



## FEATURE STORY

# Herceptin in the Spotlight

BY MONICA ZANGWILL, MD

*Eight years after its approval, Herceptin emerges as the best weapon against HER2-positive breast cancer.*

There are certain emotional moments that we all remember. The birth of a child. The death of a grandparent. The first time the doctor said, “Cancer.” For Jen Levinson, a 39-year-old breast cancer survivor from Ponte Vedra Beach, Florida, one of those moments came in a most unlikely place.

Levinson was diagnosed with stage 2 breast cancer in 2000. Shortly after her mastectomy she joined a clinical trial of a new anti-cancer drug called Herceptin (trastuzumab). Five years later, Levinson attended the 2005 meeting of the American Society of Clinical Oncology to hear the results of the study. Sitting in the audience as the data was unveiled, she says, was one of the most moving experiences of her life. “When they talked about the amazing results, ” she says, “it was really incredible.”

What Levinson heard that day was that Herceptin, when given after surgery to women with HER2-positive breast tumors, could reduce the risk of cancer recurrence by almost 50 percent. This was big news. And, as it turns out, Levinson was not the only one excited by it. Within days, doctors and patients around the world applauded the news. Few other cancer drugs had yielded such profound results in clinical trials.



Jen Levinson received Herceptin in 2000 as part of a clinical trial and traveled to an oncology meeting last year to hear the final results.

Photo by Robert Deangelo.

Doctors say the success of Herceptin, which can be used for the 20 to 25 percent of breast cancer patients who are HER2-positive, is astounding. But, like other great advances in cancer treatment, the path to success was not easy. Herceptin’s rise to prominence actually took many years and required much hard work by numerous doctors and thousands of patients.

## The History of Herceptin

Back in the 1970s, scientists noticed that certain genes in animal tumors were involved in turning normal cells into cancer cells. Looking at similar genes in

humans, doctors made some interesting discoveries. They found that one gene, called the HER2 gene, (HER stands for human epidermal growth factor receptor) that is present in normal breast cells was overly abundant in some malignant cells.

With more investigation, doctors learned that the HER2 gene can create a protein receptor that sits on the outside of cells. This HER2 receptor helps trigger the chain reactions that cause the cell to abnormally divide and grow. George Sledge, MD, an oncologist and researcher at Indiana University, says, "HER2 is involved in pretty much everything you would be interested in for cancer, including growth, invasion, and metastases." Further research on those malignant cells with extra copies of the HER2 gene revealed that not only did they have more copies of the HER2 gene, but whereas a typical breast cell has about 50,000 HER2 receptors on its surface, a breast cancer cell can have as many as 1.5 million receptors.

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—George Sledge, MD

In the 1980s doctors began to measure HER2 in the tumors of women who were newly diagnosed with breast cancer. Using an immunohistochemical (IHC) analysis that measures the receptors on the outside of the cell or a fluorescent in situ hybridization (FISH) analysis that measures the copies of HER2 genes inside the cell, doctors can look for HER2-positive cells in breast tumors. Tumors with a 2+ or 3+ reading on IHC are currently considered to have too many copies of the HER2 protein receptor (referred to as “overexpression”) and are HER2-positive. A positive FISH analysis, which registers an excessive number of copies of the HER2 gene (referred to as “amplification”), is also considered HER2-positive.

As doctors began testing more women for HER2 in the 1980s, they found that women with HER2-positive tumors had a worse prognosis than women with HER2-negative tumors. Women with HER2-positive tumors tended to have recurrences of their cancer or developed metastases more frequently than women who were HER2-negative. This early finding was disappointing. But, early on, some scientists saw a silver lining in this dark cloud. All those little copies of HER2 were just sitting on the cell like ducks in a row waiting for a specialized drug that targeted just the HER2 receptor—a drug that homed in on those cells with excess HER2 receptors, effectively picking them off and dismantling their cancer-causing apparatus. It was a great idea but one that required creating a new drug in the lab out of monoclonal antibodies, drugs that attach to proteins on the surface of cancer cells and interrupt the cell’s growth signals. A few years later, Herceptin was born.

## Herceptin on Trial

"Herceptin targets HER2 receptors outside of the cell," says Sledge, which allows

it to specifically attack cancer cells. A bonus effect of the targeted mechanism of Herceptin is that it does not affect other fast-growing cells like those in the hair follicles or stomach lining.

After the initial studies with women who had advanced breast cancer showed very promising results, the Food and Drug Administration approved Herceptin in 1998 for metastatic HER2-positive breast cancer. Although the drug was approved for weekly use, clinical trials have found Herceptin to be just as effective when given every three weeks and tripling the approved dose to 6 milligrams per kilogram of body weight.

In the early 2000s several phase III clinical trials began to test Herceptin, which costs up to \$60,000 a year, as first-line treatment after surgery for women with early-stage HER2-positive breast cancer. Levinson joined one of these clinical trials in 2000. “I enrolled in N9831,” she says about the designation of her trial, and was randomized to the arm that got Herceptin.” In the NCCTG (North Central Cancer Treatment Group)-N9831 trial, Levinson had an equal chance of being placed in one of three groups. All three groups received standard chemotherapy with Adriamycin (doxorubicin) and Cytosan (cyclophosphamide) followed by Taxol (paclitaxel). One group got Herceptin for one year starting at the same time as the Taxol treatment; a second group got Herceptin for one year but did not start the drug until chemotherapy was completed; and a third group, called the control arm, only received chemotherapy. Levinson was one of approximately 2,700 women who participated in the trial.

A similar clinical trial called NSABP (National Surgical Adjuvant Breast and Bowel Project) trial B-31 began in February 2000. This trial, which treated more than 2,000 women with early-stage HER2-positive breast cancer, had two groups. Both groups received Adriamycin and Cytosan followed by Taxol, but only one of the groups also got one year of Herceptin, which was started at the same time as Taxol.

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Because the B-31 and N9831 trials were so similar, the trials’ investigators pooled their results for analysis and presented them at last year’s ASCO meeting, where Levinson heard them. Like everyone else, the investigators were amazed with the results. “The differences between the groups were huge,” says Edith Perez, MD, a principal investigator of the N9831 trial. “Herceptin really improved outcomes when added to chemotherapy.”

A large international trial called HERA (Herceptin Adjuvant Trial), which was also discussed at last year’s ASCO meeting, found almost exactly the same results as the American trials. The HERA trial, which involved almost 5,100 women, provided more good news because it showed that giving Herceptin immediately after chemotherapy could still reduce the risk of recurrence.

When the data from these three trials (N9831, B-31, and HERA) were released at ASCO, the future for many women with HER2-positive breast cancer turned

around almost overnight. Levinson could sense it when she heard the results. “I felt so lucky to have been part of that trial because it was groundbreaking.” No longer did having a HER2-positive tumor mean a poor prognosis. Herceptin could beat HER2-positive breast cancer in many of the 250,000 women diagnosed with the disease around the world each year. Genentech, the maker of Herceptin, filed for additional approval of the drug in mid-February for early-stage HER2-positive breast cancer. If the application receives priority review status, the FDA will have to make a decision by August.

## More Questions

The latest study results ushered in a new era in treatment of HER2-positive breast cancer. But questions remain. The American trials gave Herceptin with adjuvant (after surgery) chemotherapy. The international trial gave Herceptin after chemo was finished. Which was better? In general, giving combinations of drugs at the same time is more effective because the cancer cells are essentially surrounded and pummeled from all directions. But giving one drug at a time tends to reduce side effects. Herceptin was effective in both scenarios, which led to the question of whether it should be given to women with early-stage disease who finished chemotherapy months beforehand.

"Theoretically, you should still get an effect from Herceptin as you go out further from initial treatment," says Debu Tripathy, MD, director of the Komen/University of Texas Southwestern Breast Cancer Research Program in Dallas. "Although, that effect may diminish the further you go out," he adds, "and at some point you cross the line where the benefits are smaller than the risks." But, no one knows where that crossover line may lie, and that line may be in a different place for women who are at high risk for recurrence versus low risk. Continued monitoring of the women from the clinical trials may eventually provide more answers. Patients who are interested in starting Herceptin will need to have a one-on-one discussion with their doctors to weigh their own risks and benefits. For women who finished chemotherapy more than a year ago, the possible benefit of taking Herceptin is unknown.

Also still under investigation is how long the drug should be given. While most trials tested one year of Herceptin therapy, other trials are testing longer as well as shorter durations of treatment to determine how to most effectively prevent breast cancer recurrence. Duration of treatment may also affect the likelihood of cardiac toxicity, which, according to the clinical trial results of 2005, occurs in 1 to 4 percent of women on Herceptin.

A large clinical trial called BCIRG 006 (Breast Cancer International Research Group) tested whether different Herceptin and chemotherapy combinations could decrease the chance of cardiac side effects. Diane Nathan, a 55-year-old from Delray Beach, Florida, entered the BCIRG 006 trial in 2003 after a routine mammogram found a 1.2-centimeter HER2-positive breast tumor. “I was thankfully randomized to an arm with Herceptin,” she says.

The BCIRG 006 trial had three groups for comparison. Nathan was in the group that received chemotherapy with Adriamycin and Cytosine followed by Taxotere (docetaxel) plus Herceptin. The second group received chemotherapy without

Herceptin, and the third group was given carboplatin, Taxotere, and Herceptin. Nathan continued taking Herceptin for a year and underwent numerous heart tests to monitor her heart function. “I found Herceptin to be a very tolerable drug,” she says. She had no heart damage and no significant side effects. Plus, she has not developed a recurrence or metastases since her diagnosis.

Nathan’s experience contributed to the results of BCIRG 006, which were released at the San Antonio Breast Cancer Symposium in December 2005. The trial data again showed that Herceptin decreased the risk of recurrence by almost 50 percent. The trial also revealed that the risk of heart damage was less when Herceptin was given without Adriamycin. The data suggest the benefits of Herceptin can be obtained despite removing Adriamycin, a drug that belongs to a class of older chemotherapy drugs called anthracyclines, which can raise the risk of heart damage. However, studies suggest that anthracycline-containing Herceptin regimens should be used to treat a specific subgroup of HER2-positive breast cancer patients—the approximately 40 percent of patients whose tumors co-amplify a gene called topoisomerase II alpha. The topo II alpha gene and HER2 gene are located close to each other on chromosome 17, which can sometimes result in amplification of a large segment of the chromosome that includes both genes. Because topo II alpha is a known target for anthracyclines, doctors can determine the best Herceptin combination for each patient.

## The Next Generation

Herceptin has ushered in a new wave of targeted treatment for breast cancer. In fact, new drugs that target other parts of the HER2 receptor or HER2 chain reaction are already in the works. A drug called Tykerb (lapatinib) targets the portion of the HER2 receptor that sits inside the cell as well as the HER1 receptor, also known as epidermal growth factor receptor (EGFR). Preliminary data from a phase II study of Tykerb in women with advanced or metastatic HER2-positive breast cancer showed positive results. Tykerb may be filed for FDA approval in breast cancer within the next year. The drug also appears to penetrate into the brain, which may allow it to work for women with brain metastases.

Oncologists expect that Tykerb may actually be most effective when given in combination with Herceptin. “The hope is that if you give the old ‘one-two punch’ on HER2 by targeting both the outside and the inside portions of the receptor, you will get more effectiveness than just targeting either alone,” says Sledge. A phase I trial demonstrated that combining Tykerb and Herceptin was well-tolerated and safe in women with advanced or metastatic HER2-positive breast cancer. Armed with these early promising results, larger studies are currently under way to assess Tykerb in combination with Herceptin.

Another drug called Omnitarg (pertuzumab) blocks the HER2 receptor from setting off the chain reactions that lead to cancer growth. Omnitarg, however, is still in the very early stages of development and may actually turn out to be more effective in other types of cancer besides breast cancer.

## Only the Beginning

The overwhelming success of Herceptin has motivated doctors to look for more specific targets in breast cancer tumors, including targets in women with HER2-negative cancers. “There is more work ahead,” says Perez, “but it’s been wonderful to see the product of research and the product of volunteerism of patients.”

Nathan and Levinson are also grateful for all the hard work that was put into their treatment. Levinson, who restarted Herceptin after a recurrence of breast cancer in 2003 and is now disease-free, strongly advocates participating in clinical trials. “People with breast cancer are not all the same and there’s no one-size-fits-all solution, so it’s only with clinical trials that we’re going to get the answers,” she says. More trials and more research are under way. Herceptin appears to be only the beginning.