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Smarter Trials for Smarter Drugs

BY LAURA BEIL

In a traditional scientific study, the drug that saved Elizabeth Alexander's life would have been deemed a failure. An associate professor of history at Texas Wesleyan University in Fort Worth, Alexander was diagnosed with metastatic HER2-positive breast cancer in 2000. She took Herceptin (trastuzumab), a drug that targets the HER2 molecule overproduced in about 20 percent of breast cancers.

"I think I'm really lucky," she says. But the drug doesn't work for most patients because their breast tumors don't have a high enough density of the target. So in a typical clinical trial, which would enroll women at a certain stage of breast cancer, Herceptin would have been lost in the background noise, at least statistically. To detect even a slight benefit, one researcher noted, a study that included all breast cancer patients would have needed more than 23,000 subjects.

These and other studies reveal a challenge to testing experimental treatments: A drug might work in only 5 percent of patients, but in that 5 percent, it could be a home run. So clinical trials of potential drugs are getting more sophisticated, following the lead of Herceptin and other early targeted drugs.

In Herceptin's seminal study, researchers selected women whose tumors were known to have a high density of HER2, even though the HER2 test was not very refined at the time. Similarly, researchers today realize they need to know about the molecular makeup of each patient's tumor before the study begins. Otherwise, a good drug might be lost—not because it doesn't work, but because it was tested on the wrong tumors.

"We all realize ultimately the way we're going to cure cancer is to match the right drugs with the right patients," says Roy Herbst, MD, of M.D. Anderson Cancer Center in Houston. His institution and other cancer centers are beginning to test targeted drugs in a new way.

At M.D. Anderson, the approach is almost like four studies in one: advanced lung cancer patients randomly receive either Tarceva (erlotinib), Zactima (vandetanib), Nexavar (sorafenib), or a combination of Tarceva and Targretin (bexarotene). After eight weeks, each patient is evaluated. If the cancer hasn't shown any improvement, patients can move to a different treatment. Along the way, researchers are studying the molecular properties of the tumor to understand why one treatment may outperform another.

Other study designs call for patients who are stable to be randomized to either continue treatment or stop altogether, known as a randomized discontinuation study design. Together, these approaches are termed adaptive trial designs.

The idea of updating a study while it is still in progress is becoming more common and may ultimately be the best way to get answers about targeted drugs, Herbst says. “You sort them to the group most likely to benefit.”

Such knowledge of tumors will also help after drugs are approved, keeping doctors from prescribing expensive and possibly harmful drugs to patients who are unlikely to benefit.