

# ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: Clifford A. Hudis, MD

## Updates on Therapeutic Approaches in HER2-positive Disease

Maura N. Dickler, MD  
Medical Oncologist  
Memorial Sloan-Kettering Cancer Center  
New York, New York

### **H&O** What are the characteristics of HER2-positive breast cancer?

**MD** Human epidermal growth factor receptor 2 (HER2)-positive breast cancer makes up approximately 20–25% of all breast cancers. If a patient's breast cancer is HER2-positive, there is amplification of the HER2 gene, which results in protein overexpression. HER2 is just one member of the EGFR superfamily, which also includes HER2, HER3, and HER4. All breast cancer cells have some degree of HER receptor family expression, but it is the overexpression that characterizes the HER2-positive patients. HER2 is both a prognostic and predictive marker in breast cancer. Patients who have HER2-positive breast cancer have a more aggressive biology, but their prognosis has changed with the early use of HER2-directed therapies. However, women with HER2-positive, ER-positive breast cancer have a decreased responsiveness to endocrine therapy compared with women with HER2-negative, ER-positive breast cancer.

### **H&O** Which agents are approved for the treatment of HER2-positive breast cancer?

**MD** Presently, 2 drugs are approved by the U.S. Food and Drug Administration (FDA) for patients with HER2-positive breast cancer: trastuzumab (Herceptin, Genentech) and lapatinib (Tykerb, GlaxoSmithKline). Trastuzumab is a monoclonal antibody that binds to the extracellular domain of HER2. It has been studied as a single agent and in combination with chemotherapy,

endocrine therapy, and other anti-HER2 agents in early stage as well as metastatic HER2-positive breast cancer. Lapatinib is a tyrosine kinase inhibitor that interrupts the HER1 (EGFR) and HER2 growth receptor pathway. Lapatinib was approved in 2007 in combination with capecitabine for patients with locally advanced or metastatic HER2-positive breast cancer who had prior therapy with an anthracycline, a taxane, and trastuzumab. Since its approval, it has been studied as a single agent and in combination with paclitaxel and trastuzumab.

At the 2009 San Antonio Breast Cancer Symposium (SABCS), Dr. Edith Perez updated the results of the NCCTG N9831 trial, a multicenter open-label study of adjuvant trastuzumab administered either concurrently with or following paclitaxel compared to chemotherapy alone in early stage HER2-positive breast cancer. Study findings suggest that initiating trastuzumab with the start of paclitaxel appeared to improve disease-free survival (DFS) compared to starting trastuzumab at the end of chemotherapy. These data lend support to the current practice in North America, in which practitioners typically start trastuzumab with paclitaxel and not after chemotherapy. Thus, NCCTG N9831 provides further evidence that concurrent administration in the adjuvant setting is the best approach in HER2-positive breast cancer patients.

Trial results were also presented by Dr. Dennis Slamon at SABCS. Findings from the third analysis of BCIRG 006, a 3-arm study that examined standard doxorubicin/cyclophosphamide/docetaxel (ACT), ACT with trastuzumab (AC-TH), and docetaxel/carboplatin/trastu-

zumab (TCH) in patients with early-stage HER2-positive breast cancer, demonstrated that adding trastuzumab to either ACT or TC improved DFS compared with ACT alone, and there was no statistically significant advantage for DFS between the AC-TH arm and the TCH arm. There were fewer deaths on the AC-TH arm compared with the TCH arm (94 vs 113 deaths). Of note, there were more cases of congestive heart failure reported on the anthracycline-containing arms (21 events in AC-TH group, 4 events in TCH group); however, there were no cardiac deaths. At the present time, markers such as TOP2A amplification are not yet ready for prime time to select patients who may benefit most from either anthracycline-containing or trastuzumab-based therapy. There are conflicting data in this area of investigation, and it is insufficient to base clinical decisions on such markers. Therefore, TOP2A should presently not be ordered in HER2-positive patients.

Trastuzumab has also been investigated in combination with lapatinib. At the 2009 SABCs, Dr. Kim Blackwell updated the results of the survival analysis of the GlaxoSmithKline-sponsored randomized study comparing lapatinib plus trastuzumab to lapatinib alone. Initial findings, reported by Dr. Joyce O'Shaughnessy at an earlier meeting, showed that the combination of lapatinib and trastuzumab improved progression-free survival (PFS) compared to lapatinib alone in metastatic HER2-positive patients. The updated results showed a statistically significant survival benefit, with a median overall survival (OS) of 9.5 months in the lapatinib alone group versus 14 months for the combination of trastuzumab and lapatinib (HR, 0.74;  $P=0.026$ ). The improvement in OS was seen even though patients who received lapatinib alone were allowed to cross over to the combination arm at time of progression, and crossover often reduces the benefit seen in OS. What was also impressive was that the median number of chemotherapy regimens in the enrolled patients was in the 4–5 range, and the median number of trastuzumab-containing regimens was 3; thus, this was a heavily pretreated population of patients. One can argue that the patients in this study were a select population in that they were a group of women who continued to have a good performance status and were able to receive several trastuzumab-containing regimens (therefore a population of patients with HER2-driven disease). The study results demonstrate efficacy of dual blockade of the HER2 pathway.

ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization) is an ongoing phase III study of adjuvant lapatinib and/or trastuzumab in early-stage HER2-positive disease. Patients enrolled in the study are randomized to trastuzumab alone, lapatinib alone, trastuzumab followed by lapatinib, or lapatinib in com-

bination with trastuzumab. The objective is to examine which agent is more effective, which is safer for patients, and what benefit will be derived by taking the drugs separately, in tandem order, or together. ALTTO will be one of the first trials to collect biologic materials during the conduct of the study.

**H&O** What are some agents that are currently being investigated in HER2-positive breast cancer?

**MD** Many of the newer agents that are in clinical trials are being studied in the metastatic setting. Trastuzumab-DM1 (T-DM1, Genentech/ImmunoGen), heat shock protein 90 (Hsp90) inhibitors, pertuzumab (Omnitarg, Genentech), and neratinib (HKI-272, Wyeth) are among the drugs currently being investigated.

T-DM1 is an antibody drug conjugate that combines trastuzumab with maytansine (DM1). It is a more selective antibody that targets DM1 directly into cancerous tissue, which reduces adverse events. In general, the drug has been well tolerated, with cases of fatigue, mild liver function abnormalities, and low platelet counts. A phase II study of T-DM1 in metastatic HER2-positive breast cancer presented by Dr. Charles Vogel at the 2009 American Society of Clinical Oncology meeting showed a 39% overall response rate in patients treated with T-DM1. At SABCs, Dr. Ian Krop reported results of an open-label, single-arm phase II study of T-DM1 in HER2-positive metastatic breast cancer patients previously treated with lapatinib, trastuzumab, and chemotherapy. The results demonstrated a 32.7% overall response rate with an acceptable safety profile in a heavily pretreated population who received T-DM1. A phase III trial comparing the safety and efficacy of T-DM1 to that of capecitabine and lapatinib in HER2-positive metastatic breast cancer patients is currently recruiting patients.

Another class of drugs that has been used in HER2 breast cancer is Hsp90 inhibitors. Hsp90 is a chaperone protein involved in cellular functions such as protein folding and signaling. One of the important client proteins for Hsp90 is HER2. Thus, when Hsp90 inhibitor is given, HER2 is reduced. Tanespimycin (Bristol-Myers Squibb) is an inhibitor of Hsp90 that has been studied in combination with trastuzumab in patients who either received 1 prior trastuzumab-containing regimen for HER2-positive disease or had progressive disease within 3 months after adjuvant trastuzumab. The response and clinical benefit rates seen in this study were 24% and 57%, respectively.

Pan-HER inhibitors, which belong to the tyrosine kinase family and inhibit multiple HER family members, have been under investigation, but they are early in

development. Pertuzumab is a monoclonal antibody that inhibits dimerization of HER2 and other HER family members. It appears to be active in HER2-positive breast cancer, but its use is limited to HER2-positive disease. In studies, pertuzumab has demonstrated some modest single-agent activity; however, ongoing studies are examining pertuzumab in combination with other agents (chemotherapy and trastuzumab). NEOSPHERE (Neoadjuvant treatment with Herceptin and pertuzumab) is an ongoing study examining 4 combinations of trastuzumab, docetaxel, and pertuzumab, as neoadjuvant treatment in HER2-positive patients. Another study, CLEOPATRA (CLinical Evaluation Of Pertuzumab And TRastuzumab), is an ongoing phase III study in HER2-positive metastatic breast cancer to evaluate the efficacy of the combination of pertuzumab with trastuzumab and docetaxel; patients are receiving trastuzumab plus docetaxel along with either pertuzumab or placebo. In addition, a large, randomized phase II trial looking at trastuzumab plus capecitabine plus pertuzumab (PHEREXA) in patients who have progressed after 1 line of trastuzumab-based therapy in the metastatic setting has recently opened for recruitment.

Neratinib is another drug currently being studied. Neratinib is a second-generation oral tyrosine kinase inhibitor that resembles lapatinib in that it inhibits both HER1 and HER2. This agent has shown promising single-agent activity. A previous phase II trial reported by Dr. Hal Burstein showed that neratinib given to patients with HER2-positive breast cancer resulted in response rates of 26% and 51% in patients who had prior trastuzumab exposure and in those who had not, respectively. Median PFS was 23 weeks and 40 weeks in patients who previously received trastuzumab and in those who had not, respectively. Neratinib has also been examined in combination with trastuzumab, paclitaxel, and vinorelbine, and other combination trials are currently ongoing. Eventually, our goal will be to evaluate these drugs earlier in the adjuvant setting, as well as obtain efficacy in the metastatic setting.

## H&O What are some of the active areas of investigation in HER2-positive disease?

**MD** Identifying why patients develop resistance to trastuzumab has been an active area of research. Even though trastuzumab is currently one of the most effective treatments for HER2-positive disease, many patients with HER2-overexpressing breast cancer do not benefit from the drug or develop resistance to it. Mechanisms for trastuzumab resistance include obstacles disrupting the binding of trastuzumab to HER2, upregulation of HER2 downstream signaling pathways, signaling through alternate pathways, and failure to trigger an immune-mediated mechanism to destroy tumor cells. Resistance to trastuzumab is a major problem that requires an understanding of HER2 and trastuzumab activity at the molecular and biologic levels. In order to develop strategies and subsequently create drugs to overcome trastuzumab resistance, researchers need to fully understand the mechanisms through which resistance occurs, and this has been on the forefront of breast cancer research.

## Suggested Readings

Vogel CL, Burris HA, Limentani S, et al. A phase II study of trastuzumab-DM1 (T-DM1), a HER2 antibody-drug conjugate (ADC), in patients (pts) with HER2+ metastatic breast cancer (MBC): final results. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2009;27:Abstract 1017.

Modi S, Sugarman S, Stopeck A, et al. Phase II trial of the Hsp90 inhibitor tanespimycin (Tan) + trastuzumab (T) in patients (pts) with HER2-positive metastatic breast cancer (MBC). *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2008;26:Abstract 1027.

Blackwell KL, Burstein HJ, Sledge GW, et al. Updated survival analysis of a randomized study of lapatinib alone or in combination with trastuzumab in women with HER2-positive metastatic breast cancer progressing on trastuzumab therapy. *Cancer Res* (San Antonio Breast Cancer Symposium). 2009;69:Abstract 61.

Slamon D, Eiermann W, Robert N, et al. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC-T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC-TH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2neu positive early breast cancer patients: BCIRG 006 study. *Cancer Res* (San Antonio Breast Cancer Symposium). 2009;69:Abstract 62.