

The Distinctive Nature of HER2-Positive Breast Cancers

Harold J. Burstein, M.D., Ph.D.

Related articles, pages 1659 and 1673

Breast cancer is not a single disease but a group of several important tumor subtypes, each with a different natural history and each requiring a different treatment. Overexpression of HER2 (which derives its name from human epidermal growth factor receptor 2) defines one of these unique subtypes. The *HER2/neu* gene is a member of a family of genes encoding transmembrane receptors for growth factors, including the epidermal growth factor receptor (EGFR), HER2, HER3, and HER4. The intracellular domain of HER2 has tyrosine kinase activity that regulates important aspects of the physiology, growth, and differentiation of cells.^{1,2} Extracellular domains of the HER2 protein interact with HER family members, allowing HER2 to serve as a coreceptor and to facilitate signal transduction as part of a heterodimer complex that forms after ligand binding. There is no known ligand for HER2 itself, however, suggesting that the primary role of HER2 is to modulate signals after ligand binding to other HER-family receptors.

Amplification of the *HER2/neu* oncogene and related genetic elements in the amplicon on chromosome 17 causes a marked increase (up to 100 times the usual level) in the expression of HER2 on the surface of breast-tumor cells. The mechanism of the selective amplification of *HER2/neu* is unknown. Overexpression of HER2 can transform cultured cells into a malignant phenotype

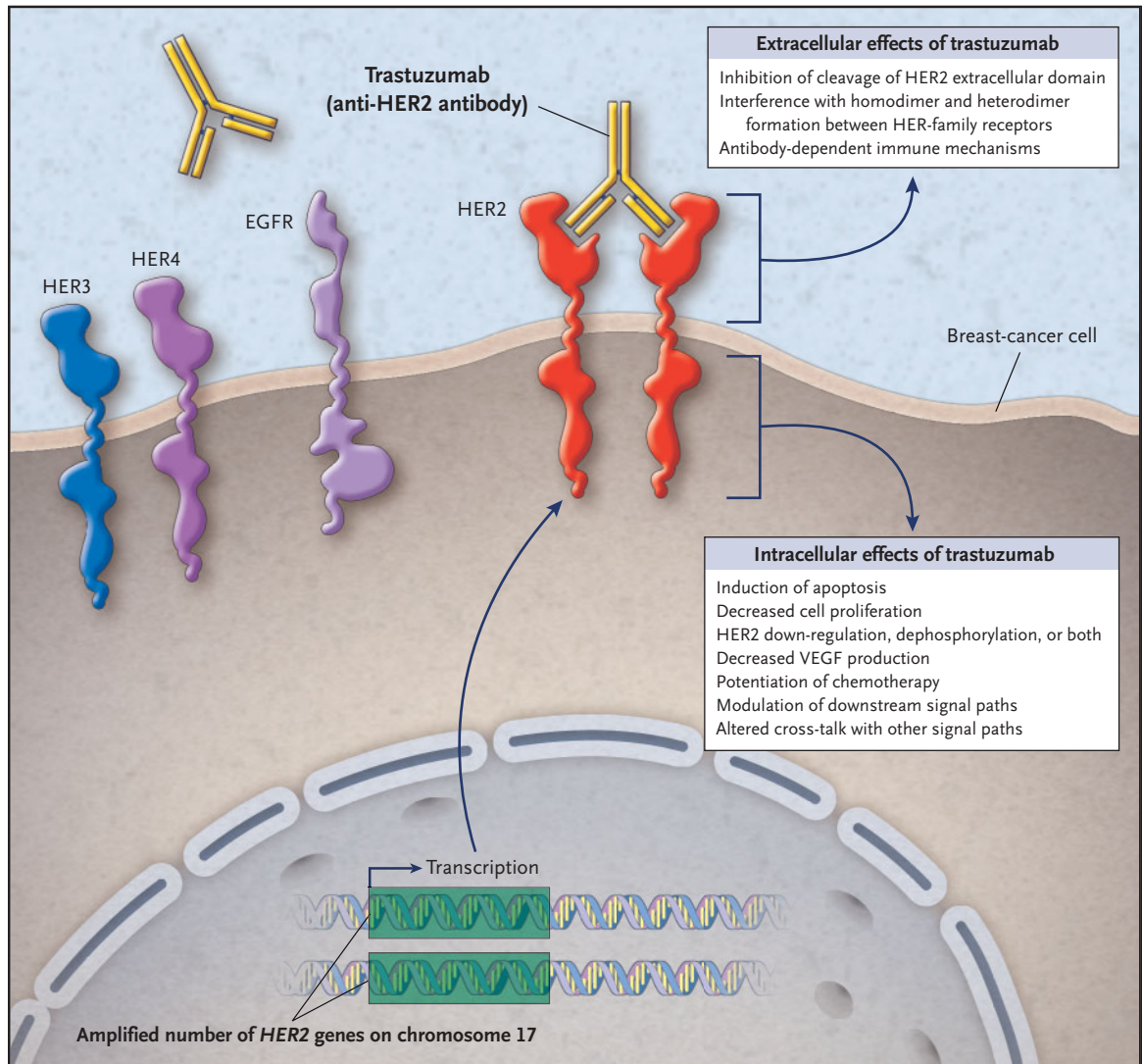
and accelerate tumorigenesis. Overexpression of HER2 appears to encourage the formation of receptor homodimers and heterodimers involving HER2, with different signaling properties than seen normally.

HER2 became clinically relevant with the demonstration that HER2-positive breast cancers have a worse prognosis than HER2-negative tumors.³ Between 15 and 20 percent of invasive breast cancers are HER2-positive; amplification of the gene and the resultant overexpression of HER2 occur during the in situ stage of tumor development. After *HER2/neu* amplification has occurred, the HER2 phenotype is thought to be fixed for the duration of the natural history of the invasive tumor. For this reason, testing for HER2 can be performed on either the primary tumor or a metastatic tumor deposit, generally with similar results.

HER2-positive breast cancers have a distinctive molecular signature, including extensive changes in the patterns of gene expression that distinguish these cancers from other types of breast cancer.⁴ They also have distinctive clinical features. Population-based studies and retrospective analyses have shown that overexpression of HER2 is an adverse prognostic factor that is associated with poorly differentiated, high-grade tumors, high rates of cell proliferation and lymph-node involvement, and a relative resistance to certain types of chemotherapy. Anthracycline-based adjuvant che-

motherapy is particularly beneficial in HER2-positive tumors. Roughly half of HER2-positive breast cancers also express the steroid hormone receptors for estrogen, progesterone, or both. However, in these tumors, the levels of steroid hormone receptors are typically lower than in HER2-negative, hormone-receptor-positive tumors, and for this reason, in part, HER2-positive breast cancer is relatively resistant to tamoxifen. All these factors contribute to the greater risk of recurrence among women with HER2-positive breast cancer than in those with HER2-negative breast cancer. *HER2/neu* gene amplification is rare outside breast cancer. Tumors other than breast cancer with some degree of HER2 positivity typically express far less HER2 than breast cancers, without evidence of gene amplification.

Trastuzumab, a humanized monoclonal antibody against HER2 created by inserting portions of the antigen-binding site of a mouse monoclonal antibody against HER2 into a human monoclonal antibody, was developed after it had been recognized that HER2 overexpression served as both a marker of aggressive disease and a target for treatment. Because laboratory and clinical studies indicated that the inhibition of cell growth by trastuzumab is limited to HER2-positive cancers, testing tumors for expression of HER2 became integral to the selection of patients for clinical trials of the



Interactions between Trastuzumab and Tumor Cells.

HER2 serves as a coreceptor with related members of the HER family of tyrosine kinase-associated growth factors. Acquired amplification of the *HER2/neu* gene on chromosome 17 in HER2-positive breast cancer leads to marked overexpression of HER2 on the cell surface, which alters normal signaling function. Trastuzumab is a humanized monoclonal antibody that binds to HER2 and inhibits tumor-cell growth through a variety of intracellular, and possibly extracellular, mechanisms.

efficacy of trastuzumab. Because of the success of these trials, HER2 testing became routine in the care of patients with breast cancer, although controversy remains as to the best method of testing.

The studies reported in this issue of the *Journal* by Piccart-Gebhart and colleagues (pages 1659–1672) and Romond and colleagues

(pages 1673–1684) are the culmination of a decade-long adventure in clinical investigation. They show that trastuzumab can dramatically improve outcomes among women with HER2-positive breast cancer. The clinical observations are clear, but the scientific basis for the effects of trastuzumab is uncertain. Laboratory studies and limited data

from clinical trials suggest myriad possible mechanisms of action of trastuzumab (see diagram). After binding to the HER2 protein, trastuzumab contributes to apoptosis, causes down-regulation of surface HER2 expression, alters downstream signaling and regulatory pathways in the cell cycle, suppresses the production of the angiogenic factor vascular

endothelial growth factor (VEGF), and potentiates the effects of chemotherapy. There may also be an extracellular effect, possibly in mediating antibody-dependent immune recognition.

Trastuzumab appears to have no clinical benefit in HER2-negative breast cancers, in which normal levels of HER2 protein are expressed. This finding suggests that a critical density or threshold of HER2 expression or gene amplification is necessary for trastuzumab to act. Similarly, trastuzumab lacks substantial activity against other non-breast tumors, even if they express moderately elevated HER2 levels. It seems likely that the clinical use of trastuzumab will be narrowly confined to the unique subtype of HER2-positive breast cancer.

A better understanding of the biologic actions of trastuzumab is critical to improving treatments that target HER2. For instance, trials of adjuvant treatment have not determined whether the potentiation of the effect of chemotherapy by trastuzumab warrants concurrent chemotherapy and trastuzumab administration, or whether sequential treatments would be adequate. Similarly, the optimal duration of therapy may depend on how, precisely, trastuzumab works. As yet, there is no defined threshold of HER2 gene amplification that predicts which HER2-positive tumors will respond to treatment. It seems probable that the greater the de-

gree of gene amplification, the greater the potential benefit, but this possibility has not been tested clinically.

Resistance to trastuzumab is now a problem, but we do not understand its mechanism. Strategies to overcome resistance include interference with the co-receptor role of HER2 by blocking interactions with other HER-family receptors or the modulation of related signaling or apoptotic pathways. In vitro models suggest important crosstalk between HER2-driven signal paths and both VEGF-receptor and estrogen-receptor pathways. Clinical trials that use both anti-HER2 and anti-estrogen therapies or an anti-VEGF antibody are under way and may prove fruitful.

The history of HER2 and trastuzumab treatment is a triumphal narrative of translational research. An oncogene, originally discovered in a rat model of chemically induced carcinogenesis, was found to have a sequence that resembled that of a normal cellular gene. The *HER2/neu* gene, when overexpressed, transforms normal cells into cancer cells. Next, overexpression of the gene was found in human breast cancers, where it was shown to contribute to a poor prognosis. A novel antibody therapy that targets the overabundant HER2 protein was developed, and this antibody now redefines the natural history of the disease and establishes a new standard of treat-

ment for breast cancer. It is a dramatic story that epitomizes the often cited cliché of “bedside to bench to bedside” research.

Like all good stories, this one has a profound lesson: not all breast cancers are the same. Hormone receptors, HER2, and increasingly, genomic profiles distinguish at least four major classes of breast cancer: HER2-positive tumors; HER2-negative, hormone-receptor-positive tumors, which can be divided into two classes, favorable and unfavorable, on the basis of genomic and pathobiologic features; and basal-like tumors that express neither HER2 nor hormone receptors. The growing appreciation of the biologic diversity of breast cancer is forcing treatment into patterns that reflect the underlying biologic features of the tumor, and it challenges us to redefine principles of therapy for each distinctive class of breast cancer.

Dr. Burstein is an assistant professor of medicine at the Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School, Boston.

1. Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. *Nat Rev Mol Cell Biol* 2001;2:127-37.
2. Cho HS, Mason K, Ramyar KX, et al. Structure of the extracellular region of HER2 alone and in complex with the Herceptin Fab. *Nature* 2003;421:756-60.
3. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987;235:177-82.
4. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature* 2000;406:747-52.