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Dual Anti-HER2 Blockade Called the Future of Breast Cancer Therapy

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EXPERT COMMENTARY

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HER2, a receptor tyrosine kinase oncogene overexpressed in about 20% of breast cancers, can be inhibited clinically through a variety of mechanisms including monoclonal antibodies to the extracellular domain and competitive inhibition of the intracellular ATP binding site. Targeted inhibition has profound clinical implications, including extending life for patients with metastatic HER2+ breast cancer and curing a fraction of patients who have micrometastatic disease in the adjuvant setting. New studies support the concept that combined HER2 blockade, using a combination of inhibitors added to standard chemotherapy, can improve results even further. Most interestingly, biological blockade with combined anti-HER2 monoclonal antibodies can achieve pathologic complete remission when used as neoadjuvant therapy of HER2+ breast cancer, even without chemotherapy, in a fraction of cases. There is still much to learn about the HER2 axis and these studies set the stage for the next plateau of improved outcome in breast cancer.

News Article

SAN ANTONIO (EGMN) - The combination of two anti-HER2 therapies, together with chemotherapy, may be markedly better than one, according to watershed randomized clinical trials presented at the San Antonio Breast Cancer Symposium.

"This is data that is preliminary; it's not to be used today in practice. But this is the way things are going to go," predicted Dr. Jose Baselga, chief of hematology/oncology at Massachusetts General Hospital, Boston, and professor of medicine at Harvard Medical School and the Autonomous University of Barcelona.

He presented the results of the Neo-ALTTO trial, a phase III, open-label, triple-arm study that randomized 455 women with HER2-positive early breast cancer to 18 weeks of neoadjuvant anti-HER2 therapy with trastuzumab (Herceptin), lapatinib (Tykerb), or both. After the first 6 weeks of anti-HER2 therapy, 12 weeks of paclitaxel was added to each study arm prior to surgery.

Pathological complete response (pCR), which was the primary study end point, occurred in 24.7% of patients in the lapatinib/paclitaxel arm, 29.5% in the trastuzumab/paclitaxel arm, and a significantly higher 51.3% in the lapatinib/trastuzumab/paclitaxel arm.

Grade 3 or worse adverse events occurred most frequently in the two lapatinib-containing arms. The most common of these was grade 3 or higher diarrhea, which occurred in 21% of the dual anti-HER2 group, 23% in the lapatinib arm, and just 2% in the trastuzumab arm. Grade 3 or higher hepatotoxicity occurred in 9% on dual anti-HER2 therapy, 13% on lapatinib, and 1% on trastuzumab. Grade 3 or higher neutropenia and skin rash followed the same pattern.

Largely as a result of toxicities, 39% and 34% of patients in the dual anti-HER2 and lapatinib arms, respectively, didn't complete neoadjuvant treatment as planned. This was the case for only 8% in the trastuzumab arm.

Based upon the success of Neo-ALLT, Dr. Baselga and coinvestigators have launched the companion ALTTO trial. Nearly 8,200 of a planned 8,400 patients with HER2-positive breast cancer have been enrolled in the trial, which will feature four adjuvant therapy arms: lapatinib, trastuzumab, both agents, and sequential trastuzumab followed by lapatinib. Study end points will include overall and disease-free survival.

Although the numerically superior pCR rate with trastuzumab/paclitaxel, compared with lapatinib/paclitaxel, didn't achieve statistical significance in Neo-ALTTO, it did in another randomized trial that was presented during the same session. Dr. Michael Untch of the Helios Clinic in Berlin presented the results of the phase II GeparQuinto study led by the German Breast Group, in which 620 patients with HER2-positive primary breast cancer were randomized to neoadjuvant therapy with either trastuzumab or lapatinib, both given in conjunction with neoadjuvant anthracycline/taxane-based chemotherapy.

The pCR rate (defined as no invasive or noninvasive residual disease in the breast or nodes) was 31.3% in the trastuzumab/chemotherapy arm, compared with 21.7% with lapatinib/chemotherapy (P less than .05).

These study results prompted extensive discussion during the conference. Dr. Eric P. Winer served as formal discussant of Neo-ALTTO, GeparQuinto, and a third neoadjuvant trial - NeoSphere - in which docetaxel plus dual anti-HER2 therapy with trastuzumab and the investigational agent pertuzumab produced a significantly higher pCR rate than did docetaxel plus either anti-HER2 biologic agent alone.

Dr. Winer argued that even though Neo-ALTTO is a phase III trial, he doesn't consider pCR rate an appropriate end point for drug approval or change in clinical practice. As a surrogate for the key end points of overall and disease-free survival, pCR simply isn't reliable enough, he said. A classic case in point was the NSABP (National Surgical Adjuvant Breast and Bowel Project) B-27 trial, in which a doubling of the pCR rate didn't lead to improvement in overall or disease-free survival.

"In my view, [the combination of] trastuzumab, lapatinib, and paclitaxel looks like a regimen of great interest. It's not ready for adjuvant therapy. It isn't ready for neoadjuvant therapy outside of a clinical trial. But we all eagerly await the results of ALTTO," said Dr. Winer, director of the breast oncology center at the Dana-Farber Cancer Institute and professor of medicine at Harvard Medical School, both in Boston.

As for trastuzumab vs. lapatinib as single-agent anti-HER2 neoadjuvant therapy in conjunction with neoadjuvant chemotherapy, the evidence from Neo-ALTTO and GeparQuinto makes it "hard to escape the conclusion that [the combination of] lapatinib and chemotherapy is a little less active and a little more toxic than trastuzumab and chemotherapy," the oncologist observed.

Dr. Baselga later commented that clinical practice in the management of HER2-positive breast cancer could change as early as next year, when the results of the ongoing CLEOPATRA trial are due to be reported. That study is comparing first-line therapies for HER-2 positive metastatic breast cancer.

In a plenary lecture, Dr. Neil L. Spector of Duke University, Durham, N.C., said that if two anti-HER2 drugs are better than one, it's entirely possible that complete blockade of HER2 via triple therapy with trastuzumab, pertuzumab, and lapatinib would be the most effective of all, albeit with an astronomical price tag.

"Total blockade may be feasible, but we're going to bust the economy," he argued. "If we're going to develop these things, and only 5 patients out of 100 can afford them, we have to rethink what the hell we're doing."

Dr. Spector said that although 15 years ago he was a major skeptic about tumor vaccines, he has recently changed his mind in response to preclinical and early clinical evidence that vaccines now in development can generate good titers of polyclonal antibodies. "What if we could generate trastuzumab- and pertuzumablike antibodies directly in patients, making total HER2 blockade more affordable?" he said. "I think vaccines have come of age."

An ongoing clinical trial at Duke shows evidence that a polyclonal HER2 vaccine in combination with lapatinib provides an enhanced anti-tumor effect, the oncologist added.

The Neo-ALTTO and GeparQuinto trials were supported by GlaxoSmithKline. Dr. Baselga and Dr. Untch declared that they have no relevant financial relationships to disclose.



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