Neoadjuvant Trials Could Speed Up Drug Approvals

By Judy Peres

In a dramatic departure from the conventional approval process, the U.S. Food and Drug Administration has cleared a drug for preoperative treatment of early breast cancer. Perhaps more striking, FDA granted pertuzumab (Perjeta) accelerated approval on the basis of pathology findings rather than improved patient survival. Many oncologists hailed the FDA’s action as a way to bring promising new agents to high-risk patients faster.

“It’s a paradigm shift,” said Claudine Isaacs, MD, professor of medicine at Georgetown University’s Lombardi Comprehensive Cancer Center in Washington, DC. “It gives us much quicker answers.”

But experts also warned it is not known (or: it is still unclear) whether the endpoint used in the trial underlying the FDA approval—pathologic complete response (pCR), or the absence of invasive cancer cells in the breast and lymph nodes at the time of surgery—will translate into better long-term outcomes for patients.

“We don’t know what [improved pCR means],” said Frances M. Visco, JD, president of the National Breast Cancer Coalition, “because we don’t know what it means for overall survival.”

Genentech, maker of the drug, is conducting a confirmatory phase III trial to answer that question; results are expected in 2016. Depending on the outcome of that trial, known as APHINITY, the accelerated approval will be either revoked or converted to full approval.

In its Sept. 30 announcement, FDA said pertuzumab may now be used in the neoadjuvant (preoperative) setting with trastuzumab (Herceptin) and docetaxel in patients with HER2-positive inflammatory or locally advanced early-stage breast cancer. Genentech spokesperson Susan Willson said the decision was based primarily on results from the 417-patient NEOSPHERE study, a randomized phase II trial that showed that adding pertuzumab to trastuzumab and docetaxel nearly doubled the rate of pCR (39.3% vs. 21.5%). Additional data from the TRYPHAENA study, as well as longer-term safety data from the phase III CLEOPATRA study of pertuzumab in metastatic breast cancer, were also submitted in support of the approval. (TRYPHAENA is a phase II study of neoadjuvant pertuzumab in early-stage breast cancer designed primarily to assess cardiac safety, but pCR was a secondary endpoint.)

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The original rationale for giving systemic treatment before surgery was to shrink tumors and perhaps to make a mastectomy patient eligible for breast-conserving surgery. But FDA and researchers alike are interested in evaluating new drugs in the neoadjuvant setting for several other reasons: Neoadjuvant therapy allows doctors to assess quickly whether a drug is working. The patient’s response may yield prognostic information. The neoadjuvant setting enables investigators to assess changes in tissue biomarkers between biopsy and definitive breast surgery. And, more than anything else, neoadjuvant trials offer an opportunity to get new drugs to patients sooner, at a stage where treatment could be curative.

“Increasing numbers of patients are being treated in the neoadjuvant setting,” said Richard Pazdur, MD, director of the Office of Hematology and Oncology Products in FDA’s Center for Drug Evaluation and Research. “By making effective therapies available to high-risk patients in the earliest disease setting, we may delay or prevent cancer recurrences.”

Traditionally, Pazdur explained, breast cancer drugs are tested and approved first in patients with late-stage or metastatic disease whose cancer has progressed while undergoing treatment with existing therapies. Those patients usually don’t have long to live, so seeing whether a new agent prolongs survival or delays disease progression is relatively easy.

Then the drugs are tested in the adjuvant (postoperative) setting in women with early-stage disease. But those trials need thousands of patients and take years to complete, because early breast cancer patients often have long life expectancies—indeed, many are actually cured after their surgery and would be fine with no adjuvant treatment. As a result, the time from initiation of a phase III trial of a drug in metastatic breast cancer to approval of its use in the adjuvant setting often exceeds 10 years. According to FDA, only one drug in the last decade, trastuzumab, has received full approval to treat early breast cancer.

Until now, neoadjuvant therapy has involved off-label use of drugs approved in the adjuvant setting, on the basis of studies showing similar outcomes in women treated before or after their surgery. Oncologists hope that pertuzumab’s...
approval for neoadjuvant use will lead to the approval of other drugs in that setting.

“I believe it could be the new model, at least for HER2-amplified and triple-negative breast cancers, where pCR has been shown to correlate with outcome,” said Rita Nanda, MD, associate director of breast medical oncology at the University of Chicago Hospitals.

FDA officials were more cautious. Pazdur said pertuzumab’s accelerated approval “could be a model—potentially, it is.” But he and Mikkael Sekeres, MD, chair of FDA’s Oncologic Drugs Advisory Committee and director of the Cleveland Clinic’s leukemia program, both stressed that the case file on pertuzumab contained much more than the results of one phase II trial with an endpoint of pCR. The regulators also considered the results of the phase III CLEOPATRA trial that led to pertuzumab’s 2012 approval in the metastatic setting—results that showed a clinically meaningful effect on overall survival and an acceptable toxicity profile. Also, Genentech has already accrued 4,800 patients for its confirmatory APHINITY trial of pertuzumab in the adjuvant setting.

“We looked at the surrogate endpoint [pCR] as reasonably likely to translate to a clinically meaningful endpoint,” said Sekeres. But because of the unique circumstances, it was “not a precedent-setting decision.”

Asked what it would take for pCR to become an acceptable endpoint for future drug trials, Sekeres said, “We’d be more confident if we saw those [pCR] results translate into progression-free, disease-free, event-free, or overall survival.”

Breast cancer patients who have a pCR have a greater chance of long-term survival than those who don’t. However, the strength of that association is not known.

In May 2012 FDA issued draft guidance suggesting that pCR could be used as an endpoint in neoadjuvant early-stage high-risk breast cancer trials for accelerated approval under certain conditions. The agency also established an international working group known as Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) to conduct a pooled analysis of data from more than 12,000 patients enrolled in neoadjuvant trials with long-term follow-up. The aim was to assess the correlation between pCR and disease-free or overall survival and the subtypes of early-stage breast cancer in which pCR is most likely to predict clinical benefit. The analysis will be published shortly in The Lancet, but preliminary results were presented at the San Antonio Breast Cancer Symposium in December 2012.

“The association between pCR and long-term outcomes is strongest in patients with more aggressive subtypes—triple-negative disease or HER2 positive, hormone receptor negative,” said Patricia Cortazar, M.D., the FDA official who wrote the study. However, she added, the magnitude of pCR improvement that predicts long-term clinical benefit could not be determined.

Several neoadjuvant studies presented at the 2013 San Antonio meeting looked at the same question. The European NeoALTO trial showed that the improved pCR rates seen in hormone receptor–negative, HER2-positive patients who received a combination of two HER2-targeted drugs did seem to translate into better long-term outcomes. But the trial was statistically underpowered to demonstrate such an outcome definitively.

Another trial being watched is I-SPY 2, a phase II study to identify new agents that show promise in treating patients with certain biomarker signatures. As of December 2013, I-SPY 2 had “graduated” two drugs expected to go on to phase III trials: veliparib, for triple-negative breast cancer, and neratinib, for HER2-positive, hormone receptor–negative tumors. In both cases, women who received the investigational drug in addition to a standard neoadjuvant regimen had much higher pCR rates than those in the control arm. Because of its statistically innovative “adaptive randomization” design, I-SPY 2 identifies drugs highly likely to perform well in patients with certain disease subtypes—so well that the confirmatory phase III trial may need to enroll as few as 300 patients.

Donald Berry, PhD, professor of biostatistics at the University of Texas M. D. Anderson Cancer Center in Houston, and one of the principal investigators of I-SPY 2, believes that such trials in the neoadjuvant setting are the future of drug development. “We’ve stopped doing adjuvant trials,” he said. “They’re huge, cumbersome, and slow—the antithesis of what cancer research needs to be.

“We’ve made great progress [in treating early breast cancer], which has led to big improvements in survival. The statistical implication is that we need bigger studies. We’ve been designing studies with 3,000, 5,000, or 10,000 patients in the adjuvant setting. This is not a tenable strategy. It’s too expensive. And by the time we get the results, the world has moved on.”

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Fifty Years Later, Many Teens Still Smoke

By Mike Fillon

January 11 marked 50 years since US Surgeon General Luther Terry’s warning linking cigarette smoking to lung cancer. Although the report caused many smokers to quit and others not to start smoking, teens still use and become addicted to nicotine at alarming rates.

The Campaign for Tobacco-Free Kids estimates that 3,500 U.S. youngsters try their first cigarette every day. Youth use of cigarettes and other nicotine-laced products is a good news–bad news dilemma. According to the 2012 National Youth Tobacco Survey released in November 2013 by the Centers for Disease Control

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