Hints of Future Progress for HER-2 Breast Cancer

By Renee Twombly

Preliminary findings of several ongoing studies presented at the 2010 San Antonio Breast Cancer Symposium got researchers talking about the possibility of treating and even curing HER-2–positive breast cancer without chemotherapy—something that would have been unheard of a decade ago.

Such a stunning reversal is breathtaking, said Neil Spector, M.D., director of translational oncology research at the Duke Cancer Institute. “We have gone from HER-2–overexpressing disease being the most lethal type of breast cancer to a subtype that we are talking about curing,” said Spector, who delivered a plenary lecture on anti–HER-2 therapies at the meeting.

The studies tested combination HER-2–targeted therapies—the so-called HER-2 blockade—for some early-stage HER-2–positive breast cancer patients. They delivered multiple anti–HER-2 therapies before surgery (neoadjuvantly) and demonstrated that combinations of trastuzumab (Herceptin) and lapatinib (Tykerb) outperformed monotherapy with either drug alone, as did combining each drug with trastuzumab. So did the newcomer pertuzumab (Omnitarg), which binds to HER-2 in a different region from trastuzumab and which is said to also prevent HER-2 receptors from pairing with HER-3 and HER-4. In one study, tumors of different region from trastuzumab and which is said to also prevent HER-2 receptors from pairing with HER-3 and HER-4. In one study, tumors of 16% of patients who received the combination of trastuzumab and pertuzumab without chemotherapy appeared to have a complete response by the time they underwent surgery.

“The whole field of HER-2 therapy is extremely exciting and hopeful,” said Nancy Davidson, M.D., director of the University of Pittsburgh Cancer Institute. “These were very difficult breast cancers to treat, but now we have options that in some cases are very effective, with the prospect of even better therapies to come.”

But no one is ready yet to declare unmitigated success. For one thing, the two combination studies featured at the meeting, Neo-ALTTO and Neosphere, tested neoadjuvant clinical benefit by using pathological complete response (pCR), or the absence of invasive cancer in the breast tissue and regional lymph nodes. Even though giving chemotherapy before or after surgery results in the same long-term outcome, researchers, especially those in the U.S., say pCR has never been firmly statistically correlated with improved disease-free and overall survival.

Therefore, results cannot be considered practice changing in that the studies were not designed to be definitive tests of survival, said Jo Anne Zujewski, M.D., head of breast cancer therapeutics at the National Cancer Institute.

“To date, we don’t know if a [pCR] correlates with long-term benefit,” said Eric Winer, M.D., director of the Breast Oncology Center at the Dana–Farber Cancer Institute. “And no drug in breast cancer has been approved on the basis of this response. But it is a hint, and a very intriguing one at that.”

Edith Perez, M.D., the Mayo Clinic oncologist who has led pivotal adjuvant studies of trastuzumab, agreed, noting that all neoadjuvant breast cancer therapy is now being used off label. She said neoadjuvant clinical trials are valuable primarily because they generate hypotheses that adjuvant studies need to corroborate. She is the American leader on one of those trials, ALTTO, which is testing the same therapies as Neo-ALTTO, in the same size population: 8,400 HER-2–positive breast cancer patients.

Combination Therapy Superior

The neoadjuvant studies presented at the San Antonio Breast Cancer Symposium clarified the difference between trastuzumab and lapatinib as single agents against HER-2–positive breast cancer as well as the benefit that a combination of both, with or without chemotherapy, may offer.

The phase III GeparQuinto clinical trial, led by the German Breast Group, of 620 patients with untreated invasive HER-2 breast cancer, showed that trastuzumab and chemotherapy offered a better pCR (31.1%) than did lapatinib and chemotherapy (21.7%). Toxic effects were greater in the lapatinib-treated group, which caused 3.45% of patients randomized to this group to discontinue treatment.

In the Neo-ALTTO trial, taking both trastuzumab and lapatinib together was the better combination. A total of 455 patients were randomized to 6 weeks of anti–HER-2 therapy alone, either with lapatinib or trastuzumab or both. All three regimens then added paclitaxel, for a total of 18 weeks of therapy before surgery. Offering chemotherapy 6 weeks after anti–HER-2 therapy allowed researchers to gauge the true first-line clinical response rate to anti–HER-2 therapies by themselves, said Jose Baselga, M.D., Ph.D., chief of the division of hematology–oncology and associate director of Massachusetts General Hospital Cancer Center. The Breast International Group conducted the study, largely in Europe.

Until recently, Baselga was based in Barcelona.

After surgery, patients received conventional chemotherapy for 3 weeks and then continued with the previously assigned completion of 1 year of anti–HER-2 therapy.
Baselga reported that the pCR rate in the tissue removed during surgery (using the National Surgical Adjuvant Breast and Bowl Project guideline of either absence of invasive cancer cells in the breast at surgery or only noninvasive in situ cancer in the breast) was 51.3% with the lapatinib–trastuzumab combination versus 24.7% for lapatinib and 29.5% for trastuzumab.

He added that the objective clinical response rate at 6 weeks was highest for the combination therapy, 67.1%. At surgery, the response rate was 80.3%, 70.5%, and 74%, for lapatinib–trastuzumab combination therapy, lapatinib-only, and trastuzumab-only, respectively, but toxicity was higher, although manageable, in the lapatinib-only arm.

“The take-home message is that dual anti–HER-2 blockade is a valid concept in HER-2–positive breast cancer.”

said Winer. “If ALTTO confirms Neo-ALTTO, then I think we can consider being in a new era where we do use [pCR] at least in HER-2–positive breast cancer as a way of identifying new regimens that might be approved.”

Doing Away With Chemotherapy?
Results of the Neosphere study also offered the prospect of avoiding chemotherapy in selected patients, said Luca Gianni, M.D., of the Fondazione IRCCS, Istituto Nazionale dei Tumori, in Milan, Italy. Neosphere is a phase II trial testing four neoadjuvant treatments: docetaxel chemotherapy and trastuzumab, docetaxel plus trastuzumab and pertuzumab, trastuzumab and pertuzumab, and docetaxel and pertuzumab. To date the pCR rates in 417 women in the four treatment arms are 29.0%, 45.8%, 16.8%, and 24.0%, respectively. That means triplet therapy worked the best, but the data also showed that “there are HER-2–positive breast cancers that can be eradicated by the HER-2–directed combination of trastuzumab and pertuzumab without need for any chemotherapy,” Gianni said. “This is a unique observation that has major implications for future studies. If we will succeed in detecting robust predictors of such sensitivity, we could move from studies to clinical practice and avoid, in some women, the use of chemotherapy.”

Winer said that the Neosphere study puts pertuzumab “very much on the map in terms of a drug that should be tested in early-stage breast cancer” and raises the question “as to whether, in selected patients, an all-biologic approach may ultimately be sufficient.”

But he and others note that a close reading of the pCR results from several of the studies reflect a complexity that is not yet understood: pCR rates were substantially higher in estrogen receptor–negative patients than in those with estrogen receptor–positive disease.

“That raises concerns about whether pCR will [statistically] correlate with ultimate outcome because we know from other studies that women with estrogen receptor–positive and HER-2–positive breast cancer actually have a better long-term outcome than women with estrogen receptor–negative and HER-2–positive breast cancer,” Winer said.

“It is possible to have a really good outcome in patients who don’t get a complete response and a really bad outcome in those who have had a good response,” said Clifford Hudis, M.D., chief of the breast cancer medicine service at Memorial Sloan–Kettering Cancer Center in New York. “I am all for neoadjuvant testing of drugs because it is a much more efficient drug development model. But we have to understand what we are seeing.”

Total Blockade Could Be Costly
The prospect of paying for HER-2 total blockade—which could ultimately include a combination of trastuzumab, lapatinib, and pertuzumab, as well as chemotherapy and possibly hormonal therapy—is also an issue that researchers are beginning to debate.

Some say the potential benefits outweigh the high costs: “I would suggest that the opportunity to receive treatment and be rendered breast cancer free and not develop metastatic disease and all the costs associated with that—both financial and personal and
psychological—is pretty important,” said Davidson.

But Spector, who described himself as a big fan of HER-2 blockade, said using multiple HER therapies in thousands of patients is “going to bust the economy. I think cost is a real consideration,” he said. “We live in a country where some states have denied health care coverage for life-saving organ transplants. The potential costs would most likely not be practical in the current health care environment.”

Another option that Spector and his Duke colleagues are testing is using HER-2 vaccines that will generate endogenous trastuzumab- and pertuzumab-like antibodies. The preclinical work has been encouraging. “There is a real possibility of achieving total HER-2 blockade that will be more practical and accessible to patients,” Spector said.

Dr. Spector has received honoraria from Genentech, which makes HER-2–targeted therapies. Dr. Baselga has served as an advisor or consultant to Roche, which owns Genentech.