

# A Patient's Guide to HER2-Positive Breast Cancer



**What Is HER2?** ■ Making the Diagnosis ■ **Treatment Strategies**  
■ Side Effects of Therapy ■ **Tips From a Survivor** ■ And More

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**IN RECENT DECADES, medical science has uncovered some important reasons why breast cancers do not all behave alike.** One of those reasons has to do with HER2, the human epidermal growth factor receptor 2. HER2 receptors are the product of a gene also called HER2, which is expressed in the normal, milk-producing cells (known as epithelial cells) that line the ducts of the breast.

**IN CANCEROUS CELLS, more than the usual two copies of the HER2 gene are sometimes present in a cell,** generating a dramatic overproduction of the receptors, which sit on the cell's surface. This fuels cell growth and sets the stage for an aggressive form of breast cancer to develop.

As many as one-quarter of the more than 180,000 breast cancers diagnosed in the U.S. each year are labeled HER2-positive, meaning the cancer cells display abnormally high numbers of HER2 proteins on their surface. Compared with cancers that are HER2-negative, those that are HER2-positive tend to grow more quickly and spread more readily, and are less responsive to hormonal therapy and chemotherapy.

However, a series of scientific developments throughout the 1980s led to new ways to treat

these cancers. By the late '80s, academic and pharmaceutical scientists had published data linking overactivity of the gene (sometimes called HER2/*neu* or ErbB2) with the more aggressive form of breast cancer.

Understanding the significance of HER2 gene activity—and how the resulting hundreds of thousands of extra receptors on the cell promote cancer growth—has allowed researchers to develop treatments aimed at disrupting this process. The first such treatment, Herceptin (trastuzumab)—developed by the drug maker Genentech, which played a key role in much of the 1980s research—was approved in 1998 for use in treating HER2-positive metastatic breast cancer. Since then, other new agents targeting HER2 are also finding their way to patients.



## Testing for HER2

**BECAUSE HER2 STATUS IS IMPORTANT in understanding how aggressive a tumor might be—and how best to treat it—testing should be performed on the biopsy or surgery sample of all newly diagnosed invasive breast cancers and at the time of a recurrence, according to expert recommendations.**

The Food and Drug Administration has approved two testing methods, known as IHC and FISH, to determine a breast cancer's HER2 status. A patient's tumor sample might be tested by either or both methods.

IHC, or immunohistochemistry, applies special antibodies that bind to the HER2 protein, along with a chemical detection method that stains the protein on the tumor cells. That staining can be evaluated under a microscope. An IHC score of 3+ (meaning intense, uniform staining of more than 30 percent of the invasive tumor cells' membranes) indicates that a patient's tumor is HER2-positive, while scores of 0 or 1+ designate the tumor is HER2-negative. A score of 2+, meanwhile, is considered borderline or "equivocal," meaning that further testing should be conducted using the FISH method.

FISH, or fluorescent in situ hybridization, allows researchers using a special microscope to count the copies of the HER2 gene in tumor cells by flagging them with fluorescent pieces of genetic material that attach to the area of the chromosome that contains the HER2 gene. Using FISH, a tumor is deemed HER2-positive if more than six copies of the HER2 gene are detected per cell, or if more than 2.2 HER2 genes are counted for every copy of chromosome 17 (also known as the HER2 chromosome enumeration probe 17 [CEP17] ratio). A tumor is negative if less than

four copies of the HER2 gene are counted per cell, or if the HER2/CEP17 ratio is less than 1.8. The result is borderline if the FISH count totals between four and six copies of the HER2 gene per cell, or between 1.8 and 2.2 HER2 genes per copy of chromosome 17. Borderline results should be followed up with counts performed in additional cells, by retesting using the FISH method or by testing with the IHC method, experts note.

To help ensure accuracy of test results, patients should ask their physicians whether the laboratory that performed the test is accredited according to American Society of Clinical Oncology/College of American Pathologists guidelines for testing.

Although the guidelines clearly define what is considered a HER2-positive versus a HER2-negative tumor, gray areas remain. Scientists have begun to explore whether a broader group of patients than those currently defined as HER2-positive could see gains from the targeted drugs.

For instance, a re-analysis of some tumor samples from one study of HER2-targeted therapy found that a portion of the tumors deemed HER2-positive were actually negative and that patients with these early-stage tumors seemed nevertheless to benefit from HER2-targeted therapy plus chemotherapy.

Another analysis of a previously conducted study found that women whose metastatic tumors were HER2-negative—but who had extra copies of chromosome 17—appeared to respond better to a combination of HER2-targeted therapy and chemotherapy than to chemotherapy alone. Other research is further identifying genetic and biochemical nuances that may better clarify when treatments that target HER2 will be most effective.



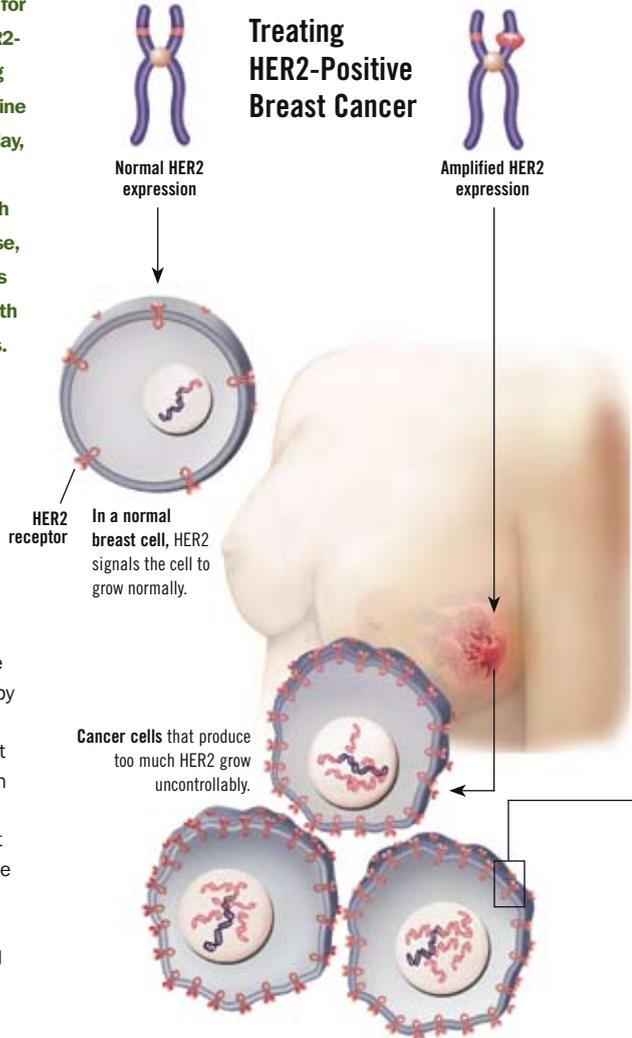
# Current Therapeutic Strategies

**IN THE 11 YEARS SINCE HERCEPTIN BECAME AVAILABLE for the treatment of metastatic HER2-positive breast cancer, a growing body of research has helped define how best to use the therapy. Today, Herceptin has also become an important option for patients with early-stage HER2-positive disease, and a second targeted agent has become available for patients with advanced HER2-positive cancers.**

Herceptin is a type of biological therapy called a monoclonal antibody, mass-produced in a laboratory instead of by the body. The treatment, delivered intravenously at either one- or three-week intervals for a year, interferes with cancer growth by blocking HER2 receptors on the surface of cancer cells, much like doors can be kept from opening by jamming their locks.

Herceptin's role as a treatment for advanced breast cancer began when research showed that, in conjunction with chemotherapy, it could increase the time before the disease progressed and increase a patient's survival time. The drug is typically used in advanced cancers either with or just after chemotherapy but sometimes is given by itself as a second- or third-line therapy.

If an advanced cancer progresses



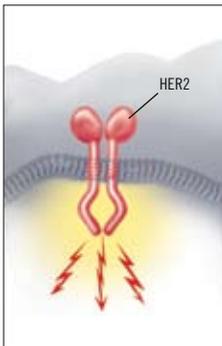
despite the use of Herceptin, the drug can be continued and combined with a different chemotherapy. Doctors also can try the most recently approved treatment regimen for advanced HER2-positive cancer—Tykerb (lapatinib) in combination with the oral chemotherapy drug Xeloda (capecitabine). The Tykerb/Xeloda combination is recommended for treating advanced HER2-positive cancers in patients who have already received therapies including an anthracycline (such as Adriamycin [doxorubicin]), a taxane (such as Taxol [paclitaxel]), and Herceptin.

Tykerb, taken orally, is a small molecule that blocks the HER2 receptor by a different means than Herceptin, making it a practical choice when Herceptin is no longer working (see illustration). In addition, Tykerb targets not just the HER2 receptor but another receptor known as HER1 (or epidermal growth factor receptor

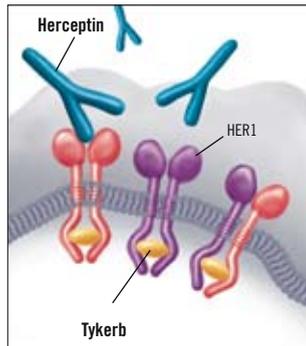
[EGFR]), a fact that potentially provides other advantages in fighting cancer.

Pivotal in the 2007 approval of the Tykerb/Xeloda regimen was a clinical trial of almost 400 women with advanced HER2-positive breast cancer that had progressed after treatment with Herceptin and other therapies. The trial compared Tykerb plus Xeloda with Xeloda alone and found that cancer progression was delayed an additional 8.5 weeks with the treatment duo versus just Xeloda (27.1 weeks compared with 18.6 weeks)—a finding dramatic enough to compel researchers to stop the study and allow patients in the Xeloda-only group to switch to the combination therapy. (Recent phase II research has suggested that Tykerb, and the Tykerb/Xeloda combination, may provide some extra benefit against brain metastases.)

Meanwhile Herceptin, which gained an



**Overabundant HER2 sends excess growth signals** that tell the cell to divide and multiply at a rapid rate.



**Herceptin binds to the outside of the HER2 receptor**, while the dual inhibitor **Tykerb** can bind to the inner portion of both HER1 and HER2. The growth signals are thus unable to reach the cell's nucleus.

ILLUSTRATION BY PAM CURRY



expanded government approval in 2006, has fast become an adjuvant treatment mainstay for patients with early-stage HER2-positive breast cancer. Clinical trials involving a total of more than 13,000 patients have found that Herceptin plus chemotherapy can increase survival time among patients with early-stage disease and reduce the risk of the cancer recurring, compared with chemotherapy alone. Findings of those studies were published in 2005.

In two of those trials—one led by the National Surgical Adjuvant Breast and Bowel Project and the other by the North Central Cancer Treatment Group—patients who had undergone surgery and completed Adriamycin/Cytoxan (cyclophosphamide) chemotherapy were then given Taxol either with or without Herceptin. A joint analysis of the trials indicated that patients given Herceptin had their risk of recurrence cut by about half, compared with patients who didn't receive Herceptin. Among more than 3,000 patients in the two trials, 85 percent of those in the Herceptin group were alive and disease-free after four years, compared with 67 percent in the other group.

One of those two studies is also attempting to establish whether Herceptin is more effective when given at the same time as chemotherapy, compared with after chemotherapy. (Herceptin has received FDA approval as part of various treatment regimens with chemotherapy, and also as a single agent after anthracycline-based chemotherapy.) Some evidence from the trial, as well as other research, suggests the simultaneous approach may be superior, but the question is not yet resolved. Updated findings are expected soon. Still other research has suggested

that Herceptin given with an extensive chemotherapy regimen before surgery may be beneficial in patients with locally advanced HER2-positive cancer.

Research has also hinted that Herceptin may be effective when administered for periods shorter than the typical year's worth of treatment. One study, the Finland Herceptin study, gave 116 women with HER2-positive cancers nine weekly infusions of Herceptin along with chemotherapy, while another 116 received only the chemotherapy. Disease-free survival over three years was 89 percent for the Herceptin group compared with 78 percent for the others. The study did not, however, directly compare the abbreviated course of Herceptin to the standard one-year regimen.

Another study, the PHARE, or Protocol of Herceptin Adjuvant with Reduced Exposure, trial launched in 2006, will do long-term follow-up comparing patient outcomes after one year or six months of Herceptin treatment in early-stage cancers. By contrast, a study known as the Herceptin Adjuvant, or HERA, trial, is examining whether Herceptin is more effective when given for two years compared with one. Final results of that study are expected in 2011.

Scientists also are attempting to maximize the benefit that patients gain from Herceptin and Tykerb. A study dubbed ALTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization) aims to recruit 8,000 participants in 50 countries to determine whether Herceptin or Tykerb is more effective against early-stage HER2-positive breast cancer. The research will also examine which therapy is safer, and whether they are best used separately, together, or sequentially.



# Investigational Therapeutic Strategies

**WITH EXISTING DRUGS MAKING HEADWAY in fighting HER2-positive breast cancers, scientists are developing new methods to target this vulnerability.**

One approach involves linking Herceptin to a cell-killing drug called DM1, in a pairing called trastuzumab-DM1 (T-DM1). This double-barreled treatment combines HER2-targeted activity with a precisely delivered drug that impacts the cancer cells' microtubules, which are crucial to cell structure and function.

One study, evaluating T-DM1 as a second-line therapy in patients whose metastatic cancer progressed during Herceptin treatment, found that tumors in 39 percent of patients shrunk by at least half—with some disappearing by a median follow-up of 19 weeks. Moreover, no cases of serious heart problems—a concern associated with Herceptin—were reported.

Data from that phase II study were released late last year. A phase III study is recruiting patients to evaluate T-DM1 compared with Tykerb/Xeloda in advanced or metastatic cancer that has progressed after treatment with a taxane and Herceptin.

T-DM1 is scheduled to be tested in combination with an antibody, pertuzumab, in metastatic patients whose cancer has progressed on Herceptin. Pertuzumab blocks the HER2 receptor's ability to associate with and activate three related HER receptors, HER1 (also known as EGFR), HER3, and HER4.

Pertuzumab is also being studied in combination with Herceptin in patients with metastatic cancer whose disease progressed on prior Herceptin therapy. Results of a phase II trial of 66 patients, released last year, show the treatment was well tolerated

and that half the patients receiving the Herceptin-pertuzumab combination exhibited tumor response or no progression for at least six months. A phase III trial, nicknamed CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) is under way to evaluate Herceptin plus Taxotere (docetaxel) with and without pertuzumab in the metastatic setting.

Another HER2-targeted treatment, the oral therapy neratinib, binds irreversibly not just to HER2 receptors but to HER1 as well as other related receptors. Phase II study results, made public last year, found that for metastatic and locally advanced HER2-positive breast cancers, daily neratinib showed activity both in patients who had previously been treated with Herceptin and in patients who hadn't. Other research on neratinib is pending, including a phase III study comparing it as a single agent against Tykerb plus Xeloda.

In yet another mode of attack, researchers are exploiting a cancer-related biochemical pathway called mTOR. Adding Afinitor (everolimus), one of two mTOR inhibitors approved for advanced kidney cancer, to Herceptin therapy has shown very preliminary promise in helping to overcome resistance to prior Herceptin in patients with metastatic disease.

Finally, scientists hope to stimulate patients' immune systems to tackle HER2-positive cancers with so-called HER2 vaccines. One such vaccine, currently in phase I testing for safety, is designed to produce a flood of HER2 receptor fragments that prompt activation of antibodies and other immune system components to attack HER2-positive tumor cells. Another HER2 vaccine already tested in humans has yielded mixed results, with initially promising findings tempered by analysis over a longer period.



# Side Effects of HER2-Targeted Therapy

**ALTHOUGH MEDICINES for HER2-positive breast cancer generally are well tolerated, it's important for patients to be prepared for potential complications of treatment.**

One area of concern with Herceptin is heart health. Before prescribing the medicine, physicians should review patients' health history and order testing, such as an echocardiogram (an ultrasound image of the heart) or a MUGA scan (which images the heart pumping blood).

While on Herceptin, patients should be monitored for potential cardiac toxicities, which can occur in a small fraction of cases. Such problems, reversible in a majority of patients, can be serious even if symptoms are not evident, and can lead to discontinuation of treatment. Problems that might arise include an impaired ability of the heart to pump blood, irregular heartbeat, weakening of the heart muscle, heart failure, and sudden loss of heart function. Symptoms usually improve on their own, but sometimes must be treated with medications that are typically used to treat heart failure.

Heart risks are greatest in Herceptin patients who also have been treated with chemotherapy drugs known as anthracyclines (for example, Adriamycin and Ellence [epirubicin]), and are also greater in older patients and those with a history of hypertension. The risk of damage increases when the anthracycline is administered at the same time as or right before Herceptin.

An anthracycline-free chemotherapy regimen consisting of Taxotere and carboplatin, used with Herceptin, has been found to be an effective cancer treatment and lowers the risk

of serious cardiac events.

Besides heart issues, serious infusion reactions occur rarely, usually during or within 24 hours of Herceptin treatment. Severe allergic reactions, swelling, and lung problems may lead to discontinuation of treatment. Other, more common side effects include flu-like symptoms such as fever, cough, headache, muscle pain, and fatigue.

As for Tykerb, cardiac toxicity has been found to be less frequent. Patients should tell their doctors if they have a history of heart problems.

Liver function, diarrhea, and rash are significant concerns, although rare with Tykerb. Patients should be tested for liver problems before and during Tykerb treatment, and should contact their physician if they experience itching, yellow coloring of the eyes or skin, dark urine, pain in the upper right abdomen, or severe fatigue.

Diarrhea, sometimes severe, is common, and can be managed with electrolytes, fluids, and antidiarrheal medicines. Patients who experience diarrhea should contact their doctor immediately; sometimes treatment may be interrupted to address the problem. Patients should also consult with their physician if they experience a dry cough or shortness of breath.

Development of a rash, on the other hand, can actually be a sign Tykerb is working. However, because these rashes can lead to an infection that might interfere with Tykerb treatment, patients should consult with their doctor right away. Rashes are often treated with antibiotics and/or topical corticosteroids.

Other side effects of Tykerb include nausea, fatigue, and hand-foot syndrome (redness and tingling or numbness of the hands and feet).



## Tips From a Survivor

BY CHRISTINE DRUTHER

■ **BE VIGILANT.** When educating yourself about HER2-positive breast cancer, explore online patient-based message boards and nonprofit organizations. Experienced survivors who have “been there, done that” can provide both information and support. Be sure your oncologist is also knowledgeable and up-to-date on research developments, and don’t be afraid to seek a second opinion.

■ **BE PATIENT.** Don’t rush into making decisions, but instead carefully weigh the pros and cons of each alternative, discuss them with your health care provider, and then decide on a course of treatment.

■ **CONSIDER ENTERING A CLINICAL TRIAL.** Herceptin and Tykerb are approved for HER2-positive breast cancer, but they do not work for everyone. There are exciting ongoing trials for HER2-positive breast cancer that you can find at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) or [www.breastcancertrials.org](http://www.breastcancertrials.org).

■ **ADOPT AN ACTIVE LIFESTYLE.** Find an activity that you enjoy and keep at it. Going out for a daily morning jog or walk not only keeps you feeling healthy and accomplished, but might even help you relax away all that mental tension.

■ **FIND SOME SPIRITUAL SUPPORT.** Relying on your faith can be a great source of comfort during such a stressful time. Having a spiritual connection will help invigorate you and strengthen your inner self.

■ **STAY POSITIVE.** Treat yourself to a day of sensible shopping, a favorite movie or funny sitcom, a healthy meal with friends, or any other activity you particularly enjoy.

*Christine Druther was diagnosed with breast cancer in 1990 that recurred nine years later. She has been in remission since 2001, when she started the HER2 Support Group website at [www.her2support.org](http://www.her2support.org).*



## Resources

### Breast Cancer Connections

[www.bcconnections.org](http://www.bcconnections.org)  
650-326-6686

### Breast Cancer Network of Strength

[www.networkofstrength.org](http://www.networkofstrength.org)  
800-221-2141

### HER Connection

(site is owned by Genentech)  
[www.herconnection.com](http://www.herconnection.com)  
888-835-2555

### HER Move

(site is owned by GlaxoSmithKline)  
[www.hermove.com](http://www.hermove.com)  
888-825-5249

### HER2 Support Group

[www.her2support.org](http://www.her2support.org)  
760-602-9178

### Living Beyond Breast Cancer

[www.lbbc.org](http://www.lbbc.org)  
888-753-5222

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