ASCO: Unique Combination of Targeted Antibody Linked to Chemotherapy Shows Positive Results in HER2-Positive Breast Cancer Patients

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Results of a large phase III trial shows that a new oncology therapy, trastuzumab emtansine (T-DM1), significantly delays progression of disease in women with HER2-positive advanced breast cancer previously treated with a taxane chemotherapy and trastuzumab (Herceptin).
Source:

Results of a large, nearly 1,000-patient trial shows that a new oncology therapy, trastuzumab emtansine (T-DM1), significantly delays progression of disease in women with HER2-positive advanced breast cancer previously treated with a taxane chemotherapy and trastuzumab (Herceptin). The phase III trial compared the investigational T-DM1 against standard therapy of capecitabine (Xeloda) in combination with lapatinib (Tykerb). Approximately 30% of all breast cancers are HER2-positive.

“T-DM1 will become standard therapy for all patients, after first-line trastuzumab–Taxotere–pertuzumab, given the very strong overall survival signal and excellent safety,” said Joyce O’Shaughnessy, co-director of Breast Cancer Research at the Baylor Charles A. Sammons Cancer Center Texas Oncology and US Oncology in Dallas, Texas. Dr. O'Shaughnessy was not involved with the trial. “All late-line patients will receive T-DM1 once it is available.”
O’Shaughnessy added that she hopes there will be an expanded access program for the drug.
Besides providing a potential new option for women with advanced-stage cancer who have few treatment options, the study also validates a novel approach—delivering chemotherapy directly to the tumor cells and thus avoiding off-target chemotherapy effects that cause many of the toxicities that plague patients.
T-DM1 is an antibody-drug conjugate delivering a one-two punch—trastuzumab, an antibody against HER2 is attached to a chemotherapy agent, DM1, through a linker, delivering the cell-killing agent specifically to HER2-positive cancer cells. Trastuzumab binds to the cancer cells that express the HER2 receptor on their surface. The antibody, attached to the chemotherapy agent is internalized by the cell, allowing the cytotoxic agent to kill the cancer cell.
The drug was developed by Genentech, a member of the Roche Group. The chemotherapy DM1 and the method of attaching the cytotoxic agent to the antibody via a linker were developed by Massachusetts-based ImmunoGen, Inc.
Roche plans to file T-DM1 with both the Food and Drug Administration (FDA) and the European Medicines Agency by the end of 2012. The submission will also include data on companion diagnostics—The HercepTest and HER2 FISH pharmDx test, both from Dako, a Denmark-based diagnostics company. Roche and Dako have partnered to file an FDA submission for both tests that will identify patients who are HER2-positive and eligible for T-DM1 treatment. Earlier this year Roche announced that T-DM1 can control metastatic breast cancer better compared to the standard treatment arm.
“[T-DM1] was significantly better than a very effective approved therapy for HER2 overexpressing metastatic breast cancer,” said Kimberly L. Blackwell, MD, professor of medicine and assistant professor of radiation oncology at Duke Cancer Institute at Duke University and lead author of the trial, in a press release. Blackwell also highlighted that T-DM1 has few dose-limiting toxicities. “Patients don’t lose their hair from this drug. For patients facing metastatic breast cancer, this is a breakthrough.”
The phase III EMILIA trial was a 991 patient randomized, open-label trial. One half of the women received T-DM1 at a dose of 3.6 mg/kg every 3 weeks, the other half received the standard treatment. Both progression-free survival (PFS) and overall survival were primary endpoints.
The phase II data, announced at the 32nd Annual San Antonio Breast Cancer Symposium in 2009 showed that 33% of patients on T-DM1 had an objective response. These patients had previously

received a staggering average of seven therapies, including chemotherapy, trastuzumab, and lapatinib. Roche had submitted an accelerated approval Biologics License Application based on these phase II data but the FDA rejected the application back in 2010, requesting data from the large-scale phase III EMILIA trial.

The Trial Results

Patients who received T-DM1 had a median 9.6 months before their disease progressed compared to 6.4 months for those in the standard therapy arm—a difference of 3.2 months that was statistically significant ($P < .0001$).

After 2 years, 65.4% of patients treated with T-DM1 were still alive compared to 47.5% on the capecitabine-plus-lapatinib treatment. This difference has not met the EMILIA trial's predetermined survival threshold. A second analysis is planned for later this year. Patients who had a response were on therapy for a median of 12.6 months for T-DM1 and 6.5 months for the capecitabine-plus-lapatinib combination.

T-DM1 was well tolerated and no unexpected toxicities were reported. Common high-grade toxicities for patients taking T-DM1 included thrombocytopenia (12.9% of T-DM1 patients compared to 0.2% of the standard therapy arm patients) and elevation in liver function test. Both toxicities were resolved when patients temporarily stopped taking the medication. Overall, dose reductions where higher for patients taking capecitabine and lapatinib compared to those taking T-DMI1 (53.4%, 27.3%, and 16.3%, respectively).

T-DM1 is also being studied in a treatment-nave HER2-positive breast cancer patient population. The three-arm trial is comparing T-DM1 in combination with pertuzumab, another HER-targeted antibody, T-DM1 alone, or trastuzumab with a taxane-based chemotherapy. The 1,000-patient trial is scheduled to read out in a few years. Pertuzumab is seen as a complimentary therapy to trastuzumab, which blocks the function of HER2. Pertuzumab is a HER2 dimerisation inhibitor that prevents intracellular HER2 signaling.

"It will be of interest to combine T-DM1 with lapatinib or pertuzumab [in the neoadjuvant setting]," commented C. Kent Osborne, director of the breast center at the Baylor College of Medicine in Houston, Texas. "I favor lapatinib plus T-DM1 because [laboratory data] and early studies in the clinic suggest that [this combination] is better. Some patients, if they can be identified, may not need chemotherapy," Osborne added. "However, this requires further study."

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