# HER2 Inhibition: From Discovery to Clinical Practice

□□ *Commentary on Buzdar et al., p. 228*

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In this issue of Clinical Cancer Research, Buzdar et al. (1) report on the success of trastuzumab, a humanized monoclonal antibody against the proto-oncogene *HER2* (c-erbB2, HER-2/*neu*), when administered with 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) and paclitaxel chemotherapy, with high pathologic complete remission rates. These results are consistent with recent data presented by large multicenter trials, confirming the high efficacy of trastuzumab in women with early stage breast cancer.

## Discovery and Inherent Properties of HER-Overexpressing Breast Cancer

The epidermal growth factor receptor/HER family of transmembrane type I receptor tyrosine kinases are enzymes that play an important role in fundamental processes like cell proliferation, differentiation, and survival. The ectodomains of HER1, HER3, and HER4 interact with specific sets of ligands, whereas no natural ligand has been identified thus far for HER2. However, HER2 can be activated by heterodimerization with other ligand-activated HER coreceptors. On ligand binding to the active domain of HER1, HER3, or HER4, these receptors preferentially recruit HER2 into a heterodimeric complex in which the HER2 kinase can modulate receptor internalization and prolong signal transduction. On dimerization, conformational changes lead to autophosphorylation and initiation of divergent signal transduction cascades (2). These type I receptors signal through the Ras/Raf/mitogen-activated protein kinase/extracellular signal-regulated kinase pathway, stimulating cell division (3). Cell line evidence also suggests that the type I receptors modulate cell survival through activation of the Akt/phosphoinositol 3-kinase pathway (ref. 4; Fig. 1). Aberrant HER1 and HER2 signaling has been causally associated with cancer cell proliferation and survival.

HER-2 was first identified as an oncogene activated by a point mutation in chemically-induced rat neuroblastomas (5). It encodes a 185-kDa transmembrane protein that is a putative growth factor receptor of the tyrosine kinase family. It was later found to be overexpressed in some human breast carcinomas (6) present on the surface of 20% to 25% of breast cancer cells. The prognosis of those patients whose tumors overexpress HER-2 is poor (7–14). Based on this association between the members of HER1/HER2 family and worse clinical outcome, antibodies and small molecules that specifically target these receptor tyrosine kinases were developed for their therapeutic efficacy.

## HER2 as a Successful Therapeutic Target

In the 1980s, a monoclonal antibody against HER-2, trastuzumab, was developed, and in 1998, it was approved for the treatment of metastatic breast cancer (15). In 2005, the results of five adjuvant trials evaluating trastuzumab, involving >10,000 women, were presented (16–18). Despite differences in study design and short follow-ups of only 1 to 2 years, these studies show the same remarkable results—adjuvant trastuzumab therapy halves the recurrence rate and reduces mortality by 30%. This benefit is, on average, higher than that of adjuvant chemotherapy and similar to that seen with adjuvant hormonal therapy. The main setback of trastuzumab is its potential for cardiotoxicity, although benefits seem to outweigh risks and the ensuing congestive heart failure is generally reversible. Today, the evaluation of HER-2 expression should therefore be mandatory in early breast cancer patients who should be offered access to this highly effective therapy.

## Predictive Markers and Mechanisms of Action and Resistance

The antitumor effects of HER2 inhibitors require the modulation of key signaling pathways and cell cycle/apoptosis regulatory molecules that mediate the transforming effects of HER2. These pathways may involve heterologous receptor networks and/or heterodimers of the HER (ErbB) family that are not affected by trastuzumab (19). For example, high expression of epidermal growth factor receptor and ligands for the Erb family predicts early escape from trastuzumab therapy (20). Another important reported mechanism of escape, and therefore resistance, is overexpression of the insulin-like growth factor-I receptor (21), a potent inducer of phosphoinositol 3-kinase and Akt. Amplification of the phosphoinositol 3-kinase pathway as a result of loss or low levels of phosphatase and tensin homologue is also associated with resistance to trastuzumab (21). These data are highly consistent with *in vivo* studies of human primary breast cancers that blocking activation of the phosphoinositol 3-kinase/Akt survival pathway is the main mechanism of action of trastuzumab (22). Similarly, patients with coamplification of cMYC and HER-2 had worse outcome when treated with chemotherapy alone, whereas the addition of trastuzumab reversed this trend with patients achieving high recurrence-free survival. These data suggest that the proapoptotic function of dysregulated cMYC may be counterbalanced by an antiapoptotic

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Received 9/29/06; revised 10/20/06; accepted 10/24/06.
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doi:10.1158/1078-0432.CCR-06-2405

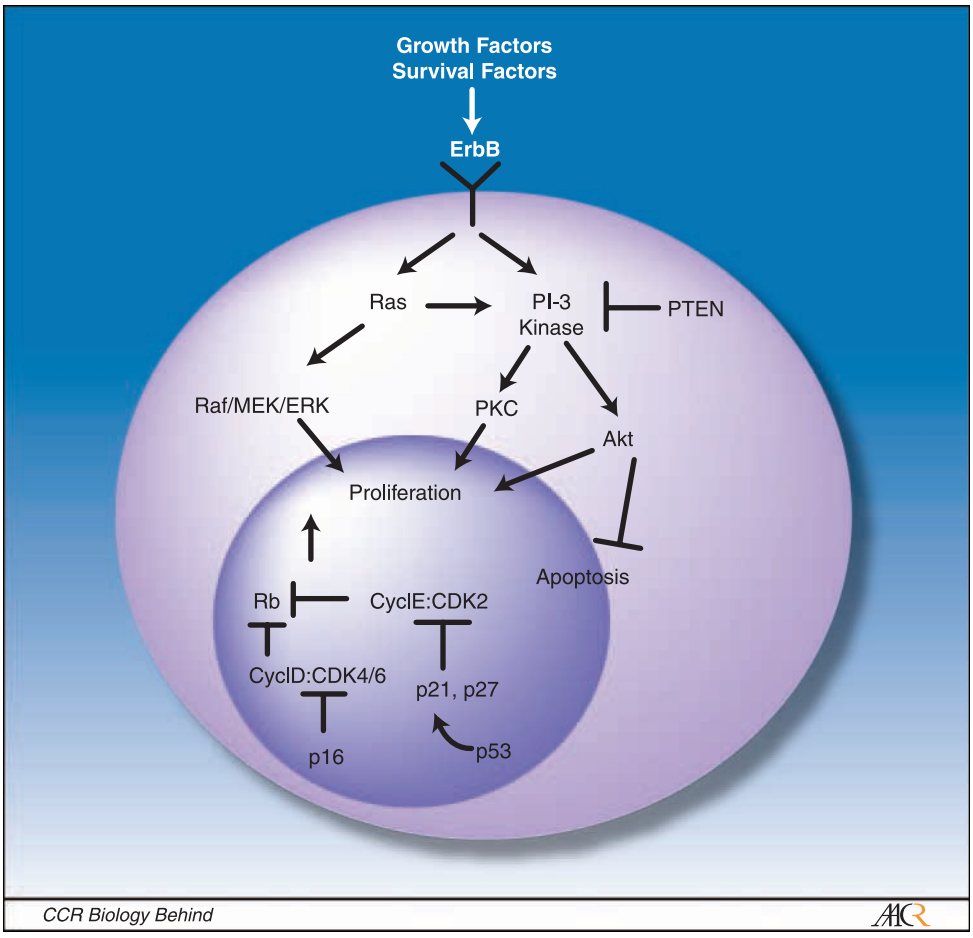


**Fig. 1.** Simplified schema of signaling through Erb receptor on dimerization. Conformational changes lead to autophosphorylation and initiation of divergent signal transduction cascades. The type I receptors signal through the Ras/Raf/mitogen-activated protein kinase (*MEK*)/extracellular signal – regulated kinase (*ERK*) pathway, stimulating cell division. Cell line evidence also suggests that the type I receptors modulate cell survival through activation of the Akt/phosphoinositol 3-kinase (*PI3-kinase*) pathway.

signal from another activated oncogene, like HER2 (23). Based on these data, approaches combining trastuzumab with therapeutic agents attacking targets that lead to resistance (e.g., insulin-like growth factor-I receptor inhibitors) are being tested. In addition, somatic mutations in the *HER2* gene have recently been reported in ~4% of non–small-cell-lung cancers (24) and may represent yet another route of escape from trastuzumab therapy. Gene expression and other high throughput studies using biopsies from women undergoing neoadjuvant trastuzumab-containing regimens may shed some light on patients who might not benefit from therapy (25, 26). Early preliminary data presented in the article by Budzar et al. failed to identify patterns to discriminate treatment benefit in this study.

To circumvent trastuzumab resistance, another approach is to block HER2 function with ATP-competitive tyrosine kinase inhibitors. For example, lapatinib is a reversible dual kinase inhibitor against the epidermal growth factor receptor and HER2 (27), which has shown antitumor activity both *in vitro* and *in vivo* (28, 29). It has recently shown remarkable activity in patients with HER2-overexpressing breast cancers when given either as first line therapy or after escape from trastuzumab (30–32). The addition of lapatinib induces tumor regressions in up to 20% of patients who have progressed previously on trastuzumab alone (33). Recent data presented at the annual meeting of the American Society of Clinical Oncology in 2006 compared capecitabine with or without the addition of lapatinib. The lapatinib arm significantly delayed the progression of breast cancer for nearly twice as long compared with capecitabine alone in patients with advanced breast cancer who had progressed following treatment with trastuzumab, with a median time to disease progression of 8.5 months, compared with 4.5 months for those treated with capecitabine alone. Thus, lapatinib will likely be approved for use in patients with HER2-overexpressing breast cancer.

## Unanswered Questions and Future Directions

Trastuzumab has been an unfettered success. Nevertheless, many questions remain, some highlighted by Budzar et al. The optimal duration of trastuzumab in the adjuvant setting, generally administered for at least 52 weeks, remains to be defined. The two studies in early stage breast cancer, Budzar et al.'s and the FinHer (Finland Herceptin) trial (16), show comparable favorable results with trastuzumab given concurrently with chemotherapy for 24 weeks or less. This shorter duration of therapy would be consistent with the body of data suggesting that apoptosis by blocking the phosphoinositol 3-kinase/Akt survival pathway is a major mechanism of action of

trastuzumab (22, 23). The current Herceptin Adjuvant (HERA) trial comparing 1 versus 2 years of trastuzumab adjuvant therapy will provide pivotal information on the value of prolonged trastuzumab, and whether shorter durations of trastuzumab therapy should be tested.

The article by Budzar et al. highlights many unanswered questions on cardiotoxicity. It is accepted that the benefits of trastuzumab therapy far outweigh the generally reversible risk of congestive heart failure. Preclinical data suggest a powerful synergistic interaction between trastuzumab and both platinum and docetaxel. In early trials, platinum-taxane-trastuzumab combinations have exhibited promising clinical activity. The potential for cardiac toxicity when trastuzumab is combined with the anthracyclines suggests a further rationale for the development of non-anthracycline regimens, especially in the adjuvant setting. Molecular markers, like the expression of *TOPO2A*, may have promise in selecting patients who may be spared anthracycline-containing trastuzumab therapy (34), which remains an important goal. Newer therapeutic agents targeting neovascularization, pan-HER2 inhibition, insulin-like growth factor receptor pathways, and the like, will invariably build on the success of HER2-targeted therapy.

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