

NEWS IN DEPTH

Q&A: Eric Winer on Neoadjuvant Clinical Trials

Uncovering strengths and weaknesses for presurgical studies of breast cancer drugs

In the 1990s, the National Surgical Adjuvant Breast and Bowel Project P-18 trial showed that patients with breast cancer who were treated with chemotherapy before surgery and responded well had better long-term outcomes than patients who received chemotherapy but did not show evidence of a response. Today, large numbers of neoadjuvant (presurgical) clinical trials of drugs are under way, notes Eric Winer, MD, professor of medicine at Harvard Medical School and director of the Breast Oncology Center at Dana-Farber Cancer Institute in Boston, MA. He discussed what drives these trials and the roles they may eventually play in drug approvals with *Cancer Discovery's* Eric Bender.

Why are we seeing so many neoadjuvant trials for breast cancer?

In clinical practice, there is the view that it is entirely safe to give women with breast cancer neoadjuvant therapy, and we know that, for some patients, the therapy makes it possible to do less-invasive surgery. Women who might otherwise need a mastectomy can have a lumpectomy, and more recently there's even the thought that women may be spared more extensive lymph node surgery.

As a research tool, neoadjuvant studies have become very popular for two reasons. One, there is this sense that pathologic complete response [pCR] in the breast (and usually the lymph nodes as well) can predict long-term outcome. So it's a way of quickly identifying a surrogate marker of survival and getting an answer in weeks, rather than waiting for years and years. The other issue, of course, is that the biopsy is a readily available source of tissue. When standard adjuvant therapy is used, the breast tissue hasn't been exposed to the treatment in question. While correlative studies and analyses are clearly possible in adjuvant trials, there is much more that can be done when one is working with tissue that has been treated with chemotherapy and/or targeted therapy. Any residual tumor is, by definition, relatively resistant to the therapy that was administered and can be interrogated for markers of resistance.

How good is pCR as a surrogate marker for survival?

This question is really the crux of the issue facing the U.S. Food and Drug Administration [FDA]. Last year, the FDA put forward provisional guidance that suggested that the neoadjuvant setting might be one avenue for drug approval in high-risk, early-stage breast cancer.

In triple-negative and HER2+ cancers, the hope is that the neoadjuvant setting can be a setting where drugs can be evaluated rapidly, where we can get the answers as to whether a new approach is perhaps more effective, and where there might, and I emphasize might, be a role for

provisional drug approval based on a neoadjuvant study. The FDA guidance opened up this possibility but certainly made no promises. We'll see attempts to get accelerated drug approvals based on some neoadjuvant trials in the triple-negative setting, and we'll have to see how those play out.

However, there are settings in which it is quite clear that pCR after neoadjuvant therapy *isn't* a good surrogate for long-term outcomes. For example, in patients who have ER+ and HER2- breast cancer, the response, at least to chemotherapy, generally does not allow you to distinguish between patients who are likely to do well versus those who are likely to do poorly.

Neoadjuvant trials are almost by definition more complicated than adjuvant trials, so unless there's a compelling reason to study a new treatment only in the neoadjuvant setting, we should also be thinking about standard adjuvant trials, because sometimes these will be completed more rapidly. There also are some situations where we should probably include both adjuvant and neoadjuvant patients in the same trial—you could have the same randomization, drug A versus drug B, and allow the patient to get the treatment after surgery or before surgery.

What are some major neoadjuvant trials for breast cancer?

ISPY-2 is an adaptive trial that was designed very deliberately to look for a large signal, a therapy that will make a big, big difference. Neo-ALTTO was for women with HER2+ cancer, and is an example of a neoadjuvant study that tries to obtain biologic insights that will make it easier to interpret the corresponding adjuvant trial, in this case ALTTO. The Cancer and Leukemia Group B (now the Alliance) just completed two separate neoadjuvant trials, one for patients with HER2+ disease and the other for patients with triple-negative disease.

When are "window of opportunity" trials, very-short-term neoadjuvant trials designed primarily to gather data rather than treat disease, appropriate?

Although there's a lot of enthusiasm for these trials, as a way of determining if a drug hits a target and answering other biologic questions, I haven't seen too many examples yet where they have led to a particularly profound biologic insight. They also are in many ways the trials that I think are most problematic, because you are essentially giving a patient the drug without therapeutic intent. You're asking a patient to be a volunteer without any real hope that it will help them. This approach is appropriate in some situations with informed consent, but you have to be very careful that you have a clear sense of the safety and tolerability of the drug in question. This is a setting where we don't want to cause significant toxicity at a time when a patient is gearing up for surgery. ■



"We'll see attempts to get accelerated drug approvals based on some neoadjuvant trials in the triple-negative setting, and we'll have to see how those play out," says Eric Winer, MD.

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