Targeting the HER/EGFR/ErbB Family to Prevent Breast Cancer

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Abstract

Preventing breast cancer is possible with selective estrogen receptor (ER) modulators and aromatase inhibitors, which reduce the risk of invasive disease by up to 65% (up to 73% for ER-positive and no effect for ER-negative cancer) and the risk of preinvasive disease [ductal carcinoma in situ (DCIS)] by up to 50%. Clearly, approaches for preventing ER-negative, and increased prevention of ER-positive breast cancers would benefit public health. A growing body of work (including recent preclinical and clinical data) support targeting the HER family [epidermal growth factor receptor (EGFR), or human epidermal growth factor receptor (HER) 1 or ErbB1) and HER2, HER3, and HER4] for preventing ER-negative and possibly ER-positive breast cancer. Preclinical studies of HER family–targeting drugs in mammary neoplasia show suppression of (i) ER-negative tumors in HER2-overexpressing mouse strains, (ii) ER-negative tumors in mutant Brca1/p53−/− mice, and (iii) ER-positive tumors in the methylNitrosourea (MNU) rat model; tumors arising in both the MNU and mutant Brca1/p53−/− models lack HER2 overexpression. Clinical trials include a recent placebo-controlled phase IIb presurgical trial of the dual EGFR HER2 inhibitor lapatinib that suppressed growth of breast premalignancy [including atypical ductal hyperplasia (ADH) and DCIS] and invasive cancer in patients with early-stage, HER2-overexpressing or -amplified breast cancer. These results suggest that lapatinib can clinically suppress the progression of ADH and DCIS to invasive breast cancer, an effect previously observed in a mouse model of HER2-overexpressing, ER-negative mammary cancer. The preclinical and clinical signals provide a compelling rationale for testing HER-targeting drugs for breast cancer prevention in women at moderate-to-high risk, leading perhaps to combinations that prevent ER-negative and ER-positive breast cancer. Cancer Prev Res; 4(8); 1149–57. ©2011 AACR.

Introduction

Notwithstanding major advances in breast cancer prevention since the late 1990s, the incidence of breast cancer remains high and treating metastatic breast cancer remains challenging. Clearly, effective new preventive strategies for this disease are needed. Large phase III clinical trials have identified several estrogen receptor (ER)-targeting drugs that prevent breast cancer in moderate-to-high–risk women. Selective ER modulators (SERMs; e.g., tamoxifen, raloxifene, and lasofoxifene; refs. 1, 2) and the aromatase inhibitor (AI) exemestane (3) reduce the risk of breast cancer in women without prior breast cancer. Predictably, these drugs only prevent ER-positive tumors. Therefore, there is an urgent need to identify targetable pathways for preventing ER-negative breast cancer, which accounts for approximately one third of breast cancers in the United States and for a substantially higher proportion in Asian countries such as India and China. Increasing evidence, including 2 articles appearing elsewhere in this issue of the journal (4, 5), supports the HER family as potentially useful targets for preventing ER-negative breast cancer.

The HER family [also called the ErbB or epidermal growth factor receptor (EGFR) family] comprises 4 transmembrane receptor tyrosine kinases, EGFR itself (also called HER1) and HER2, HER3, and HER4 (also called ErbB2, ErbB3, and ErbB4). Signaling occurs through both homo- and heterodimeric HER complexes (Fig. 1) and can induce cell proliferation, motility, and invasion. Dysregulated expression and activity of HER family members is prevalent in human neoplasia (6). Strikingly, up to 30% of breast carcinomas overexpress HER2, frequently as a consequence of genomic amplification of a region of the long arm of chromosome 17 (17q21) that includes the HER2 locus. HER2 overexpression may be more frequent in ER-negative than in ER-positive cancers, drives aggressive disease, and thus represents an important therapeutic target. The humanized monoclonal antibody trastuzumab (Herceptin) was the first agent developed for HER2 targeting and has dramatically improved outcomes among women with HER2-overexpressing breast cancer.
with HER2-positive (defined by HER2 overexpression and/or amplification) breast cancer.

Effective small-molecule inhibitors of EGFR/ErbB tyrosine kinases, including the EGFR inhibitors gefitinib (Iressa) and erlotinib (Tarceva) and the dual EGFR/HER2 inhibitor lapatinib (Tykerb), have also been developed. Lapatinib is U.S. Food and Drug Administration (FDA)-approved for treating advanced or metastatic HER2-overexpressing breast cancer. The initial approval was for use in combination with capecitabine in patients with metastatic breast cancer who had received prior therapy including an anthracycline, a taxane, and trastuzumab (7). Lapatinib is also approved for use in combination with the AI letrozole to treat postmenopausal women with hormone receptor [ER or progesterone receptor (PR)]-positive, HER2-positive advanced breast cancer (http://www.cancer.gov/cancertopics/druginfo/fda-lapatinib). Subgroup analyses of clinical breast cancer therapy trials identified HER2 overexpression as a key determinant of sensitivity to lapatinib (8–10), whereas EGFR expression does not appear to be predictive (11).

Agents targeting the ER and HER axes have a spectrum of preclinical and FDA-approved clinical activity in the prevention and treatment of breast cancer (Fig. 2). Lapatinib has more complete activity in blocking HER signaling (vs. the other major HER family–targeting agents), indicating its potential for preventing ER-positive and -negative breast cancer (Fig. 1). Given that HER2 is overexpressed in a large proportion of preinvasive ductal carcinomas in situ (DCIS; refs. 12–14), lapatinib and other HER family–targeting drugs have a strong potential for breast cancer prevention.

Preclinical studies

Several studies have explored ErbB inhibitors for chemoprevention in animal breast cancer models (Table 1). The Arteaga group provided early proof of principle for the preventive efficacy of EGFR inhibition in work using bigenic mice expressing neu (the rat HER2 homologue) and TGFα expressed from the mouse mammary tumor virus (MMTV) promoter (15). Simultaneous expression of mammary-targeted transgenes encoding neu and TGFα (an EGFR ligand) provides a model for human breast cancers coexpressing HER2 and EGFR. Administration of the EGFR tyrosine kinase inhibitor tyrphostin (AG1478) from 8 weeks onward significantly delayed tumor onset in virgin female mice. Short-term tyrphostin administration suppressed DNA synthesis in tumor cells as well as in uninvolved epithelium, but induction of apoptosis was not observed, suggesting that antiproliferative effects were the primary antitumor mechanism. Consistent with the observed reduction in proliferation, tumor lysates from tyrphostin-treated animals exhibited decreases in cyclin D1 levels and cyclin-dependent kinase 2 (cdk2) activity and increased levels of the cell-cycle inhibitor p27kip1.

Two subsequent studies examined the EGFR inhibitor gefitinib in the FVB MMTV/neu (16) and BALB/c MMTV/ neuT (17) mouse models of breast cancer, in which tumor formation is driven by expression of the wild-type (in the
As observed for both gefitinib and tyrphostin, lapatinib suppressed proliferation in mammary epithelium, with no effect on apoptosis. Mechanistic analyses indicated commensurate molecular alterations including decreased cyclin D1 expression and increased p27 transcripts.

All of the studies discussed above utilized HER2-overexpressing mouse strains, a rational choice based on a predicted model in which ErbB inhibitors suppress HER2 signaling via modulation of EGFR–HER2 heterodimers. Intriguingly, however, 2 recent studies, one of gefitinib (19) and the other of lapatinib (5), showed that HER targeting can also be effective in a non–HER2-overexpressing model (although a physiologic level of HER2 is present). Both gefitinib and lapatinib suppressed tumor multiplicity and caused regression of established tumors in methylNitosourea (MNU)-treated rats, a widely used model of ER-positive disease. Phospho-EGFR and phospho-HER2 levels were reduced in tumor tissues from the lapatinib-treated rats, suggesting that lapatinib effects are mediated by HER1 dimers and possibly also work through suppressing physiologic levels of HER2 (Fig. 1). No reduction in phosphorylated extracellular signal–regulated kinase (phospho-ERK) levels was detected in MNU-induced tumors from lapatinib-treated rats, which contrasts with previously reported effects of gefitinib and tyrphostin on phospho-ERK in HER2/neu transgenic strains (15–17) and of lapatinib on breast cancer cell lines (20, 21). Instead, phosphorylation of Src family kinase members Lyn and Lck was reduced, as were levels of phospho-AKT and IGF-1R. Molecular markers of increased apoptosis were also identified, although apoptosis was not directly assayed. The observed reduction of IGF-1R in lapatinib-treated, MNU-induced mammary tumors (5) is intriguing and potentially indicates cross-talk between the HER family and IGF-1R (22). Lapatinib is known to suppress the migration and invasion of cultured breast cancer cell lines induced by leptin and IGF-1 (23). Because these factors are elevated in association with obesity, lapatinib could potentially modify the increased breast cancer risk that has been identified for obese postmenopausal women. Therapeutic trials of lapatinib clearly identify HER2 overexpression as the key determinant of lapatinib sensitivity (8–10), whereas Li and colleagues found that lapatinib was active preclinically in a model where HER2 was present but not overexpressed (5). This apparent discrepancy suggests that ER-driven breast neoplasia could be differentially sensitive to signaling input from the HER family at preinvasive stages compared with later stages of tumor progression.

A recent study from Gerburg Wulf’s group suggests that EGFR inhibition may be clinically significant in the absence of HER2 amplification, specifically in the context of BRCA1 deficiency (24). This group found that EGFR expression increased in cultured mammary epithelial cells in response to siRNA-mediated BRCA1 depletion, particularly in the subset expressing the putative stem cell marker aldehyde dehydrogenase 1 (ALDH1). Corresponding EGFR upregulation occurred in the actin of Brca1-deficient mammary glands from MMTV/Cre transgenic females administered gefitinib.
Erlotinib treatment initiated at 3 months of age. Tumors that did develop tended to lack EGFR expression and to be ER-negative, showing a selective suppression of ER-negative tumor formation. Furthermore, tumors from erlotinib-treated animals lacked ALDH1 expression, potentially suggesting a reduced stem cell component. This study suggests the exciting possibility that EGFR inhibition may be a viable strategy for reducing ER-negative breast cancer risk in carriers of mutant BRCA1 alleles (25).

Clinical trials

Anti-HER2 drugs have been used for years for treating HER2-positive breast cancer. The humanized monoclonal antibody trastuzumab was the first anti-HER2 drug shown to be active in breast cancer (Table 2). Its effectiveness was initially shown in treating metastatic HER2-positive breast cancer (26) and subsequently in treating early-stage, HER2-positive breast cancer (27) and in neoadjuvant settings involving HER2-positive disease (before surgical resection; ref. 28). Two phase III adjuvant trials of trastuzumab recently showed a dramatic prolongation of median disease-free survival in women with early-stage, HER2-positive breast cancer (29). This dramatic efficacy revolutionized the treatment of this form of breast cancer, thus converting the outcome of HER2-positive patients from relatively poor to relatively good (compared to HER2-negative, hormone receptor–negative patients).

Two new anti-HER2 antibodies have been tested clinically with promising results. Pertuzumab functions by inhibiting heterodimerization of HER2 with HER3. This antibody suppresses the growth of breast tumors, including tumors that do not have HER2 overexpression, in mouse xenograft experiments (30), was active in early-phase clinical trials (31) and is now being tested clinically in combination with trastuzumab in the Neoadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation (NeoSPHERE) trial (32). Trastuzumab–DM1 is a HER2 antibody drug conjugate in which trastuzumab is fused to the antimicrotubule agent DM1. Trastuzumab–DM1 is effective in treating HER2-positive metastatic breast cancer that is resistant to trastuzumab or lapatinib (33).
### Table 2. Clinical studies of ErbB inhibitors in breast cancer

<table>
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<tr>
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<th>Target</th>
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<tr>
<td>Tras (I-line, randomized phase II)</td>
<td>HER2</td>
<td>Metastatic HER2-positive</td>
<td>I-line Tras produced a 26% objective response rate; response rate in 3-HER2 overexpression was 35%, with a CBR of 48%</td>
<td>(26)</td>
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<tr>
<td>Tras (phase III HERA trial; initial results)</td>
<td>HER2</td>
<td>Early-stage, HER2-positive</td>
<td>Tras for 1 y after adjuvant chemotherapy improved DFS; Tras HR (vs. observation) = 0.54 (95% CI: 0.43–0.67; P &lt; 0.0001)</td>
<td>(49)</td>
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<tr>
<td>Tras (longer-term HERA results)</td>
<td>HER2</td>
<td>Early-stage, HER2-positive</td>
<td>Tras for 1 y after adjuvant chemotherapy improved overall survival—HR for risk of death (vs. observation) was 0.66 (95% CI: 0.47–0.91; P = 0.0115)</td>
<td>(27)</td>
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<tr>
<td>Tras (phase III neo-adjuvant)</td>
<td>HER2</td>
<td>HER2-positive</td>
<td>Tras + chemotherapy (paclitaxel followed by FEC) improved pCR (65.2%) vs. chemotherapy alone (26%; P = 0.016)</td>
<td>(50)</td>
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<tr>
<td>Tras + chemotherapy (two phase III adjuvant trials)</td>
<td>HER2</td>
<td>Early-stage, HER2-positive</td>
<td>Dramatically prolonged median DFS—HR = 0.48 (P &lt; 0.0001), and produced 33% reduced risk of death (P = 0.015)</td>
<td>(29)</td>
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<tr>
<td>Pertuzumab (phase I)</td>
<td>HER2</td>
<td>Metastatic cancer</td>
<td>PR in 2 patients (nonbreast cancer); stable disease lasting &gt;2.5 m in 6 patients</td>
<td>(31)</td>
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<tr>
<td>Tras-DM1 (phase II)</td>
<td>HER2</td>
<td>Metastatic HER2-positive, resistant to HER2 therapy</td>
<td>Produced 26% objective response rate</td>
<td>(33)</td>
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<tr>
<td>Gefitinib (phase II)</td>
<td>EGFR</td>
<td>Advanced/metastatic</td>
<td>0% CR + PR</td>
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<td>Erlotinib (phase II)</td>
<td>EGFR</td>
<td>Advanced/metastatic</td>
<td>3% PR</td>
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<td>Lapat (phase III)</td>
<td>EGFR/HER2</td>
<td>Metastatic HER2-positive</td>
<td>Lapat + capecitabine prolonged TTP (vs. capecitabine; HR = 0.49; 95% CI: 0.34–0.71; P &lt; 0.001)</td>
<td>(37)</td>
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<tr>
<td>Lapat (phase II)</td>
<td>EGFR/HER2</td>
<td>Refractory, metastatic</td>
<td>Modest activity (6% clinical benefit)</td>
<td>(61)</td>
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<td>Lapat (1st-line phase III)</td>
<td>EGFR/HER2</td>
<td>Metastatic</td>
<td>Lapat + paclitaxel improved TTP (HR = 0.53; 95% CI: 0.31–0.89; P = 0.005) and event-free survival (HR = 0.52; 95% CI: 0.31–0.86; P = 0.004)—all vs. placebo</td>
<td>(9)</td>
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<tr>
<td>Lapat + letrozole (1st-line phase III)</td>
<td>EGFR/HER2</td>
<td>Metastatic, hormone-receptor-positive</td>
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<td>(10)</td>
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<tr>
<td>Lapat (phase II neoadjuvant)</td>
<td>EGFR/HER2</td>
<td>Inflammatory breast cancer</td>
<td>Lapat monotherapy followed by Lapat + paclitaxel produced a 78% clinical response rate in HER2-positive disease</td>
<td>(38)</td>
</tr>
<tr>
<td>Lapat, Tras (phase III)</td>
<td>EGFR/HER2</td>
<td>Tras-resistant metastatic HER2-positive</td>
<td>Lapat + Tras delayed progression, was superior to Lapat-alone for PFS (HR = 0.73; 95% CI: 0.57–0.93; P = 0.008) and CBR (24.7% vs. 12.4%)</td>
<td>(40)</td>
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(Continued on the following page)
In addition to these intravenous monoclonal antibodies, oral anti-EGFR therapies have also been tested for the treatment of breast cancer. Erlotinib and gefitinib have been tested in metastatic breast cancer, where they have had limited activity (34, 35). The dual tyrosine kinase inhibitor lapatinib was highly active in combination with chemotherapy for treating HER2-positive metastatic breast cancer (36, 37) and in inflammatory breast cancer, which is an aggressive, biologically distinct form with a higher frequency of HER2 overexpression versus other breast cancer (38, 39). Recent therapeutic trials show that lapatinib plus trastuzumab delayed tumor progression in patients who had previously failed on trastuzumab alone (40). This effect may be due to the ability of lapatinib to inhibit EGFR (ErbB1) dimers (Fig. 1B). This clinical activity of lapatinib in the metastatic setting led to FDA approval of lapatinib in combination with capecitabine for the treatment of HER2-positive breast cancer and also provided the rationale for testing lapatinib in the clinical setting of early-stage, HER2-positive breast cancer, which is currently ongoing in the Tykerb Evaluation after Chemotherapy (TEACH) trial.

Several trials have tested anti-HER2 therapies in the neoadjuvant setting. Results from the phase III neoadjuvant GeparQuinto and Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (NeoALTTO) trials, both comparing lapatinib and trastuzumab, were presented at the San Antonio Breast Cancer Symposium in December 2010. The GeparQuinto trial compared lapatinib plus standard chemotherapy with trastuzumab plus standard chemotherapy given prior to definitive surgery. The NeoALTTO trial compared standard chemotherapy plus lapatinib and trastuzumab with standard chemotherapy plus either lapatinib or trastuzumab. The primary endpoint for both trials was pathologic complete response at the time of surgery.

The GeparQuinto trial showed that both lapatinib and trastuzumab induced pathologic complete responses, although trastuzumab was significantly more active in the metastatic setting. In the early-stage setting, lapatinib plus chemotherapy was associated with a higher pathologic complete response rate compared to trastuzumab plus chemotherapy. These results support the use of lapatinib in combination with chemotherapy in the early-stage setting for patients with HER2-positive breast cancer.
The NeoALTTO trial showed that the pathologic complete response rate was 51.3% in the lapatinib plus trastuzumab (plus standard chemotherapy) arm versus 24.7% in the lapatinib (plus standard chemotherapy) arm and 29.5% in the trastuzumab (plus standard chemotherapy) arm, with the first (lapatinib plus trastuzumab) being superior to the last (trastuzumab; P ≤ 0.0001). The complete response rates of chemotherapy with lapatinib alone (24.7%) and with trastuzumab alone (29.5%) were not statistically significantly different (P = 0.34; ref. 42). Assessments of safety, overall survival, and disease-free survival are ongoing in both trials. Future reports from these 2 important studies will help clarify the use of anti-HER2 therapy in treating breast cancer in the neoadjuvant setting.

Trastuzumab plus lapatinib without chemotherapy has also been tested clinically. The preliminary report of a multicenter phase II trial showed that trastuzumab plus lapatinib produced a high pathologic response rate in locally advanced HER2-positive breast cancer—28% overall (21% in ER-positive and 40% in ER-negative disease; ref. 43). All of the previously discussed clinical studies were for treating invasive breast cancer. Recent clinical studies have also tested anti-HER2 drugs for breast cancer prevention. Kuerer and colleagues studied the effect of a single dose of trastuzumab given 14 to 28 days prior to surgical resection in women with DCIS lesions (44). There was no pathologic response or change in Ki67 staining (as compared with pretreatment), but there was evidence of significantly augmented antibody-dependent cell-mediated cytotoxicity in 100% of the trastuzumab-treated women. Of note, the DCIS showed HER2 overexpression in only 24 of 69 enrolled patients (35%). The substantial proportion of subjects with HER2-negative DCIS may have accounted for the lack of reduction in Ki67 staining.

DeCensi and colleagues tested a short (3 weeks) course of lapatinib for activity in ductal intraepithelial neoplasia [DIN; comprising atypical ductal hyperplasia (ADH) and DCIS], ductal hyperplasia (DH) without atypia, and invasive breast tissue in a randomized, placebo-controlled phase II presurgical trial in early-stage, HER2-positive breast cancer patients (4). Lapatinib reduced Ki67 in breast cancer tissue by 9.3% (compared with pre-lapatinib treatment), whereas placebo treatment was associated with a 15% increase in proliferation (vs. pretreatment; P = 0.008); these findings are consistent with other recent short-term lapatinib data (45). The antiproliferative effect of lapatinib (4) was statistically significant in ER-negative/PR-negative tumors but was only a trend in ER-positive/PR-positive tumors. These results suggest that HER2-positive, ER-negative tumors are more sensitive to lapatinib (vs. HER2-positive, ER-positive tumors) which is supported by some evidence from the therapeutic setting (43, 46). In addition this study suggested that phosphatase and tensin homolog (PTEN) overexpression was a potential predictive marker, consistent with other preclinical and clinical data on phosphoinositide 3-kinase (PI3K) pathway activation (47). Src pathway activation in preclinical and clinical studies is also a promising predictive marker for lapatinib (48).

Regarding effects in preinvasive tissue surrounding breast cancer in the DeCensi and colleagues trial, lapatinib treatment did not affect the prevalence of DIN lesions but did produce a trend toward reduced proliferation in DIN cells (Ki67 labeling index of 17.0%) versus placebo (23.4%; P = 0.067) and significantly reduced proliferation in DH cells (1.8%) versus placebo (2.5%; P = 0.006). These results support the hypothesis that lapatinib will suppress the progression of DH and DIN (ADH and DCIS) lesions to invasive breast cancer in humans, also supported by relevant preclinical results in MMTV/neu mice (18). An intriguing, unanswered question is whether cells of these DH and DIN lesions overexpressed HER2 or EGFR, an issue relevant to the development of predictive markers for prevention about which DeCensi and colleagues do not comment. Such results would be particularly useful for future testing of lapatinib in women with DIN or DH lesions. Despite this caveat, the results of DeCensi and colleagues provide strong support for testing lapatinib and other oral receptor tyrosine kinase inhibitors for the prevention of HER2-overexpressing breast cancer.

Conclusions

Including very recent preclinical and clinical data (4, 5), the growing body of work on HER family targeting certainly advances the field of treatment and prevention of EGFR- and HER2-positive breast cancer, including both ER-negative and -positive disease. Given the strong antiproliferative and anticaner activity of lapatinib and its generally acceptable toxicity profile, it is time to test lapatinib and other HER2-targeting drugs for breast cancer prevention in women at a high risk of this disease. The most appropriate population for prevention with anti-HER2 drugs would be women with HER2-positive DCIS lesions. Indeed, the NSABP is currently testing trastuzumab in an ongoing phase III trial in women with HER2-positive DCIS (NSABP B-43, NCT00769379), and investigators at MD Anderson Cancer Center are conducting a phase II multicenter presurgical trial of lapatinib in patients with EGFR- or HER2-positive DCIS (NCT00555152). These studies should provide further evidence bearing on the utility of anti-HER2 therapy for preventing invasive breast cancer. Another unanswered question is whether lapatinib will prevent the development of cancers that do not overexpress HER2. Li and colleagues provide provocative data, suggesting that lapatinib may prevent tumors that do not overexpress HER2 (presumably through its effect on EGFR and/or lower levels of HER2; ref. 5). To address this issue, it will be necessary in the future to conduct clinical trials testing lapatinib’s effect on non-HER2-overexpressing DCIS.

Predictive markers (as discussed above) and risk markers remain a very important issue for future clinical prevention trials of lapatinib and other HER family–targeting drugs. Risk models integrating family history, breast density, target-tissue markers, and germ line changes (e.g., BRCA
mutations and single-nucleotide polymorphisms) are helping to identify high breast cancer risk. The overall data on breast cancer prevention with estrogen-targeting and HER family–targeting agents suggest the possibility of developing combinations that may prevent ER-negative breast cancer and increase prevention of DCIS and ER-positive invasive disease.

Disclosure of Potential Conflicts of Interest

P.H. Brown is a consultant/advisory Board for Susan G. Komen for the Cure organization.

References


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