Accelerated Approval for Pertuzumab in the Neoadjuvant Setting: Winds of Change?
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Abstract
Accelerated approval for agents that improve the frequency of complete pathologic response in the primary breast cancer setting heralds a broadening of the opportunities to get effective agents to the market more quickly. However, these new pathways will require identifying the signature or subtype for which the agent is most effective, and evidence of enrollment of patients to a trial that enables the ascertainment of event-free survival. The recent approval of pertuzumab for use in the neoadjuvant setting is evidence that the FDA is committed to supporting the accelerated approval pathway. The situations in which approval is likely to be granted are discussed.

Introduction
Getting a new oncology drug to market can take more than 10 to 15 years and costs in the range of 1 to 2 billion dollars (1, 2). Increasingly, now that we recognize that cancers are heterogeneous diseases, we need to target agents to specific cancer subtypes which may or may not be applicable across different organ sites. To make it possible to afford the development of these agents, we will need more creative ways to test agents and a path for accelerated approval for agents that demonstrate the ability to change outcomes.

Many compelling agents are in the development pipeline, but few of them are made available for women who present with life-threatening breast cancer at the time of primary diagnosis when their disease might be curable. On September 30, 2013, the U.S. Food and Drug Administration granted accelerated approval to pertuzumab for use in combination with trastuzumab and docetaxel for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer (3). This landmark action was the first such approval to come from a new draft guidance issued by the FDA in June 2012, which outlined a pathway for accelerated approval based on data from the neoadjuvant setting (4). The implementation of this accelerated approval pathway has important implications for drug development and patient care.

The Decision to Grant Accelerated Approval
Pertuzumab is a humanized monoclonal antibody that targets the extracellular dimerization domain of HER2 at a site separate and distinct from that bound by trastuzumab. Pertuzumab blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3, and HER4, and targets the dimerization of the HER2.

The data that led to accelerated approval were based upon three key pieces of information: (i) a phase III randomized controlled trial in the metastatic setting (CLEOPATRA) demonstrating improvement in progression-free survival (which had already led to the approval of pertuzumab for advanced breast cancer), (ii) two randomized, open label, phase II trials in the neoadjuvant setting demonstrating improvement in pathologic complete response (pCR; NeoSphere and TRYPHAENA), and (iii) a randomized, controlled adjuvant trial (APHINITY), which had completed accrual with results expected in 2016. The question that many are asking is whether all three of these conditions are required for accelerated approval in the neoadjuvant setting. What does this approval mean for other companies who wish to follow a similar path? The draft guidelines help to clarify this question. To better understand the basis for considering accelerated approval for early-stage disease, a
brief review of the data that have helped to support this pathway is in order. The randomized phase III trial in metastatic breast cancer, CLEOPATRA, compared the efficacy and safety of pertuzumab, trastuzumab, and docetaxel with placebo, trastuzumab, and docetaxel in the first-line setting in 808 patients. Median progression-free survival was significantly better in the pertuzumab group (HR, 0.66; 95% CI, 0.51-0.85; ref. 5). Overall survival (OS) was reported with a median follow-up of 30.1 months for the placebo group and 29.7 months for the pertuzumab group (5). With 267 events in follow-up, the hazard ratio for the pertuzumab group was 0.62 (95% CI, 0.49-0.78; P = 0.0008).

In the neoadjuvant setting, NeoSphere enrolled 417 women with stage II or III HER2+ breast cancer (based on immunohistochemistry 2+ or 3+ overexpression and amplification by FISH; ref. 6). Women were randomized to one of four neoadjuvant regimens including docetaxel/trastuzumab, docetaxel/trastuzumab/pertuzumab, trastuzumab/pertuzumab, or docetaxel/trastuzumab (the last added after the start of the trial to provide an estimate of the activity of this doublet). All patients were scheduled to receive four cycles given every 3 weeks, followed by surgical resection and then three cycles of FEC chemotherapy and 9 additional months of infusions of trastuzumab every 3 weeks. The pCR (ypT0/is ypN0) rates were 39.3% and 21.5% in the docetaxel/trastuzumab/pertuzumab and docetaxel/trastuzumab arms, respectively, netting a 17.8% improvement in the pCR rate for patients who received pertuzumab. The pCR (ypT0/is ypN0) rates were 17.7% and 11.2% for docetaxel/pertuzumab and pertuzumab/trastuzumab, respectively (6).

The second neoadjuvant trial, TRYPHAENA, was designed primarily as a cardiac safety study, randomizing a similar group of 225 women to receive six cycles of therapy with FEC/trastuzumab/pertuzumab × 3 followed by docetaxel/trastuzumab/pertuzumab × 3 versus FEC × 3 followed by docetaxel/trastuzumab/pertuzumab × 3 versus docetaxel/carboplatin/trastuzumab(TCH)/pertuzumab × 6. After surgery, patients completed a year of trastuzumab. Although there was no control (non–pertuzumab-containing arm), the pCR rates for the three arms were all even higher than those seen in NeoSphere (61.6%, 57.3%, and 66.2%, for the arms above, respectively), reflecting the inclusion of all chemotherapy in the neoadjuvant setting (7).

The adjuvant trial, APHINITY, has completed enrollment of 3,800 patients. Patients were allowed to have any standard adjuvant regimen (either TCH or any anthracycline/taxane combination) and were then randomized to pertuzumab versus placebo. Although the results of this trial are not known, and will not be announced before 2016, the company demonstrated that they had completed accrual of the adjuvant trial that would definitively determine whether or not the addition of adjuvant pertuzumab would result in a better disease-free survival (DFS) endpoint. The completed accrual was critical to the decision to grant accelerated approval.

Why Use the Neoadjuvant Setting for Drug Development

Over the past 30 years, several agents that have improved progression-free survival but not OS in the metastatic setting have gone on to phase II and III adjuvant trials in which they demonstrated a survival benefit. To date, no treatment introduced in the metastatic setting has resulted in a meaningful population of cured patients. This suggests that there is likely to be greater benefit to introducing agents earlier in the disease process. Consider the example of chronic myelogenous leukemia. After the discovery of the mechanism for malignant transformation and the introduction of imatinib, there was a dramatic reduction in death for those patients in the accelerated phase of their disease. The chance of cure went from 10% before the introduction of imatinib to >80% to 90% with the introduction of the tyrosine kinase inhibitors that target and prevent phosphorylation of BCR-Abl. However, the same benefit was not realized when treatment was initiated in blast crisis (8). This suggests that the introduction of agents earlier in the disease process is potentially more likely to result in cure.

For patients with breast cancer destined to die of systemic disease, surgical treatment alone will not be curative. It is the ability of systemic therapy to eliminate micrometastases that will make the difference of whether or not these patients will survive. A number of trials have demonstrated that the order of therapy (surgery followed by systemic therapy vs. systemic therapy followed by surgical therapy) does not alter survival. However, giving the systemic therapy first enables the critical readout of response to therapy.

For stage II and III breast cancer with features suggesting early (<5 years) recurrence, where there is no question that chemotherapy will be recommended, there is no reason not to initiate treatment with systemic therapy before definitive surgical resection, so-called neoadjuvant therapy. Women whose tumors disappear completely (pCR) have a much better outcome than those with substantial residual disease (9). Importantly, the I-SPY 1 trial (CALGB 150007/150012, ACRIN 6657) showed that pCR is a better predictor of recurrence-free survival by cancer subtype than for all patients as a whole, even among women with high-risk disease (10, 11). These results were corroborated by the meta-analysis of randomized neoadjuvant trials (12).

The meta-analysis established several critical points. First, it standardized the definition of pCR, which is now clearly defined as absence of all invasive disease in the breast and axillary lymph nodes. Importantly, sentinel or full axillary dissection before systemic therapy makes it impossible to evaluate the residual disease in the nodes. Enrolling patients in neoadjuvant trials with a pCR endpoint requires proper evaluation of the nodes (clinical exam and imaging with ultrasound or MRI and confirmation of the presence of disease by either fine-needle aspiration or core biopsy, or...
positron emission tomography). Second, the meta-analysis demonstrated the need to define a proliferative subset of hormone positive (HR\(^+\)) tumors for inclusion in neoadjuvant trials in which pCR would predict better survival. And third, this analysis again showed that in each subset, a higher rate of pCR translated to better survival, even in the HER2\(^+\) HR\(^+\) subset, where pCR is not as predictive of a good outcome as in the HR\(^-\) subsets (13).

Thus, the most important opportunity created by the use of neoadjuvant therapy is the ability to more quickly understand the benefit of treatment. This setting provides an important opportunity to target drug evaluation and improve outcomes. However, before the issuance of the draft guidance in 2012, the neoadjuvant setting was not considered to be a potential path for drug approval.

The Road to Accelerated Approval

In May 2011, the I-SPY 2 consortium sponsored a workshop to address ways to promote precompetitive collaboration and a path to accelerated approval in the neoadjuvant breast cancer setting with representatives from the pharmaceutical industry, academia, and the FDA (14). It was suggested that the entire industry would benefit from investment in trials that would help us to learn, early in the process, which tumor subtypes an agent was most effective against, and to introduce an intermediate endpoint that would help predict a high chance of success in a phase III trial. A suggested path forward was described (15), in which biomarker agent pairs could be identified and moved forward for confirmatory trials. If success could be replicated, accelerated approval for the agent, and approval of the biomarker or companion diagnostic, would be possible (see Fig. 1; ref. 13).

The draft FDA guidelines for accelerated approval in the neoadjuvant setting of breast cancer subsequently were released in 2012 (4). This guidance states that there are two pathways forward for the accelerated approval pathway (see Fig. 2). One is to perform a single randomized trial in which all patients are treated neoadjuvantly but a sufficient number of patients are accrued to demonstrate both the early pCR endpoint as well as the later event-free survival (EFS) endpoint. Once all patients are accrued for both endpoints, and if the pCR endpoint is replicated, the company can file for accelerated approval. At the 3-year EFS endpoint, full approval would ensue if the EFS confirms superiority of the new agent. In the event that EFS is not improved, accelerated approval would be revoked. The other option is to perform a neoadjuvant trial for pCR assessment, and simultaneously initiate an adjuvant confirmatory trial. If the pCR endpoint is positive, accelerated approval would only be considered once all patients have been accrued to the adjuvant trial. This latter model was the basis for accelerated approval of pertuzumab in the neoadjuvant setting.

Clinical Implications of Accelerated Approval

Although accelerated approval has led to patient access to pertuzumab in the neoadjuvant setting, it also creates challenges for care providers and clinical researchers. The accelerated FDA approval is not necessarily intended to
change the standard of care, given the lack of long-term confirmation of improvement in DFS or OS. However, many oncologists will change their own "standard" when facing a patient with HER2+ breast cancer who fits the profile of patients treated in the NeoSphere or TRYPHAENA trials. The opportunity to add an agent that seems likely to improve outcome is compelling, and the goal of neoadjuvant trials should indeed be to help accelerate the pace at which promising agents become available. Again, full approval will have to await the results of the adjuvant trial, but accelerated approval provides access in the intervening years to an agent with a solid resume of improved response.

Some clinicians may not change their practice at this time, however. Phase II studies can overestimate the potential benefits of an investigational therapy, as was seen in the initial phase II trial of iniparib, which failed to reach its primary endpoints in phase III (16, 17).

In addition, the approved regimens that incorporate pertuzumab from NeoSphere and TRYPHAENA use chemotherapy "backbones" that are less commonly used in the United States, including the FEC regimen (5-fluorouracil, epirubicin, and cyclophosphamide for three cycles), or the use of docetaxel versus paclitaxel. Finally, as the approval is limited to the neoadjuvant setting only and does not allow for pertuzumab to be used adjuvantly after surgery, insurers are also unlikely to cover the drug in this situation. The abbreviated 12-week neoadjuvant exposure may not provide the long-term effects that may be seen in the pivotal adjuvant APHINITY trial, in which 52 weeks of therapy is given. Explaining these caveats to patients who are distressed and anxious at having recently received a diagnosis of breast cancer, and who need to make a real-time treatment decision, is challenging. Patients need the fullest picture of risks and benefits of each treatment option possible; without DFS or OS data, some clinicians may feel they cannot provide a complete picture.

**Implications of Accelerated Approval for Existing Neoadjuvant Trials**

What is essential is the importance of adjusting ongoing trials to incorporate advances in the field. Creative ways to incorporate new regimens into trials and enable ongoing innovation and improvement are critical. Given the advantages of the neoadjuvant setting for drug development and the possibility of accelerated approval by the FDA, there has been a plethora of new neoadjuvant trials of novel agents in the past 3 years. In 2010, the I-SPY 2 trial was launched with the express purpose of testing novel agents in combination with standard chemotherapy for women with stage II and III breast cancers with a high risk for early recurrence. The goal of the trial is to graduate agents and biomarker pairs that predict an 85% chance of success in a confirmatory neoadjuvant phase III trial. To use this information for patient benefit, we used our precompetitive consortium as a forum to explore how the neoadjuvant setting could be a platform for accelerated drug and biomarker approval.

The control arm of I-SPY 2 for patients with HER2+ breast cancer was designed as weekly paclitaxel/trastuzumab for 12 weeks, followed by doxorubicin/cyclophosphamide for four cycles. The challenge for I-SPY and other neoadjuvant trials currently in progress is whether the FDA accelerated approval of pertuzumab should prompt the immediate incorporation of this agent into the standard control arm, or if this is premature. Approval for subsequent new agents is unlikely to require superiority over the trastuzumab/pertuzumab combination before full approval. However, obtaining consent and randomizing patients to chemotherapy/trastuzumab without pertuzumab raises ethical issues of whether this is an appropriate stand-alone therapy. In the case of I-SPY 2, an arm consisting of paclitaxel/trastuzumab/pertuzumab was added in May 2013, and serves as a real-time comparator to paclitaxel/trastuzumab alone. In addition, there is an arm that consists of TDM-1/pertuzumab.
All treatments are followed by Adriamycin (doxorubicin) plus cyclophosphamide (AC). The goal is to determine whether there is indeed an increase in pCR in the setting where AC is given after paclitaxel/trastuzumab/pertuzumab before surgical excision. At the time of FDA accelerated approval of pertuzumab, several active investigational arms were still accruing that are being compared with the paclitaxel/trastuzumab combination. The I-SPY 2 trial is undertaking statistical approaches such as the method of indirect comparisons (to a standard regimen such as paclitaxel/trastuzumab) and noninferior assessment of tumor response with modalities such as MRI-generated tumor volume to identify patients who will not achieve pCR with paclitaxel/trastuzumab alone to provide patients with the best possible treatment in the context of critically needed clinical trials that enable ongoing innovation. This situation is likely to occur with increasing frequency as other agents are found to increase pCR rates, and may also be granted accelerated approval. Consequently, these and other novel approaches to adapt neoadjuvant trial designs to a changing treatment landscape will be needed.

In summary, the accelerated approval of pertuzumab in the neoadjuvant treatment of breast cancer is the realization of a new paradigm for getting active new drugs to patients in the curative setting through smaller, cheaper, faster trials, and the FDA should be applauded for embracing this need and acting upon it. The pipeline of new agents promises additional trials of active agents that can use this approach. Interpreting these data, incorporating them into standard “off-study” treatment, and adapting ongoing clinical trials are challenges, but these challenges can and should be overcome to bring potentially lifesaving treatments faster to patients who need them.

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