

FEATURE STORY

A New Era

BY ELIZABETH WHITTINGTON

As data emerge from a surge of new therapies, doctors combine the best of the best.

In a minute's time, Kristine Kulowiec went from total despair to excitement. Herceptin® (trastuzumab) and chemotherapy had stopped working for her recurrence of HER2-positive metastatic breast cancer, which meant the 49-year-old qualified for a clinical trial of a new targeted drug combination.

“When the physician’s assistant told me the CT (computed tomography) scan came back showing growth, I didn’t really hear anything else after that,” Kulowiec says. She was barely listening to the information the assistant was giving her about a clinical trial when her oncologist walked in.

“Now we can really get down to business,” Kulowiec remembers her doctor saying with a big smile.

“She was so excited about this trial and wanted to tell me,” says Kulowiec, who lives in Wake Forest, North Carolina. “Seeing her excited made me really excited about it. All of a sudden, I realized this was really important.”

Because Kulowiec’s cancer had progressed on Herceptin, she qualified for a study examining a combination of Herceptin and Tykerb® (lapatinib)—another targeted agent that inhibits HER2, but by a different mechanism. She started the combination in September 2006, and by mid-March of this year, Tykerb was approved for metastatic disease in combination with an orally administered chemotherapy called Xeloda® (capecitabine).



Kristine Kulowiec's breast cancer stabilized during a clinical trial combining Herceptin with Tykerb. Photo by Greg Allen.

Because breast cancer treatment has become individualized based on stage, hormone receptor sensitivity, genetics, menopausal status, protein overexpression and lifestyle, breast cancer is no longer “just” breast cancer.

“I think we’re entering a new era,” says Julie Gralow, MD, associate head of the Breast Cancer Program at the Fred Hutchinson Cancer Research Center in Seattle. “There are multiple benefits in assessing individual tumors in individual patients instead of lumping everything together as breast cancer.”

Currently, two traits pathologists primarily look for when diagnosing breast cancer are HER2 overexpression and estrogen status, which help doctors decide the best course of treatment—essentially eliminating therapies that would have little or no effect. But scientists are beginning to examine many other targets, including vascular endothelial growth factor, or VEGF, a substance cancer cells secrete to spur blood vessel growth to the tumor. Scientists are taking this rapidly growing arsenal of targeted agents, chemotherapies and anti-estrogens—even if they showed little benefit alone or lost benefit over time—and are finding that combining them can enhance their effects.

The Targets

[HER 2] Herceptin ushered in the age of personalized breast cancer therapy in the 1990s. Researchers found cancer cells that overexpress the HER2 protein on their surface make good targets for the monoclonal antibody, which was first approved for metastatic breast cancer in 1998. In 2005, an analysis of two large phase III clinical trials showed Herceptin plus chemotherapy cut the recurrence rate in early-stage breast cancer by half compared with chemotherapy alone, and the Food and Drug Administration consequently approved the drug for that indication in 2006. Side effects of Herceptin include fever, nausea and, rarely, heart damage.

Newly approved Tykerb targets both HER2 and the epidermal growth factor receptor (EGFR), also called HER1. The Tykerb/ Xeloda combination delayed disease progression for 27.1 weeks compared with 18.6 weeks for patients taking Xeloda alone. Researchers are still waiting to see if an overall survival benefit

results from the combination. Because Tykerb had such positive results in advanced cancer, experts believe the benefit in early-stage cancer will be even more dramatic, as was the case with Herceptin.

But that's where the comparison ends, says Neil Spector, MD, director of the Translational Research Oncology program at Duke Comprehensive Cancer Center, who contributed to the development of Tykerb, which began nearly a decade ago. One of the attributes that distinguishes Tykerb from Herceptin is its administration—oral versus Herceptin's intravenous delivery. But it also works differently.

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“The best analogy is if you looked at the tumor cell as a room with a bunch of wall sockets, with the sockets providing power that promotes the growth and survival of the room. Herceptin is the childproof cap,” Dr. Spector says, whereas Tykerb “cuts the wire inside the wall.”

For 16 weeks, Kulowiec saw her tumors shrink on the Tykerb and Herceptin combination, a response even her doctors didn't expect. At 24 weeks, her cancer has stabilized. “I feel so much better now than I did six months ago—to me, that's the miracle,” Kulowiec says, who no longer has to take naps because of severe fatigue and can drive herself to treatment. Patients taking Tykerb may experience diarrhea, vomiting and rash.

[Estrogen] Even before the approval of the anti-estrogen therapy tamoxifen 30 years ago, scientists knew not all breast cancers behaved the same way. Tamoxifen was the first drug approved for the type of breast cancer fueled by hormones—namely estrogen. It works in about half of all women with estrogen receptor-positive breast cancer by mimicking the hormone and binding to its receptor to shut down cancer growth. At the time, it was considered a huge success and is still the standard treatment for breast cancer in premenopausal women. The drug may cause hot flashes and increased risk of blood clots and uterine cancer, though this is rare.

Another type of anti-estrogen therapy called aromatase inhibitors (AIs), which include Aromasin[®] (exemestane), Arimidex[®] (anastrozole) and Femara[®] (letrozole), work by reducing estrogen production, primarily from the adrenal glands and fat tissue since the ovaries in postmenopausal women no longer produce estrogen. AIs, which can cause significant bone loss, have been found to be effective in early-stage and advanced breast cancers, but are only used in postmenopausal women.

Although estrogen receptor-positive breast cancers have been studied for decades, evidence shows these cancer cells may be “smarter” than previously

thought. Cancers sometimes develop resistance to drugs like tamoxifen, especially in advanced-stage disease. “One of the frustrating aspects is you often see very dramatic clinical responses where the tumor just melts away, but unfortunately the tumor comes roaring back,” says Dr. Spector. “The question is what is in the tumor that enables it to develop resistance?”

Scientists suspect some hardy tumor cells that use estrogen to fuel growth change their growth pathway from estrogen to HER2 when flooded with anti-estrogens. Likewise, while HER2-positive breast cancer cells may respond tremendously to Tykerb or Herceptin at first, after a while some cells become resistant. Therefore, researchers are pounding the cancer with multiple drugs that target estrogen receptors and HER2 at the same time to destroy cancer cells before they begin to alter their growth pathway.

“We found that if we treated [cancer cells] upfront with Tykerb and an anti-estrogen—the most effective being fulvestrant (Faslodex[®]),” says Dr. Spector, “you could essentially prevent the development of resistance in cell culture (laboratory tests).”

In a human study published in the journal *Cancer* in 2005, 240 patients with no previous therapy for their estrogen-sensitive, HER2-negative cancer were treated with either tamoxifen or Femara. At the time of disease progression, 26 percent of patients were found to have cancers that converted from HER2-negative to HER2-positive disease.

“Does this mean we have the possibility of preventing all acquired resistance in patients receiving these [therapies]? We certainly hope so,” Dr. Spector says. “Clinical trials that are ongoing—combining aromatase inhibitors and Tykerb, Faslodex and Tykerb, tamoxifen with Tykerb—will hopefully validate the lab findings.”

View Illustration: Cross-Talking Receptors

[VEGF] A target scientists have utilized to create several new drugs is the VEGF protein. Avastin[®] (bevacizumab) neutralizes VEGF, thus inhibiting a process known as angiogenesis in which the tumor secretes proteins to attract the growth of new blood vessels to deliver oxygen and nutrients to the tumor. Approved for lung and colorectal cancers, Avastin has been studied in breast cancer for a number of years in different combinations and sequences. The drug showed benefit for metastatic disease primarily when combined with chemotherapy, and current trials are studying the antiangiogenic drug in early stage breast cancer. Patients taking Avastin experienced high blood pressure and increased risk of blood clots.

Investigators hope to find successful breast cancer therapy regimens using different combinations of targeted agents, including Avastin, Herceptin, Tykerb, Xeloda and Sutent[®] (sunitinib), another antiangiogenic drug recently approved for kidney cancer.

In a phase III study published in the *Journal of Clinical Oncology* in 2005, Kathy Miller, MD, associate professor in the division of hematology/oncology at the Indiana University School of Medicine, and colleagues reported that adding

Avastin to Xeloda in previously treated metastatic breast cancer patients increased the response rate from 9 percent to nearly 20 percent, but the combination didn't significantly improve overall survival. (A response was defined as tumor shrinkage of 30 percent or greater.)

Preliminary results from another Avastin/Xeloda study, a phase II trial known as XCALIBr, were presented at the San Antonio Breast Cancer Symposium late last year. Unlike the JCO study, the metastatic breast cancer patients enrolled in XCALIBr are all HER2-negative and have received no prior treatment. Early data show 34 percent of patients taking the combination have at least 30 percent tumor shrinkage and another 38 percent have stable disease.

Dr. Miller has also combined Avastin with Taxol® (paclitaxel) in patients without prior chemotherapy for metastatic breast cancer, resulting in a nearly doubled progression-free survival over Taxol alone (11 months compared with 6.1 months). She's now excited about a new trial comparing that combination to Sutent/Taxol.

The Avastin/Taxol combination proved very effective for Terry Farrer, 54, of Royal Center, Indiana. After a mastectomy, chemotherapy and tamoxifen to treat her initial diagnosis in 1993, breast cancer was the last thing on Farrer's mind when doctors found a mass on her ovary in 2002. After removing her ovary and testing the molecular make-up of the tumor, doctors confirmed it was breast cancer that had probably spread from her first cancer (no cancer was ever detected in her remaining breast).

"I know now that once you have cancer, there's always the possibility of it returning, but I had gone on with my life and thought it was behind me," Farrer says.

After Femara and then Faslodex failed to prevent the cancer from spreading, she enrolled in the Avastin/Taxol trial. The tumor responded so well that she continued with Avastin for another nine months after the trial ended. When the cancer began growing again, her doctor switched her to another combination—Herceptin/Taxol—because her tumor tested positive for HER2 overexpression. For nearly a year, Farrer has had no signs of cancer, but she remains on Herceptin to keep the cancer at bay.

"I feel really good about the future and the prognosis, and I just heard that Tykerb was approved for HER2-positive cancer and women can take it if the Herceptin stops working," Farrer says. "But I intend for the Herceptin to work for a very long time."

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—Ingrid Mayer, MD

Breast Cancer's Future

About 30 clinical trials examining breast cancer vaccines are in the works. Based on the notion that vaccines can spur the body's immune system to prevent recurrence or destroy existing cancer, scientists have developed several different types of experimental breast cancer vaccines, including those based on HER2 or MUC1, another protein target.

By isolating and purifying a piece of the HER2 protein found on cancer cells and giving it to patients along with immune-boosting factors once a month for six months, breast cancer recurrence dropped by 50 percent, according to a study presented at last year's San Antonio Breast Cancer Symposium. Indeed, after two years of follow-up, fewer than 6 percent of vaccinated patients had a recurrence compared with nearly 15 percent of patients who did not receive the vaccine. Although numerous vaccines with HER2 have been unsuccessful in treating breast cancer, this study has given scientists the idea that perhaps these vaccines would work best as a preventive measure.

"We've been working for decades on how to use our own immune system, but for breast cancer we haven't had anything close to a home run," says Dr. Gralow, who is hopeful researchers will find the right target for a breast cancer vaccine, including MUC1. Dr. Gralow's team is in talks with a number of companies to make antibodies for the protein, which is found on a large percentage of breast cancer cells. MUC1 can also be a useful marker of circulating tumor cells in the bloodstream.

Scientists are even looking at old drugs to use in new ways, such as MPA (medroxyprogesterone acetate), a dated steroid initially used as contraception and then as anti-estrogen therapy, but fell out of favor once tamoxifen became widely used. Scientists found MPA decreases the ability of cancer cells to metastasize and may affect angiogenesis, and ironically "it's able to do that in cells that are completely insensitive to estrogen," says Dr. Miller, who will soon collaborate on a study involving MPA in hormone receptor-negative breast cancer. "It's a fascinating story."

The biggest advancement may not be one single drug at all, but how we test certain therapies for effectiveness in breast cancer. "There is a shift in the way we're designing and looking at clinical trials," says Ingrid Mayer, MD, an oncologist at Vanderbilt-Ingram Cancer Center in Nashville.

Taking the tumor's molecular make-up one step further, scientists are now exploring how best to gauge the effectiveness of treatments on the cellular level. Researchers would examine the tumor at the initial biopsy, give the patient neoadjuvant therapy (treatment before surgery) and then examine a follow-up biopsy sample before the tumor is removed. The process may help investigators see if a new drug has any effect on the tumor at the molecular level—essentially speeding up the process because you're looking for molecular changes, not survival or time to progression, which can take several years and require hundreds or even thousands of patients to be enrolled in a trial.

"You don't waste money, you don't waste time and you don't waste women's

lives,” Dr. Mayer says. “People won’t have to wait a long time to see if a drug works or not. It’s very innovative and it’s really going to revolutionize the way we test drugs.”