Published in final edited form as:

Cancer Prev Res (Phila). 2011 August ; 4(8): 1149–1157. doi:10.1158/1940-6207.CAPR-11-0334.

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

Louise R. Howe¹ and Powel H. Brown²

¹Department of Cell and Developmental Biology, Weill Cornell Medical College. 1300 York Avenue, New York, NY 10065

²Department of Clinical Cancer Prevention, The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030

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 estrogen receptor (ER)-positive and no effect for ER-negative cancer] and the risk of pre-invasive disease [ductal carcinoma *in situ* (DCIS)] by up to 50%. Clearly, approaches for preventing ER-negative, and increased prevention of ER-positive, cancers would benefit the public health. A growing body of work (including recent preclinical, clinical data) support targeting the HER family [epidermal growth factor receptor (EGFR, or HER1 or ErbB1) and HER2, -3, and -4] for preventing ER-negative and possibly ER-positive breast cancer. Preclinical studies of HER family-targeting drugs in mammary carcinogenesis demonstrate suppression of 1) ER-negative tumors in *HER2*-overexpressing mouse strains, 2) ER-negative tumors in mutant-*BRCA1/p53*^{+/-} mice, and 3) 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 a moderate-to-high risk, leading perhaps to combinations that prevent ER-negative and ER-positive breast cancer.

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

Corresponding Author: Powel H. Brown, MD, PhD, Professor, Department of Clinical Cancer Prevention, The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030. Phone: 713-792-4509; Fax: 713-794-4679; phbrown@mdanderson.org.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

approximately one-third of breast cancers in the U.S. and for a substantially higher proportion in Asian countries such as India and China. Increasing evidence, including two papers 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 four transmembrane receptor tyrosine kinases, EGFR (also called HER1) itself and HER2, -3, and -4 (also called ErbB2, -3, and -4). 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 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-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 used 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).

HER- and other molecular-targeted agents have a spectrum of preclinical and FDA-approved clinical activity in the prevention and treatment of breast cancer (Fig. 1A). Lapatinib has more complete activity in blocking HER signaling (versus the other major HER family-targeting agents), indicating its potential for preventing ER-positive and -negative breast cancer (Fig. 1B). 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 homolog) and transforming growth factor α (TGF α) expressed from the mouse mammary tumor virus (MMTV) promoter (15). Simultaneous expression of mammary-targeted transgenes encoding *neu* and TGF α (an EGFR ligand) provides a model for human breast cancers co-expressing HER2 and EGFR. Administration of the EGFR tyrosine kinase inhibitor tyrphostin (AG1478) from eight 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 p27^{kip1}.

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 FVB MMTV/*neu* model) or mutationally activated (in the BALB/c MMTV/*neuT* model) rat *HER2* homolog. Tumors in *HER2/neu* transgenic mice generally lack ER α expression, and thus these strains simultaneously provide a model of *HER2*-overexpressing and ER-negative disease. Both studies demonstrated preventive efficacy of gefitinib. Lu and colleagues showed a substantial delay in tumor onset (median tumor latency increased from 230 to more than 310 days) in virgin FVB MMTV/*neu* females administered gefitinib from three months of age (16), and Piechocki et al. observed a striking reduction in tumor multiplicity in BALB/c MMTV/*neuT* mice treated with gefitinib for 9 weeks (from age 5 to 14 weeks; ref. 17). Mechanistic studies indicated that gefitinib suppressed mammary tumor development predominantly through antiproliferative effects.

More recently, the dual EGFR/*HER2* inhibitor lapatinib was also evaluated for cancer prevention (5, 18). As does gefitinib, lapatinib suppresses ER-negative mammary tumor development in FVB MMTV/*neu* mice in a dose-dependent manner, again apparently through an antiproliferative effect (18). Of note, limited-duration (five-months) treatment suppressed the formation of premalignant lesions and microscopic invasive tumors. 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, two recent studies—one of gefitinib (19), 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 methylnitrosourea (MNU)-treated rats, a widely used model of ER-positive disease. Phospho-EGFR and phospho-*HER2* levels were reduced in tumor tissues from lapatinib-treated rats (5), suggesting that the lapatinib effects are mediated by *HER1* dimers and possibly also work through suppressing physiologic levels of *HER2* (Fig. 1B). No reduction in phosphorylated extracellular signal-regulated kinase (phospho-ERK) levels was detected in MNU-induced tumors from lapatinib-treated rats, which is surprising in view of contrasting effects on phospho-ERK with gefitinib and tyrphostin in *HER2/neu* transgenic strains (15–17) and with lapatinib in 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 insulin-like growth factor-1 receptor (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 suppressed the migration and invasion of cultured breast cancer cell lines induced by leptin and IGF-1 (23). Since 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 et al. 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 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 small-interfering RNA (siRNA)-mediated *BRCA1* depletion, particularly in the subset expressing the putative stem cell marker aldehyde dehydrogenase 1 (ALDH1). Corresponding EGFR upregulation occurred in the acini of *BRCA1*-deficient mammary glands from MMTV/Cre, *BRCA1^{flox/flox}/p53^{+/-}* mice. Mammary tumor latency in these mice was significantly increased by erlotinib treatment initiated at three months of age. Tumors that did develop tended to lack EGFR expression and to be ER-positive, demonstrating 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 demonstrated in treating metastatic HER2-positive breast cancer (26) and subsequently in treating early-stage HER2-positive breast cancer (27) and in neo-adjuvant settings involving HER2-positive disease (before surgical resection; ref. 28). Two phase III adjuvant trials of trastuzumab recently demonstrated 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 (vis-à-vis HER2-negative, hormone receptor-negative patients).

Two new HER2 antibodies have been tested clinically with promising results. The HER2 monoclonal antibody 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 with encouraging results 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 anti-microtubule agent DM1. Trastuzumab-DM1 is effective in treating HER2-positive metastatic breast cancer that is resistant to trastuzumab or lapatinib (33).

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 significantly more so with trastuzumab (31.3%) than with lapatinib (21.7%; $P < 0.03$; ref. 41). 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 two important studies will help clarify the use of anti-HER2 therapy in treating breast cancer in the neoadjuvant setting.

Trastuzumab plus lapatinib *without* chemotherapy also has 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 co-investigators 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 pre-treatment), 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 et al. tested a short (three-weeks) course of lapatinib for activity in ductal intraepithelial neoplasia [DIN, comprising atypical ductal hyperplasia (ADH) and DCIS], ductal hyperplasia without atypia (DH), and invasive breast tissue in a randomized, placebo-controlled phase II presurgical trial in early-stage, HER2-positive breast-cancer patients (4); Lapatinib reduced Ki-67 in breast cancer tissue by 9.3% (compared with pre-lapatinib treatment), whereas placebo treatment was associated with a 15% increase in proliferation (versus pre-treatment; $P = 0.008$); these findings are consistent with other recent short-term

lapatinib data (45). The anti-proliferative 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 (versus HER2-positive, ER-positive tumors) to lapatinib, as is supported by some evidence from the therapeutic setting (43, 46). In addition to suggesting HER2 and ER status, this study suggested that phosphatase and tensin homolog (PTEN) overexpression was a potential predictive marker, as is consistent with other preclinical and clinical data on phosphoinositide 3-kinase (PI3K) pathway activation (46). Src pathway activation in preclinical and clinical studies is also a promising predictive marker for lapatinib (47).

Regarding effects in pre-invasive tissue surrounding breast cancer in the DeCensi et al. trial, lapatinib treatment did not affect the prevalence of DIN lesions but did produce a trend towards reduced proliferation in DIN cells (Ki-67 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 [17]. 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 et al. 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 et al. 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 or -positive disease. Given the strong anti-proliferative and anti-cancer 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 M. D. Anderson Cancer Center are conducting a phase II multi-center pre-surgical 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 et al. 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 germline 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.

Acknowledgments

P.H. Brown acknowledges (and is a member of) the Scientific Advisory Board for the Susan G. Komen for the Cure organization.

Grant Support

This work was supported in part by NIH grants R01-CA078480 (to PHB) and R01-CA131219 (to LRH) and a grant from the Breast Cancer Research Foundation (to PHB).

References

1. Cuzick J, et al. Preventive therapy for breast cancer: a consensus statement. *Lancet Oncol.* 12(5): 496–503. [PubMed: 21441069]
2. Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, et al. Update on the national surgical adjuvant breast and bowel project study of tamoxifen and raloxifene (STAR) P-2 trial: Preventing breast cancer. *Cancer Prev Res (Phila).* 2010; 3:696–706. [PubMed: 20404000]
3. Goss PE, et al. Exemestane for Breast-Cancer Prevention in Postmenopausal Women. *N Engl J Med.* 2011
4. DeCensi A, Puntoni M, Pruneri G, Guerrieri-Gonzaga A, Lazzeroni M, Serrano D, et al. Lapatinib Activity in Premalignant Lesions and HER2-positive Cancer of the Breast in a Randomized, Placebo-controlled Presurgical Trial. *Cancer Prev Res.* 2011; 4
5. Li J, Cho Y-Y, Langfald A, Carper A, Lubet RA, Grubbs CJ, et al. Lapatinib, a preventive/therapeutic agent against mammary cancer, suppresses RTK-mediated signaling through multiple signaling pathways. *Cancer Prev Res.* 2011; 4
6. Arteaga CL, Moulder SL, Yakes FM. HER (erbB) tyrosine kinase inhibitors in the treatment of breast cancer. *Semin Oncol.* 2002; 29(3 Suppl 11):4–10. [PubMed: 12138392]
7. Ryan Q, et al. FDA drug approval summary: lapatinib in combination with capecitabine for previously treated metastatic breast cancer that overexpresses HER-2. *Oncologist.* 2008; 13(10): 1114–1119. [PubMed: 18849320]
8. Burstein HJ, et al. A phase II study of lapatinib monotherapy in chemotherapy-refractory HER2-positive and HER2-negative advanced or metastatic breast cancer. *Ann Oncol.* 2008; 19(6):1068–1074. [PubMed: 18283035]
9. Di Leo A, et al. Phase III, double-blind, randomized study comparing lapatinib plus paclitaxel with placebo plus paclitaxel as first-line treatment for metastatic breast cancer. *J Clin Oncol.* 2008; 26(34):5544–5552. [PubMed: 18955454]
10. Johnston S, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J Clin Oncol.* 2009; 27(33):5538–5546. [PubMed: 19786658]
11. Press MF, et al. HER-2 gene amplification, HER-2 and epidermal growth factor receptor mRNA and protein expression, and lapatinib efficacy in women with metastatic breast cancer. *Clin Cancer Res.* 2008; 14(23):7861–7870. [PubMed: 19047115]
12. Bartkova J, et al. Immunohistochemical demonstration of c-erbB-2 protein in mammary ductal carcinoma in situ. *Hum Pathol.* 1990; 21(11):1164–1167. [PubMed: 1977679]
13. Park K, et al. HER2 status in pure ductal carcinoma in situ and in the intraductal and invasive components of invasive ductal carcinoma determined by fluorescence in situ hybridization and immunohistochemistry. *Histopathology.* 2006; 48(6):702–707. [PubMed: 16681686]
14. Ramachandra S, et al. Immunohistochemical distribution of c-erbB-2 in in situ breast carcinoma--a detailed morphological analysis. *J Pathol.* 1990; 161(1):7–14. [PubMed: 1973459]
15. Lenferink AE, et al. Blockade of the epidermal growth factor receptor tyrosine kinase suppresses tumorigenesis in MMTV/Neu + MMTV/TGF-alpha bigenic mice. *Proc Natl Acad Sci U S A.* 2000; 97(17):9609–9614. [PubMed: 10931950]
16. Lu C, et al. Effect of epidermal growth factor receptor inhibitor on development of estrogen receptor-negative mammary tumors. *J Natl Cancer Inst.* 2003; 95(24):1825–1833. [PubMed: 14679152]

17. Piechocki MP, et al. Gefitinib prevents cancer progression in mice expressing the activated rat HER2/neu. *Int J Cancer*. 2008; 122(8):1722–1729. [PubMed: 18076070]
18. Strecker TE, et al. Effect of lapatinib on the development of estrogen receptor-negative mammary tumors in mice. *J Natl Cancer Inst*. 2009; 101(2):107–113. [PubMed: 19141783]
19. Lubet RA, Szabo E, Christov K, Bode AM, Ericson ME, Steele VE, et al. Effects of gefitinib (Iressa) on mammary cancers: preventive studies with varied dosages, combinations with vorozole or targretin, and biomarker changes. *Mol Cancer Ther*. 2008; 7:972–979. [PubMed: 18375820]
20. Konecny GE, et al. Activity of the dual kinase inhibitor lapatinib (GW572016) against HER-2-overexpressing and trastuzumab-treated breast cancer cells. *Cancer Res*. 2006; 66(3):1630–1639. [PubMed: 16452222]
21. Xia W, et al. Truncated ErbB2 receptor (p95ErbB2) is regulated by heregulin through heterodimer formation with ErbB3 yet remains sensitive to the dual EGFR/ErbB2 kinase inhibitor GW572016. *Oncogene*. 2004; 23(3):646–653. [PubMed: 14737100]
22. Jin Q, Esteva FJ. Cross-talk between the ErbB/HER family and the type I insulin-like growth factor receptor signaling pathway in breast cancer. *J Mammary Gland Biol Neoplasia*. 2008; 13(4):485–498. [PubMed: 19034632]
23. Saxena NK, et al. Bidirectional crosstalk between leptin and insulin-like growth factor-I signaling promotes invasion and migration of breast cancer cells via transactivation of epidermal growth factor receptor. *Cancer Res*. 2008; 68(23):9712–9722. [PubMed: 19047149]
24. Burga LN, et al. Loss of BRCA1 leads to an increase in epidermal growth factor receptor expression in mammary epithelial cells, and epidermal growth factor receptor inhibition prevents estrogen receptor-negative cancers in BRCA1-mutant mice. *Breast Cancer Res*. 2011; 13(2):R30. [PubMed: 21396117]
25. Antoniou AC, Wang X, Fredericksen ZS, McGuffog L, Tarrell R, Sinilnikova OM, et al. A locus on 19p13 modifies risk of breast cancer in BRCA1 mutation carriers and is associated with hormone receptor-negative breast cancer in the general population. *Nat Genet*. 2010; 42:885–892. [PubMed: 20852631]
26. Vogel CL, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol*. 2002; 20(3):719–726. [PubMed: 11821453]
27. Smith I, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet*. 2007; 369(9555):29–36. [PubMed: 17208639]
28. Buzdar AU, et al. Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: an update of the initial randomized study population and data of additional patients treated with the same regimen. *Clin Cancer Res*. 2007; 13(1):228–233. [PubMed: 17200359]
29. Romond EH, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005; 353(16):1673–1684. [PubMed: 16236738]
30. Friess T, Scheuer W, Hasmann M. Combination treatment with erlotinib and pertuzumab against human tumor xenografts is superior to monotherapy. *Clin Cancer Res*. 2005; 11(14):5300–5309. [PubMed: 16033849]
31. Agus DB, et al. Phase I clinical study of pertuzumab, a novel HER dimerization inhibitor, in patients with advanced cancer. *J Clin Oncol*. 2005; 23(11):2534–2543. [PubMed: 15699478]
32. Spector, N. Drug Development—targeting HER2 beyond trastuzumab. 33rd Annual San Antonio Breast Cancer Symposium; 2010.
33. Burris HA 3rd, Rugo HS, Vukelja SJ, Vogel CL, Borson RA, Limentani S, et al. Phase II study of the antibody drug conjugate trastuzumab-DM1 for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer after prior HER2-directed therapy. *J Clin Oncol*. 2011; 29:398–405. [PubMed: 21172893]
34. Baselga J, et al. Phase II and tumor pharmacodynamic study of gefitinib in patients with advanced breast cancer. *J Clin Oncol*. 2005; 23(23):5323–5333. [PubMed: 15939921]
35. Dickler MN, et al. Efficacy and safety of erlotinib in patients with locally advanced or metastatic breast cancer. *Breast Cancer Res Treat*. 2009; 115(1):115–121. [PubMed: 18496750]

36. Burris HA 3rd, et al. Phase I safety, pharmacokinetics, and clinical activity study of lapatinib (GW572016), a reversible dual inhibitor of epidermal growth factor receptor tyrosine kinases, in heavily pretreated patients with metastatic carcinomas. *J Clin Oncol.* 2005; 23(23):5305–5313. [PubMed: 15955900]
37. Geyer CE, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med.* 2006; 355(26):2733–2743. [PubMed: 17192538]
38. Boussen H, et al. Phase II study to evaluate the efficacy and safety of neoadjuvant lapatinib plus paclitaxel in patients with inflammatory breast cancer. *J Clin Oncol.* 2010; 28(20):3248–3255. [PubMed: 20530274]
39. Kaufman B, Trudeau M, Awada A, Blackwell K, Bachelot T, Salazar V, et al. Lapatinib monotherapy in patients with HER2-overexpressing relapsed or refractory inflammatory breast cancer: final results and survival of the expanded HER2+ cohort in EGF103009, a phase II study. *Lancet Oncol.* 2009 Oct.:581–588. [PubMed: 19394894]
40. Blackwell KL, et al. Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. *J Clin Oncol.* 2010; 28(7):1124–1130. [PubMed: 20124187]
41. Untch M, et al. Lapatinib vs Trastuzumab in Combination with Neoadjuvant Anthracycline-Taxane-Based Chemotherapy: Primary Efficacy Endpoint Analysis of the GEPARQUINTO STUDY (GBG 44). *SABCS.* 2010; (S3-1)
42. Baselga J, et al. First Results of the NeoALTTO Trial (BIG 01-06 / EGF 106903): A Phase III, Randomized, Open Label, Neoadjuvant Study of Lapatinib, Trastuzumab, and Their Combination Plus Paclitaxel in Women with HER2-Positive Primary Breast Cancer. *SABCS.* 2010; (S3-3)
43. Chang JC, Mayer IA, Forero-Torres A, Nanda R, Goetz MP, Rodriguez AA, et al. TBCRC 006: a multicenter phase II study of neoadjuvant lapatinib and trastuzumab in patients with HER2-overexpressing breast cancer. *J Clin Oncol.* 2011; 29 suppl (abstr 505).
44. Kuerer HM, et al. Biologic and immunologic effects of preoperative trastuzumab for ductal carcinoma in situ of the breast. *Cancer.* 2011; 117(1):39–47. [PubMed: 20740500]
45. Dave B, Migliaccio I, Gutierrez MC, Wu MF, Chamness GC, Wong H, et al. Loss of phosphatase and tensin homolog or phosphoinositol-3 kinase activation and response to trastuzumab or lapatinib in human epidermal growth factor receptor 2-overexpressing locally advanced breast cancers. *J Clin Oncol.* 2011; 29:166–173. [PubMed: 21135276]
46. Finn RS, et al. Estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 (HER2), and epidermal growth factor receptor expression and benefit from lapatinib in a randomized trial of paclitaxel with lapatinib or placebo as first-line treatment in HER2-negative or unknown metastatic breast cancer. *J Clin Oncol.* 2009; 27:3908–3915. [PubMed: 19620495]
47. Wang L, Zhang Q, Sun S, Guo H, Jia Z, Wang B, et al. PI3K pathway activation results in low efficacy of both trastuzumab and lapatinib. *BMC Cancer.* 2011; 11:248. [PubMed: 21676217]
48. Rexer BN, Ham AJ, Rinehart C, Hill S, de Matos Granja-Ingram N, González-Angulo AM, et al. Phosphoproteomic mass spectrometry profiling links Src family kinases to escape from HER2 tyrosine kinase inhibition. *Oncogene.* 2011 (Epub ahead of print).
49. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med.* 2005; 353:1659–1672. [PubMed: 16236737]
50. Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas ES, Theriault RL, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. *J Clin Oncol.* 2005; 23:3676–3685. [PubMed: 15738535]
51. Burstein HJ, Storniolo AM, Franco S, Forster J, Stein S, Rubin S, et al. A phase II study of lapatinib monotherapy in chemotherapy-refractory HER2-positive and HER2-negative advanced or metastatic breast cancer. *Ann Oncol.* 2008; 19:1068–1074. [PubMed: 18283035]
52. Di Leo A, Gomez HL, Aziz Z, Zvirbule Z, Bines J, Arbushites MC, et al. Phase III, double-blind, randomized study comparing lapatinib plus paclitaxel with placebo plus paclitaxel as first-line treatment for metastatic breast cancer. *J Clin Oncol.* 2008; 26:5544–5552. [PubMed: 18955454]

53. Johnston S, Pippen J, Pivot X, Lichinitser M, Sadeghi S, Dieras V, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J Clin Oncol*. 2009; 27:5538–5546. [PubMed: 19786658]

Figure 1.

HER-family targeting for breast cancer prevention. A, potential clinical preventive applications of lapatinib (along with known applications of trastuzumab, SERMs, and AIs). The major circle segments reflect HER2-positive cancer (violet; ~20% of total disease) and HER2-negative cancer (sky blue; ~80% of total disease). Divisions within segments reflect the rough proportions of HR (ER, PR)-positive and -negative disease, which, respectively, are 50%/50% in HER2-positive cancer and 75%/25% in HER2-negative cancer (the rough proportions in all cancers are 70% HR-positive and 30% HR-negative). Doubled blocking lines indicate settings of greater HER-targeting drug effect. B, signaling pathways involved in HER-targeting agent effects. MAPKs, mitogen-activated protein kinases; JNK, c-JUN N-terminal kinase; mTOR, mammalian target of rapamycin; S6K, p70 S6 ribosomal kinase; 4EBP1, 4E-binding protein 1; TF, tissue factor.

Table 1

Preclinical studies of ErbB inhibitors for mammary-tumor prevention

Drug	Target	Animal model	ER status	Results	Ref.
Typhostin	EGFR	Bigenic MMTV/-neu, MMTV/-TGF α mice	Unknown	Daily IP injections (50mg/kg, from 8 weeks old) substantially delayed tumor onset; tumor incidence = 90% (controls) vs 20% (tyrphostin) at 250 days ($P = 0.0007$)	(15)
Gefitinib	EGFR	MMTV/neu mice	ER-negative tumors	Daily gavage (6 d/wk; 100 mg/kg, from 3 months old) delayed median time-to-tumor from 230 to > 310 days ($P < 0.001$), when 75% of gefitinib-treated versus 0% of control mice were tumor-free	(16)
Gefitinib	EGFR	BALB-neuT mice	ER-negative tumors	Oral gavage (5 d/wk; 75mg/kg, increasing to 135mg/kg, between 5 and 14 weeks old) reduced mean number of tumor-bearing glands/mouse from 9.6 to 0.6 ($P < 0.0001$)	(17)
Gefitinib	EGFR	Methylnitrosourea-treated rats	ER-positive tumors	10 Mg/kg daily reduced cancer multiplicity by 91% ($P < 0.01$) and reduced size of established tumors	(19)
Lapatinib	EGFR/HER2	MMTV/neu mice	ER-negative tumors	Twice daily gavage (6 d/wk; 75mg/kg, from 3 months old) reduced tumor incidence from 100% to 31% at 418 days old ($P < 0.001$)	(18)
Lapatinib	EGFR/HER2	Methylnitrosourea-treated rats	ER-positive tumors	Daily gavage (7 d/wk, from 55 days old) reduced tumor multiplicity by 31% (25mg/kg) and 81% (75mg/kg) at 198 days old	(5)
Erlotinib	EGFR	MMTV/Cre, BRCA/flox/flox/p53 ^{+/-} mice	ER-positive, -negative tumors	Daily gavage (7d/wk; 100mg/kg, from 3 months old) increased tumor latency from median 256 days to 365 days ($P = 0.0003$) with selective suppression of ER-negative tumors	(24)

Table 2

Clinical studies of ErbB inhibitors in breast cancer

Drug/trial design	Target	Setting	Results	Ref.
Tras (1st-line, randomized phase II)	HER2	Metastatic HER2-positive	1st-Line Tras produced a 26% objective response rate; response rate in 3+ HER2 overexpression was 35%, with a CBR* of 48%	(26)
Tras (phase III HERA trial; initial results)	HER2	Early-stage HER2-positive	Tras for 1 year after adjuvant chemotherapy improved DFS; Tras HR (versus observation) = 0.54 (95% CI, 0.43–0.67; $P < 0.0001$)	(49)
Tras (longer-term HERA results)	HER2	Early-stage HER2-positive	Tras for 1 year after adjuvant chemotherapy improved overall survival--HR for risk of death (versus observation) was 0.66 (95% CI, 0.47–0.91; $P = 0.0115$)	(27)
Tras (phase III neo-adjuvant)	HER2	HER2-positive	Tras + chemotherapy (paclitaxel followed by FEC) improved pCR (65.2%) versus chemotherapy alone (26%; $P = .016$)	(50)
Tras + chemotherapy (two phase III adjuvant trials)	HER2	Early-stage HER2-positive	Dramatically prolonged median DFS—HR = 0.48 ($P < 0.0001$)—and produced 33% reduced risk of death ($P = 0.015$)	(29)
Pertuzumab (phase I)	HER2	Metastatic cancer	PR in 2 patients (non-breast cancer); stable disease lasting > 2.5 months in 6 patients	(31)
Tras-DM1 (phase II)	HER2	Metastatic HER2-positive, resistant to HER2 therapy	Produced 26% objective response rate	(33)
Gefitinib (phase II)	EGFR	Advanced/meta-static	0% CR + PR	(34)
Erlotinib (phase II)	EGFR	Advanced/meta-static	3% PR	(35)
Lapat (phase III)	EGFR/HER2	Metastatic HER2-positive	Lapat + capecitabine prolonged TTP (vs capecitabine; HR = 0.49; 95% CI, 0.34–0.71; $P < 0.0001$)	(37)
Lapat (phase II)	EGFR/HER2	Refractory, metastatic	Modest activity (6% clinical benefit)	(51)
Lapat (1st-line phase III)	EGFR/HER2	Metastatic	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 + paclitaxel—in HER2-positive disease	(52)
Lapat + letrozole (1st-line phase III)	EGFR/HER2	Metastatic, hormone-receptor-positive	Letrozole + lapat reduced risk of disease progression vs letrozole-alone in HER2-positive disease (HR = 0.71; 95% CI 0.53–0.96; $P = 0.019$); no improved outcome in HER2-negative cancer	(53)
Lapat (phase II neoadjuvant)	EGFR/HER2	Inflammatory breast cancer	Lapat monotherapy followed by Lapat + paclitaxel produced a 78% clinical response rate in HER2-positive disease	(38)
Lapat, Tras (phase III)	EGFR/HER2	Tras-resistant metastatic HER2-positive	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%)	(40)
Lapat or Tras (phase II neoadjuvant)	HER2/EGFR	Early-stage	Lapat suppressed Ki-67 proliferation index in breast tissue approximately 20% after 4 weeks; Tras did not suppress Ki67 index	(45)
Lapat vs Tras (phase III neoadjuvant GeparQuinto trial)	EGFR/HER2	Early-stage	pCR to Lapat (21.7%) and Tras (31.3%; $P < 0.03$)	(37)

Drug/trial design	Target	Setting	Results	Ref.
Laplat, Tras, Laplat + Tras (phase III neoadjuvant NeoALTTO trial)	EGFR/HER2	Early-stage	pCR was 51.3% for Laplat + Tras (+ chemotherapy) vs 24.7% for Laplat-alone (+ chemotherapy) and 29.5% for Tras-alone (+ chemotherapy; $P \leq 0.0001$ vs laplatinib + Tras combination)	(42)
Tras + docetaxel vs Tras + pertuzumab + docetaxel vs Tras + pertuzumab vs docetaxel (4-arm phase II neoadjuvant NeoSPHERE trial:)	EGFR/HER2	Early-stage HER2-positive	Higher pCR with Tras/pertuzumab/docetaxel (46%) vs Tras/docetaxel (29%; $P = 0.014$), and higher than in the Tras/pertuzumab arm (18%; $P = 0.019$)	(32)
Tras (single-dose, pre-surgery)	HER2	DCIS	No pathologic response or change in Ki67 staining (versus pre-treatment)	(44)
Laplat + Tras (phase II neoadjuvant)	HER2/EGFR	Early-stage, HER2-positive	Laplat + Tras (without chemotherapy) produced a high pCR rate (overall 28%), especially in ER-negative disease (40%)	(43)
Laplat (phase II pre-surgery)	HER2/EGFR	Early-stage, HER2-positive	Reduced proliferation (Ki-67) in cancer ($P = 0.008$), DH ($P = 0.006$), and DIN ($P = 0.067$)	(4)

Abbreviations: Tras, trastuzumab; CBR, clinical benefit rate; HERA, Herceptin Adjuvant; DFS, disease-free survival; FEC, fluorouracil, epirubicin, cyclophosphamide; pCR, pathologic complete remission; PR, partial response; Laplat, lapatinib; TTP, time to progression; MTID, maximum tolerated dose; PFS, progression free survival.

* Generally defined as CR or PR or as stable disease lasting ≥ 6 months.