



## FEATURE STORY

# Targeting the Triple Threat

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*There's now something to take aim at in triple-negative breast cancer.*

"I've basically lived my entire life knowing I was going to get cancer," says Nancy Truesdale, a 42-year-old teacher from Key Largo, Florida. "It was just a matter of when." Having lost her mother to ovarian cancer and her grandmother to breast cancer, Truesdale knew her cancer risk was high. So she wasn't surprised when, in July of last year, a routine breast exam revealed a lump in her right breast.

The biopsy on Truesdale's tumor revealed triple-negative breast cancer, or TNBC, which means the tumor cells lack expression of three proteins common to various other types of breast cancer—the receptors for the hormones estrogen and progesterone, and a growth factor receptor called HER2.

After surgery to remove the lump (the tumor was found to be stage 2), two 12-week rounds of chemotherapy, a bilateral mastectomy, a hysterectomy because she's at high risk for ovarian cancer, and later participation in a clinical trial for Avastin (bevacizumab), Truesdale is cancer-free. "I've basically done everything I can do to rid my body of cancer," she says. "There's really nothing else I can do but sit and wait."



Because of her family history of cancer, Nancy Truesdale wasn't surprised by her triple-negative breast cancer diagnosis. Photo by Richard Knowles.

Of the roughly 190,000 new cases of breast cancer diagnosed in the U.S. each year, 10 to 20 percent are triple-negative.

The diagnosis of TNBC may be a fearful one, partly because these tumors tend to be aggressive with a high risk of metastasis, and partly because some of the most effective targeted therapies, such as Herceptin (trastuzumab) for HER2-positive breast cancer, and tamoxifen and aromatase inhibitors for hormone receptor-positive breast cancer, don't work in these patients. As such, the current standard treatment for TNBC has been classic breast cancer chemotherapy, which is particularly effective against TNBC, perhaps because the tumor cells divide rapidly—the hallmark of chemotherapy's target.

But that standard may soon change. Although TNBC currently lacks its own version of Herceptin, researchers have begun defining TNBC's unique molecular features in the hope of identifying new targeted drugs. And if recent clinical trial

results are any indication, targeted therapies for TNBC are just around the corner.

## The Nuts and Bolts

TNBC, which is more prevalent among premenopausal and African-American women, is a fast-growing cancer that has a higher risk of early recurrence in the first three to five years after diagnosis than do cancers expressing hormone receptors.

Although it's clear which molecular features triple-negative tumors lack, it's trickier to define them in concrete terms. "Triple-negative is a bit of a waste-basket terminology," explains Mark Pegram, MD, an oncologist at the Sylvester Comprehensive Cancer Center in Miami. "The majority of, but not all, triple-negatives are basal tumors," he says.

An estimated 65 to 90 percent of triple-negative cancers are basal-like tumors, meaning the cells express proteins typical of basal breast cells (the progenitor cells or stem cells that give rise to mature glandular breast cells), and are associated with a poorer prognosis than non-basal tumors.

Basal-like also describes most cases of inherited forms of breast cancer associated with mutations in the BRCA1 gene, which encodes a protein that helps repair damaged DNA. In fact, most BRCA1-associated breast cancers are basal-like and triple-negative. But the relationship is not one-to-one; only 5 to 15 percent of TNBC patients have a mutated BRCA1 gene.

## The Treatment Plan

Although hearing the word negative is usually a relief when associated with cancer—such as a negative biopsy or negative lymph node scan—it's not quite the same when it comes to TNBC.

Without the option of targeted drugs as first-line therapy, the mainstay of treatment for TNBC—regardless of tumor stage—is standard breast cancer chemotherapy, often with a combination called ACT, which stands for Adriamycin (doxorubicin), Cytosan (cyclophosphamide), and Taxol (paclitaxel). In patients such as Truesdale, whose cancer had not yet spread to her lymph nodes (stage 1 or 2), treatment usually begins with surgical removal of the tumor tissue. These patients are then given chemotherapy, often followed by localized radiation therapy.

"Chemo has gotten an undeserved bad rap," says Lisa Carey, MD, medical director of the University of North Carolina Breast Center in Chapel Hill. "It is far more effective and less toxic than it was years ago and not necessarily worse in terms of side effects than some targeted therapies. And if the chemotherapy works well (tumor shrinkage or disappearance when chemotherapy is given prior to surgery), then the prognosis is great."

Of course, not everyone thinks chemo's rap is so undeserved. Chris Cooper, a

59-year-old banking executive from Atlanta, was on ACT for about four months in 2006 after being diagnosed with TNBC, and her memories are not particularly fond.

“They call it the ‘red devil,’ ” she says, referring to the deep red color of Adriamycin. “It makes you lose your hair. You’re tired, and you just generally feel terrible.” Still, following treatment, scans found Cooper clear of cancer, and her hair eventually grew back—though it came back white instead of its previous brunette hue.

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—Lisa Carey, MD

Joyce O’Shaughnessy, MD, co-director of breast cancer research at Baylor Charles A. Sammons Cancer Center at Dallas, says many patients see a diagnosis of triple-negative as a death sentence. “But that’s not the case at all,” she says, pointing out that the majority of patients with stage 1 or 2 TNBC are cancer-free many years after treatment. Many patients with lymph node-positive disease (stage 3 or 4) also respond well to chemotherapy.

The reason triple-negative cancer has such a bad reputation, O’Shaughnessy explains, is that the disease recurs within five years after diagnosis in about 32 percent of patients, compared with only around 15 percent of patients with other breast cancer types (a 2008 study showed the five-year recurrence rate was 13 percent for women with hormone receptor-positive disease who underwent treatment after surgery). And the average survival time for TNBC after recurrence is only nine months.

The chance of recurrence highlights the need for more effective treatments. Studies are currently examining whether certain chemotherapies are more effective than others. Showing particular promise are carboplatin and cisplatin, which are already used to treat metastatic TNBC and are undergoing more rigorous testing. Because these agents disturb cellular repair pathways that many TNBC cells rely on, “it’s not unreasonable to think they may be better than standard [ACT therapy],” says Eric Winer, MD, director of the Breast Oncology Center at Dana-Farber Cancer Institute in Boston.

### Broadening the Arsenal

New studies of targeted drugs may add a beneficial boost to chemotherapy. “I consider clinical trials at all points in time for my patients,” says Winer. “I don’t believe that they’re only for when all else has failed.” Recent successes indicate that targeted therapies are making their way into the TNBC arsenal.

Some of the biggest news comes from a class of drugs called PARP (poly ADP-ribose polymerase) inhibitors, which may be of particular help to patients such as Truesdale who carry a mutated BRCA1 gene. Cells that lack a normal

BRCA1 gene are robbed of a major DNA repair mechanism and thus must rely on backup pathways for life-saving DNA repair. One of these backups involves repair proteins called PARPs, which mend breaks in DNA strands. PARP inhibitors are thought to kill tumor cells by crippling this important repair mechanism, while leaving healthy cells unharmed. These drugs have completed phase II testing in TNBC and in breast and ovarian cancer patients with a BRCA1 mutation. They are also being tested for the treatment of patients with melanoma and certain types of brain cancer.

### View Illustration : Turning Off DNA Repair

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A phase II study unveiled this summer at the American Society of Clinical Oncology's annual meeting examined a PARP inhibitor called olaparib as a late-line therapy for patients with BRCA1 or BRCA2 mutation-related tumors. For 10 of the 27 patients receiving high-dose olaparib, the tumor shrank by at least half, and most side effects were mild.

Early analysis of a randomized phase II trial led by O'Shaughnessy showed promising results for another PARP blocker called BSI-201. With BSI-201, overall survival times reached 9.2 months compared with 5.7 months for those treated with chemotherapy alone, and progression-free survival doubled, from 3.3 months to 6.9 months. A phase III trial of BSI-201 in TNBC is now recruiting patients.

Another success story has been Avastin, which blocks blood vessel growth to tumors by inhibiting a growth-inducing protein called vascular endothelial growth factor, or VEGF. Without VEGF, tumors are starved of the nutrients they need to survive. Avastin is approved for use in multiple cancers, including brain, lung, and colorectal, and was approved in 2008 for metastatic HER2-negative breast cancer and in 2009 for metastatic kidney cancer.

For Cooper, two different regimens of Avastin plus chemotherapy helped reduce metastatic spots that were found on her lungs in early 2008, although some of the spots have returned.

"That's just typical for triple-negative cancer," says Cooper. "The darn cells always seem to figure out how to beat the drug." She is down from six spots on her lungs to two, and is currently feeling good while taking a break from chemo.

A recent phase III clinical trial of patients with metastatic breast cancer, including some patients with TNBC, showed that adding Avastin to Taxol doubled progression-free survival -to 11.8 months, compared with 5.9 months with Taxol alone. Overall survival rates, however, did not change. A study now recruiting patients will test whether adding Avastin to chemotherapy has any benefit in non-metastatic disease, but it will be years before the results are known.

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—Eric Winer, MD

Winer says that, so far, nothing else has been as impressive as the PARP inhibitors, but other targeted therapies are in the works. TNBC tumor cells often have high levels of the epidermal growth factor receptor, or EGFR, which may help the tumor cells grow. Drugs such as Erbitux (cetuximab), which is used to treat some cases of metastatic colorectal cancer, block EGFR and thus may also be useful in metastatic TNBC.

Another therapy in early clinical trials is the leukemia drug Sprycel (dasatinib), which targets cellular enzymes called src kinases that transmit growth and survival signals to the tumor cell. These enzymes run amok in many types of tumor cells, including some TNBC subsets.

### What Lies Ahead

Although TNBC is still defined by its lack of distinguishing characteristics, physicians are optimistic that progress will be made in treating the disease once there is a better understanding of the biology.

“No one even talked about this type of cancer six or seven years ago,” says Winer. “But many of us predicted that once pharma and academia recognized the unmet need, new therapies would follow.”

While waiting for Winer’s prediction to come to fruition, the self-educating Truesdale comforts herself with numbers. Instead of focusing on the 30 percent chance that her cancer will come back, Truesdale concentrates on the 70 percent chance that it won’t. “That’s pretty darn good!”