

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Neoadjuvant Pertuzumab in Early HER2-Positive Breast Cancer



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H&O Please discuss the recent vote for the accelerated approval of pertuzumab.

MS Pertuzumab (Perjeta, Genentech) came before the Oncologic Drugs Advisory Committee (ODAC, of which I am the chair) in a first-of-its-kind indication for the neoadjuvant treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer. The drug went through an accelerated approval mechanism because the primary endpoint for the study that formed the basis of the approval was pathologic complete response (pCR), defined as the absence of invasive cancer in the breast and lymph nodes. Last year, a draft guidance issued by the US Food and Drug Administration (FDA) suggested that this endpoint can be used in neoadjuvant early-stage, high-risk breast cancer trials for accelerated approval.

The FDA reviewed pertuzumab's use for neoadjuvant treatment under the priority review program, which provides for an expedited review of drugs that may offer major advances in treatment. The goal of the FDA's accelerated approval program is to provide access to promising drugs to treat serious or life-threatening conditions while confirmatory clinical trials are conducted. Pertuzumab in this setting fit that definition very well, as women with HER2-positive breast cancer are a population of patients who are in great need of better therapies.

H&O What findings supported the ODAC's recommendation for accelerated approval of pertuzumab in this setting?

MS This consideration was based on the results of the 417-patient open-label NeoSphere (Neoadjuvant Study of

Pertuzumab and Herceptin in an Early Regimen Evaluation) trial, which was previously published in the *Lancet*. Patients were randomly assigned to receive 1 of 4 neoadjuvant regimens prior to surgery as follows: trastuzumab plus docetaxel; pertuzumab plus trastuzumab and docetaxel; pertuzumab plus trastuzumab; or pertuzumab plus docetaxel. The trial's primary endpoint was pCR rate, defined as the absence of invasive cancer in the breast. In this study, 39% of patients who received pertuzumab plus trastuzumab and docetaxel achieved pCR, whereas only 21% of patients who received trastuzumab plus docetaxel achieved pCR ($P=.0063$).

H&O What is most exciting about this expanded indication?

MS This pertuzumab regimen is the first neoadjuvant regimen formally approved by the FDA for any type of cancer, which is a huge milestone. Neoadjuvant regimens are being used to treat a large percentage of women with breast cancer. Drugs have been translated from the adjuvant setting to the neoadjuvant setting, and studies have shown equivalence of outcome when drugs have been used in both indications. However, these drugs have not been approved specifically for the neoadjuvant setting. Thus, it is very exciting to see this specific indication approved so that we may administer the drug on label to women who are receiving neoadjuvant therapy.

H&O Please discuss the role of pCR as a study endpoint. What are areas of concern?

MS ODAC voted 13 to 0 (with 1 abstention) in support of pertuzumab to approve pertuzumab in the neoadjuvant

setting based on the pCR endpoint data. We agreed to this indication because of the totality of data that were presented to us. When ODAC decides whether or not to vote to approve a drug, we are obviously considering the balance of safety and efficacy. But we are also considering other factors, like whether another drug has been approved for that specific indication or whether the drug in question has already been approved for another indication. Are data available already regarding the drug's safety and efficacy for another indication? Can we look at those safety data in an expanded population prior to considering whether or not to vote to approve a drug for a different indication? In this case, pertuzumab is already on the market for women with metastatic HER2-positive breast cancer, and the phase 3 study demonstrated a survival advantage in that group. Thus, we have a drug that is active in HER2-positive breast cancer and we are comfortable with the safety profile among patients who have already received treatment. We considered those data in addition to the data that were presented to us from the NeoSphere study. Although there were not many patients involved in this study, there are a lot of women in the United States and worldwide who have been treated with pertuzumab for a similar indication. That increased our comfort level. As I mentioned before, we were excited about a new indication for this drug in a neoadjuvant setting. Thus, we looked at pCR as an acceptable surrogate endpoint that is reasonably likely to translate to a clinically meaningful outcome.

During the ODAC meeting, I quizzed some of ODAC's breast cancer experts about which patients they would choose to treat with neoadjuvant therapy. The obvious indication was breast cancer that is inflammatory and has essentially infiltrated the skin around the breast. The other major indication for neoadjuvant therapy is the hope that in giving chemotherapy up front, doctors will be able to convert a tumor that was previously considered to be unresectable and required a modified radical mastectomy to one that can be treated with more conservative surgery.

When reviewing the data from the pivotal registration trial, there was no difference in the ability to undergo more conservative therapy between the pertuzumab arm and the arm that did not contain pertuzumab.

H&O Please discuss the confirmatory trial.

MS The confirmatory study is the APHINITY (Adjuvant Pertuzumab and Herceptin in Initial Therapy of Breast Cancer) trial. It is a large phase 3 trial designed to confirm earlier results and also examine the long-term

effects of pertuzumab. Approximately 4800 patients with HER2-positive breast cancer who have had breast cancer surgery and are at high risk for disease recurrence are enrolled. Results from this trial are expected in 2016. The study had actually completed accrual by the time ODAC met, but data were not yet available for us to consider. However, another reason that we felt comfortable in voting with a majority to approve pertuzumab in the neoadjuvant setting was that not only was there an ongoing confirmatory study, but it was actually a completed confirmatory study.

If results from APHINITY are negative, we strongly recommend the removal of pertuzumab from the market for use in this neoadjuvant setting. Nevertheless, we are hoping that the confirmatory study will demonstrate the same magnitude of benefit with pCR that the registration study did. We also hope that that magnitude of benefit will translate to a clinically meaningful endpoint, namely an advantage in either progression-free survival or overall survival.

H&O Is there anything that you would like to emphasize?

MS A point that ODAC tried to make very clearly, and that the FDA emphasized, is that this approval should not be considered precedent-setting. Rather, this is a unique opportunity for us to vote to approve a drug under the accelerated approval paradigm in a neoadjuvant setting.

One of the main drivers for us to vote to approve pertuzumab in this setting was the totality of data available for this drug in a similar population. If another drug were to come before the FDA or ODAC with a similar pCR rate and similar numbers of patients on a study, it cannot be assumed that it would automatically get approved if it lacked some of the same totality of data that we had for pertuzumab.

Suggested Readings

Gianni L, Pienkowski T, Im Y-H, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2012;13(1):25-32.

Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol.* 2013;24(9):2278-2284.

ClinicalTrials.gov. A study of pertuzumab in addition to chemotherapy and herceptin (trastuzumab) as adjuvant therapy in patients with HER2-positive primary breast cancer. <http://clinicaltrials.gov/show/NCT01358877>. Identifier: NCT01358877. Accessed November 7, 2013.