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Trastuzumab-Based T-DM1 Delays Breast Cancer Progression

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STOCKHOLM – Novel antibody-guided trastuzumab emtansine therapy not only improved progression-free survival by 5 months in women with HER2-positive metastatic breast cancer, but it also had an impressively tame side effect profile, according to Dr. Sara Hurvitz.*

Treatment with trastuzumab emtansine (T-DM1) resulted in a median progression-free survival of 14 months vs. 9 months with trastuzumab (Herceptin) and docetaxel (Taxotere) in a phase II open-label study with 137 women. T-DM1 reduced the relative risk of disease progression by 41% with a hazard ratio of 0.59 (P = .0353), she reported at the European Multidisciplinary Cancer Congress.

"These results validate the hypothesis that the unique properties of T-DM1 may lead to an improved therapeutic index," said Dr. Hurvitz of the Jonsson Comprehensive Cancer Center at the University of California, Los Angeles.

An antibody drug conjugate, T-DM1 retains the targeting properties of monoclonal antibody trastuzumab in HER2-positive breast cancer while transporting a potent cytotoxic agent (DM1) that inhibits tubulin polymerization and microtubule dynamics into cancer cells.

Invited discussant Dr. Martine J. Piccart-Gebhart talked excitedly about the results, but also urged caution.

"You have to remember that this is an open-label study. I am saying that because I believe that T-DM1 is the magic drug for medical oncologists – the drug that we have been waiting for, for so many years. It is a clever drug. It brings the cytotoxic agent inside the cancer cell," said Dr. Piccart-Gebhart of the Jules Bordet Institute at the Université Libre de Bruxelles in Belgium.

However, "in an open-label study, you have to worry a little bit because we want to give this T-DM1 drug to our patients," so it may be tempting to interpret the results too favorably, she told attendees at the joint congress of the European Cancer Organization, the European Society for Medical Oncology, and the European Society for Radiotherapy and Oncology.

The researchers recruited 137 women with HER2-positive, recurrent locally advanced breast cancer or metastatic breast cancer. The patients were randomized to receive either trastuzumab and docetaxel or T-DM1 alone.

Trastuzumab was given as an 8-mg/kg loading dose and then as 6 mg/kg every 3 weeks. Docetaxel was given in a dose of 75 mg/m^2 or 100 mg/m^2 for 3 weeks. T-DM1 was given intravenously at a dose of 3.6 mg/kg every 3 weeks. In all, 70 women received trastuzumab and docetaxel and 67 received T-DM1.

The primary end points were progression-free survival by investigator assessment and safety. Data analyses

were based on clinical data as of Nov. 15, 2010, and prior to any T-DM1 crossover. Overall survival data are expected in 2012. Quality of life data will be presented as a poster at the San Antonio Breast Cancer Symposium this December.

Most of the patients in each group (85%) had centrally confirmed HER2-positive breast cancer. "Relatively few patients had received neoadjuvant or adjuvant trastuzumab. This was likely owing to the international nature of the study and the lack of availability at some centers for trastuzumab in the adjuvant setting," said Dr. Hurvitz.

Dr. Piccart-Gebhart observed that one-third of patients in this study were stage IV at diagnosis and only 20%-25% were exposed to adjuvant trastuzumab. These numbers are likely to change with time, as more patients are exposed to trastuzumab.

At the time of data cutoff, 21% of patients on trastuzumab and docetaxel were still on the treatment, compared with 43% of those in the T-DM1 arm. "The majority of patients came off of treatment for disease progression," she said.

The objective response rate was similar – 58% for the T-DM1 arm vs. 64% for the control arm. Patients in the trastuzumab/docetaxel arm had a median duration of response of 9.5 months. The duration of response in the T-DM1 arm has not yet been reached.

"In terms of safety and tolerability, it is very clear that the safety profile of T-DM1 is far better than the one for docetaxel and trastuzumab," said Dr. Piccart-Gebhart. Patients who received T-DM1 had many fewer adverse events of grade 3 or greater – 32 vs. 59.

Among hematologic adverse events, neutropenia of any grade was more common in the control arm – 63.6% compared with 17.4% – but any grade thrombocytopenia was more common in the T-DM1 arm (30% vs. 6%).

Among nonhematologic events, any grade alopecia was less than 4% for the T-DM1 arm compared with 67% for the control arm. Likewise, the incidence of any grade diarrhea was much lower in the T-DM1 arm – 16% for those on T-DM1 compared with 46% for those on the trastuzumab/docetaxel. Peripheral edema of any grade was also much lower in the T-DM1 arm (10% vs. 44%).

"Cardiac safety is important to look at whenever you're talking about HER-2 targeting agent," said Dr. Hurvitz.

Adjuvant anthracyclines were given to 45% and 49% of patients in the T-DM1 arm and control arm. On local assessment two patients in the control arm, compared with none in the T-DM1 arm, had a postbaseline left ventricular ejection fraction of 40% or less.

"There were no clinically significant cardiac events reported," she noted.

Dr. Hurvitz and Dr. Piccart-Gebhart agreed that large phase III trials are needed to confirm these findings. The drug is being evaluated in three large phase III clinical trials for HER2-postive metastatic breast cancer.

The study was funded by F. Hoffmann-La Roche. Dr. Hurvitz reported that she has no relevant financial disclosures. Dr. Piccart-Gebhart has previously reported that she is a consultant for and has received research support from several pharmaceutical companies, including Roche.

** Clarification, 9/29/2011:* The original version of this article stated that trastuzumab emtansine improved disease-free progression. However, it is more accurate to say that it improved progression-free survival. This version has been updated.

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