trials in the neoadjuvant setting, which use directly observed clinical response as an endpoint, have indicated a lower response to tamoxifen in breast cancers with high HER2 expression and a selective sensitivity of these



**Figure 1** Estrogen receptor functions and crosstalk with growth factor receptor pathways in breast cancer endocrine resistance – a working model. (A) In estrogen receptor (ER)-positive tumors with low levels of growth factor receptors (GFR), genomic ER activity in the nucleus (N) is predominant, though some nongenomic activity mediated by ER proteins residing at the membrane (M) or the cytoplasm (C) may also occur. These tumors are mostly estrogen (E)-stimulated but tamoxifen (T)-inhibited. (B) In tumors with overexpression or hyperactivation of GFRs, both genomic and nongenomic ER activities are augmented through crosstalk with the GFR pathways. These tumors may be resistant or even stimulated by SERMs like tamoxifen, presumably through activation of the nongenomic ER activity. However, aromatase inhibitors (AI) or pure antiestrogens such as fulvestrant (F), which can block both ER activities and thus halt the crosstalk with the growth factor pathways, may still inhibit these tumors. Alternatively, a combination of anti-ER therapy together with anti GFR-inhibitors, such as tyrosine kinase inhibitors (TKI), antibodies, or other signal transduction inhibitors (STIs), can eliminate the crosstalk and overcome *de novo* endocrine resistance. This strategy may also delay or prevent the development of acquired endocrine resistance that is associated with increased growth factor receptor signaling.

tumors to estrogen deprivation using aromatase inhibitors (Ellis *et al.* 2001, Zhu *et al.* 2004, Dowsett *et al.* 2005). As mentioned above, from a molecular perspective, it does appear that there might be an advantage for using an aromatase inhibitor and the ER downregulator fulvestrant in the treatment of women with ER-positive, HER2-positive breast cancer, since these two treatments can block both genomic and nongenomic activities of ER, thus reducing the crosstalk with growth factor receptor signaling in these tumors.

Since we know from preclinical data that ER function is augmented by crosstalk with growth factor signaling, especially that of EGFR/HER2, and that this crosstalk can be associated with tamoxifen resistance, one strategy to overcome this resistance would be to use tamoxifen in combination with growth factor receptor pathway inhibitors. Preclinical studies have indeed shown that tamoxifen's antitumor activity can be restored or significantly improved in a variety of HER2-overexpressing breast cancer model systems using various growth factor receptor inhibition strategies (Kunisue *et al.* 2000, Kurokawa *et al.* 2000, Argiris *et al.* 2004, Shou *et al.* 2004, Chu *et al.* 2005). In addition, use of growth factor tyrosine kinase inhibitors have been demonstrated to delay resistance to tamoxifen in breast cancer cell systems both *in vitro* (Gee *et al.* 2003) and *in vivo* (Massarweh *et al.* 2002b). Based on these preclinical studies of combining tamoxifen with inhibition of growth factor receptors, a number of clinical studies have been initiated to examine this strategy using a variety of available small molecule inhibitors (Johnston *et al.* 2003). Other clinical studies are looking at combining aromatase inhibitors or fulvestrant with growth factor inhibitors, supported by preclinical evidence for a role for EGFR/HER2 in resistance to these forms of endocrine therapy (McClelland *et al.* 2001, Massarweh *et al.* 2002a,c). A variety of inhibitors are used in these trials, including agents directed at tyrosine kinase moieties, antibodies against surface growth factor receptors, or other drugs which target key signal transduction mediators of growth factor signaling, such as farnesyl transferase inhibitors to block the Ras pathway, mTOR inhibitors, Raf inhibitors, etc. (Johnston 2005). Most of these trials are phase II studies, some of them randomized, with many requiring pretreatment and on-treatment biopsies to detect molecular changes with treatment. In addition, since experimental and, to some extent, clinical evidences suggest that a complete signaling blockade of these growth factor receptor pathways is needed to achieve tumor eradication or long-lasting antitumor effects (Arpino *et al.* 2004b), combinations

of various signaling inhibitors together with endocrine therapy are presently being tested as well. Results from these ongoing trials are likely to become available in the next several years. It will be interesting to see whether these results will confirm predictions from the preclinical models that formed the rationale for these studies in patients. For example, since in various experimental systems tamoxifen has been shown to have the clearest demonstrable resistance pattern that is dependent on molecular crosstalk between ER and other redundant growth factor receptor pathways (Ring & Dowsett 2004, Schiff *et al.* 2004), it is likely that differences in outcome will be more clearly apparent in randomized trials that involve tamoxifen. One might also predict that combining aromatase inhibitors with molecularly targeted therapies such as tyrosine kinase inhibitors would be most effective in the subset of patients who have growth factor pathway overexpressing cancers. Clearly, selection of patients will be important in determining the outcome of these trials, and including biopsy studies during therapy will help validate molecular targets in parallel with clinical endpoints, and will help suggest additional strategies to modulate endocrine therapy response and resistance.

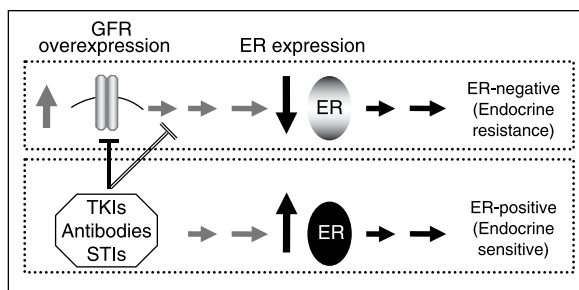
### **Exploiting the dynamic inverse relationship between growth factor signaling and expression of ER – additional therapeutic opportunities**

In breast cancers that are initially endocrine responsive but later develop acquired resistance, it has been a traditionally held belief that ER expression remains a stable phenotype throughout the course of disease (Robertson 1996). This belief is supported by laboratory data that tumors developing resistance to tamoxifen continue to express ER and remain sensitive to subsequent endocrine therapies (Osborne *et al.* 1994). However, we do know that tumor response to sequential endocrine therapies declines progressively with time, and as these tumors become increasingly ER-independent, there is a distinct possibility that some may actually lose ER expression altogether. The question of whether ER can be lost upon disease progression or relapse is relevant clinically, since these patients would, by definition, no longer benefit from endocrine therapy and would thus be candidates for alternative therapeutic modalities. Indeed, some clinical observations do suggest that loss of ER expression may occur in a subset of patients who are initially ER-positive, and this loss is associated with lack of response to subsequent endocrine therapy (Johnston *et al.* 1995, Kuukasjarvi *et al.* 1996, Franco *et al.* 2004).

Potential mechanisms for the loss of ER expression are currently uncertain, but emerging evidence suggests that overactivation of growth factor receptor pathways may contribute to ER loss (Fig. 2). In fact, it has been known for some time that breast cancers which overexpress growth factor receptors such as HER2 are more likely to be ER-negative, and that ER content is negatively correlated with EGFR and HER2 levels in tumors that express both growth factor and estrogen receptors (Zeillinger *et al.* 1989, Ciocca *et al.* 1992, Konecny *et al.* 2003, Arpino *et al.* 2004a). Furthermore, increased expression of growth factor receptors may occur during the progression of breast cancer and might actually promote the acquired loss of ER expression. Indeed, preclinical data suggest that increased growth factor signaling induced by receptor-specific ligands like EGF, IGF-1, transforming growth factor  $\beta$ , and heregulin can downregulate ER protein expression (Stoica *et al.* 1997, 2000a,b) and lead to a more endocrine-independent phenotype (Tang *et al.* 1996). In other experiments, transfection of constitutively active growth factor signaling molecules such as activated HER2, MEK1, and Raf1 led to a marked decrease in ER expression and genomic signaling (Liu *et al.* 1995, El-Ashry *et al.* 1997, Oh *et al.* 2001). More recent data suggest that downstream of growth factor receptors, p42/44 MAPK overactivity may downregulate ER through the transcription factor nuclear factor-kappa B (NFkB) (Holloway *et al.* 2004), which is also elevated in *de novo* ER-independent breast cancer (Biswas *et al.* 2000). Based on these data, it is conceivable that sustained intense overactivity of growth factor receptors such as HER2 may eventually

lead to a complete loss of ER expression and hormone independence (Fig. 2).

This hypothesis is supported by recent observations in our xenograft model of ER-positive HER2-overexpressing breast cancer (Massarweh *et al.* 2006). MCF-7/HER2 tumors (Benz *et al.* 1992) implanted as xenografts in nude mice rapidly grow in the presence of estrogen but quickly regress when estrogen is withdrawn (equivalent to treatment with aromatase inhibitors). However, after 2–3 months of growth inhibition, these tumors resume growth independent of estrogen, thus becoming resistant to estrogen withdrawal. Molecular analysis of these tumors reveals complete loss of ER expression along with a marked increase in phosphorylated HER2 and phosphorylated p42/44 MAPK, supporting the hypothesis that growth factor hyperactivity may indeed induce loss of ER expression. Other clinical observations, though yet fairly limited, also suggest that some ER negative-tumors that overexpress HER2 may actually become ER-positive after treatment with trastuzumab (Munzone *et al.* 2006), and most important, these patients can subsequently benefit from endocrine therapy (Fig. 2). If confirmed, the ability to restore ER expression by targeting growth factor signaling would create an additional opportunity to exploit the dynamic ER interaction with growth factor receptors and could refine even further our approach to breast cancer endocrine therapy. Future studies should examine changes in the expression of therapeutic targets in response to treatment and upon disease progression, since this additional information may help select rational treatments at different stages of breast cancer progression in individual patients.



**Figure 2** Growth factor receptor signaling and tumor estrogen receptor status. Downstream signaling from hyperactive growth factor receptor (GFR) pathways, such as MAPK, downregulates or completely represses estrogen receptor (ER) expression, resulting in ER-negative tumors that cannot respond to endocrine therapy (top). Inhibition of this hyperactive GFR signaling by tyrosine kinase inhibitors (TKIs), antibodies, or other signal transduction inhibitors (STIs) can restore ER expression, and thus, endocrine sensitivity (bottom).

## Summary

Recent advances in understanding ER signaling have revealed a complex web of signaling interactions with other growth factor signaling pathways. Targeting the ER as an isolated pathway may not be an optimal strategy and simultaneous inhibition of other active signaling elements that interact with ER may be necessary to improve endocrine response and prevent resistance. Exploring new targeted therapies in combination with classical endocrine modalities is ongoing in clinical trials and carries the promise of changing our strategies when approaching a patient with potentially endocrine responsive breast cancer.

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