

# ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

*In Focus: Breast Cancer*

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## Advances in HER2-positive Breast Cancer

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### **H&O** What are the most exciting recent findings in the setting of HER2-positive breast cancer?

**GS** To begin, it is known that HER2-positive breast cancer represents 15–20% of all cases of breast cancer. Women who have HER2-positive disease are at a higher risk of recurrence and death due to breast cancer, largely driven by the biology of the disease, which tends to make the malignant cells more invasive and aggressive. It is known that if the HER2 molecule is targeted, in a variety of ways, that targeting can be used to help shut down the cancer cell. This finding has led to the widespread introduction of trastuzumab (Herceptin, Genentech), initially in the metastatic setting and, starting in 2005, in the adjuvant setting. More recently, lapatinib (Tykerb, GlaxoSmithKline), which is a small-molecule receptor tyrosine kinase inhibitor of HER1 and HER2, was approved for use by the US Food and Drug Administration (FDA).

There is a broad amount of data in the adjuvant and metastatic settings regarding trastuzumab. Two recently identified trends have generated interest. Much attention has been focused on long-term follow-up of some of the initial studies of this agent. First, data presented within the last year by Dr. Dennis Slamon, for example, suggest that many patients with HER2-positive breast cancer may benefit in the adjuvant setting from a nonanthracycline-based regimen, such as carboplatin, docetaxel, and trastuzumab, as used in the Breast Cancer International Research Group (BCIRG) 006 trial. An update from that

trial certainly suggests that this approach may be beneficial and may reduce the amount of cardiotoxicity otherwise seen. Secondly, other updates, from the National Surgical Adjuvant Breast and Bowel Project (NSABP) and The Breast Cancer Intergroup (TBCI), have looked at the question of what constitutes HER2 positivity. An interesting and as yet unexplained finding is that some of the patients who are labeled HER2-positive by a local pathologist but HER2-negative by a central pathologist nevertheless appear to benefit from adjuvant trastuzumab. Many in the oncology community are wondering whether this finding is an example of pathologists disagreeing over what to call HER2-positive disease or evidence of some unexplained biologic characteristic of the disease that would open a broader population to therapeutic intervention. No one would recommend targeting HER2 in a patient with HER2-negative disease, but this concept is interesting and will be pursued in clinical trials going forward.

### **H&O** Why is there interest in refining the definition of HER2 positivity?

**GS** At the simplest level, HER2 positivity by fluorescence in situ hybridization (FISH) in the original clinical trials of trastuzumab was considered to be a ratio of HER2 to chromosome 17 of 2.0 or greater. The current American Society of Clinical Oncology and College of American Pathologists guidelines delineate a ratio of greater than 2.2 as positive, 1.8–2.2 as indeterminate, and less than 1.8 as negative. Unfortunately, these ratios are not based on data from prospective clinical trials. In my view, the community lacks a perfect sense of the cut-off for HER2 positivity with an assay such as FISH. In the

future, I believe we will learn more about assessments of positivity.

**H&O** Can you elaborate on evaluations of cardiotoxicity associated with treatment of HER2-positive breast cancer?

**GS** It has been known since the early days of research into trastuzumab that the combination of anthracyclines and this agent leads to an increased risk of cardiotoxicity, particularly congestive cardiomyopathy. Therefore, researchers have been seeking ways to avoid this toxicity. In the adjuvant setting, a simple way to avoid this toxicity was not to administer trastuzumab and doxorubicin at the same time. Therapies in the adjuvant setting were traditionally sequential, with anthracyclines followed by trastuzumab. Still, congestive heart failure occurred in 3–4% of patients, which is higher than would be expected with anthracyclines alone. The next step in research was to investigate whether anthracyclines could be avoided entirely. The early results of BCIRG 006, which had an anthracycline arm and a nonanthracycline arm, suggest that it is possible to avoid or at least decrease cardiotoxicity. Another open question, answers to which are expected from upcoming data, is whether other HER2-targeted agents will have the same cardiotoxic effects. It has been assumed, based on preclinical work done at the Salk Institute, that a great deal of cardiotoxicity is due to the fact that HER2 is important for cardiac myocytes as a prosurvival/antiapoptotic factor. If this hypothesis is true, the problem of cardiotoxicity could be a class effect of all agents that target HER2. Emerging data with lapatinib suggest that this agent may be less cardiotoxic than trastuzumab, for reasons that are currently unclear. Dr. Anna Maria Storniolo presented a relatively large database of patients receiving lapatinib that suggested the possibility that the baseline of cardiotoxicity with this agent is lower than it is with trastuzumab, albeit in populations that have often received prior trastuzumab and therefore may suffer from selection bias. It is unclear whether novel HER2-targeting agents will engender the same risk of cardiotoxicity as trastuzumab. It is hoped that equally efficacious but safer drugs will emerge.

**H&O** What new agents show the most promise in the setting of HER2-positive breast cancer?

**GS** As I mentioned, lapatinib targets HER1 and HER2. Clinical trial data with lapatinib suggest that its activity in the clinic is predominantly mediated through targeting HER2 rather than HER1. It does not offer significant benefit to patients with tumors that are HER1-positive

but HER2-negative. Lapatinib's approval was based upon a trial in patients who had received prior anthracyclines, taxanes, and trastuzumab, in which it was demonstrated that patients who received lapatinib plus capecitabine versus capecitabine alone achieved prolonged progression-free survival (roughly double). This agent is now progressing fairly quickly into a variety of phase III trials in the metastatic and adjuvant settings. For instance, the four-arm Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) trial, which is open now, will assign approximately 8,000 women in the adjuvant setting to receive either trastuzumab or lapatinib as single agents, the combination of trastuzumab and lapatinib, or the sequence of trastuzumab followed by lapatinib. This trial is an international effort of TBCI in the United States and the Breast International Group in Europe. Hopefully, this trial will answer the question of whether co-targeting HER2 with a molecule targeting the external membrane domain plus a receptor tyrosine kinase inhibitor would be better than targeting HER2 with either one alone.

The other quite exciting new agent is pertuzumab (Genentech), a monoclonal antibody that, like trastuzumab, targets the extracellular membrane domain of the HER2 molecule. It does so at a different place on the molecule than trastuzumab; as a result, it has a different mechanism of action. In preclinical work, pertuzumab, unlike trastuzumab, appears to prevent receptor dimerization. Because HER2 is the preferential dimerization partner with HER1 and HER3 (and in cells that overexpress HER2, it dimerizes with itself), preventing dimerization is another way of interfering with HER2 metabolism in HER2-positive breast cancer cells. This approach has been of interest in the laboratory in the past, but it has now entered the clinic in two phase II trials that were reported in 2007. Both trials enrolled women who had received and progressed on trastuzumab for well-documented HER2-positive disease. Patients then went on to receive a combination of pertuzumab and trastuzumab. In both trials, approximately 15% of patients who had progressed on trastuzumab alone seemed to respond to the combination. In addition to the patients who demonstrated an objective response, there was a similar-sized population of women who experienced prolonged disease stabilization. The overall rate of clinical benefit—the combination of responders and patients with disease stabilization—was between 30% and 40%. This agent may allow us to bypass some of the resistance to trastuzumab that has been seen.

In addition, it is important to mention agents that target vascular endothelial growth factor (VEGF), such as bevacizumab (Avastin, Genentech). Dr. Mark Pegram and colleagues have presented data suggesting that the com-

combination of bevacizumab and trastuzumab could confer a fairly high response rate (~53%) in patients with metastatic breast cancer. This high response rate, seen in the absence of chemotherapy, is exciting, and it suggests that such targeting may have a role in the future in the treatment of this disease. TBCI has just opened a trial (E1105) to evaluate the role of targeting VEGF in patients with HER2-positive breast cancer.

### **H&O** How common is resistance to frontline trastuzumab?

**GS** In the purest case, which is women receiving front-line therapy for metastatic breast cancer, both lapatinib and trastuzumab as single agents have objective response rates between 25% and 30%. Other patients experience prolonged stabilization of disease, but the majority of patients still do not achieve what would be considered clinical benefit. Similarly, in the adjuvant setting, the relative reduction of risk of recurrence conferred by trastuzumab is always approximately 50%. Of the patients who were fated to recur, trastuzumab prevents approximately half the recurrences. Thus, a significant population of HER2-positive patients do not benefit from agents that target HER2, representing a fertile area for research.

### **H&O** What is known about the mechanisms of a lack of response?

**GS** There has been research in the laboratory into the mechanism of resistance to trastuzumab, and researchers are also beginning to learn about resistance to lapatinib. There are several potential mechanisms of resistance seen in the laboratory. First, the drug might not reach its correct target for pharmacologic reasons. Alternately, once the drug reaches its target, the target itself could be altered on the surface of the cancer cell in such a way that, for

instance, trastuzumab might not bind to an extracellular membrane protein due to a mutation in that protein. To cause resistance to an agent like lapatinib, there could be a mutation in the receptor tyrosine kinase of the HER2 molecule. Alternately, the intracellular HER2 pathway can be turned on downstream of the receptor complex despite upstream targeting. Finally, there could be upregulation of other receptors that are involved in the growth, invasion, and metastasis of cancer cells. For example, researchers have noted breast cancer that is estrogen receptor-positive and HER2-positive, which, once HER2 is blocked by an agent like lapatinib, has an upregulation of the estrogen receptor; in turn, this upregulation acts as a growth mechanism. It has been suggested that the insulin-like growth factor-1 receptor may also play a similar role in some patients with breast cancer. Therefore, although there are many potential mechanisms of resistance, it is unknown which is predominant in the clinic, or if one does predominate. Furthermore, it is unknown whether the mechanisms of resistance to monoclonal antibodies will be seen with small-molecule receptor tyrosine kinase inhibitors.

### **Suggested Readings**

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