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Biomarker analysis identified women most likely to benefit from T-DM1

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For women with metastatic, HER2-positive breast cancer, the amount of HER2 on their tumor might determine how much they benefit from a drug called trastuzumab emtansine (T-DM1), according to data from a subanalysis of the phase III clinical trial that led the U.S. Food and Drug Administration to approve the drug on Feb. 22, 2013. These findings were presented by José Baselga, M.D., Ph.D., physician-in-chief at Memorial Sloan-Kettering Cancer Center in New York, N.Y., at the AACR Annual Meeting 2013, held in Washington, D.C., April 6-10.

"EMILIA was a landmark phase III clinical trial," said Baselga. "It showed that T-DM1 prolonged progression-free and overall survival for patients with HER2-positive metastatic breast cancer that had been previously treated with trastuzumab and a taxane chemotherapy compared with lapatinib plus capecitabine. Also, it provided proof-of-concept that a new class of drugs called antibody-drug conjugates can benefit patients."

Antibody-drug conjugates consist of an antibody attached to a toxic chemotherapy, according to Baselga. In the case of T-DM1, the antibody is trastuzumab and the toxic chemotherapy is emtansine. Trastuzumab recognizes the protein HER2, which is found at high levels in HER2-positive breast cancers, and targets the emtansine to the HER2-positive cancer cells, which are killed by the toxic chemotherapy.

In this subanalysis, Baselga and colleagues analyzed tissue samples from patients enrolled in EMILIA to examine whether tumor levels of HER2,

as assessed by the amount of HER2 messenger ribonucleic acid (mRNA), affected treatment response. Patients with tumor samples expressing greater than the median amount of tumor HER2 mRNA were considered to have high levels of HER2. Those with tumor samples expressing the median amount of tumor HER2 mRNA or less were considered to have low levels of HER2.

"Even though everyone enrolled in the clinical trial had breast cancer expressing elevated levels of HER2, we know that each person's tumor has different molecular features," said Baselga. "Even the degree to which HER2 expression is elevated differs from patient to patient."

Consistent with the prior analysis, he and his colleagues found that all patients treated with T-DM1 had significantly longer progression-free and overall survival compared with those treated with lapatinib and capecitabine (9.6 months progression-free survival versus 6.4 months; and 30.9 months for overall survival versus 25.1 months).

Patients with tumors expressing higher levels of HER2 derived greater benefit from treatment with T-DM1 compared with patients with tumors expressing lower levels of HER2: Overall survival was 34.1 months for those with high levels of HER2 versus 26.5 months. For patients with tumors expressing higher levels of HER2, those receiving T-DM1 had a 47 percent decreased risk for death compared with those receiving lapatinib and capecitabine.

The researchers also investigated whether tumor mutations in the PIK3CA gene affected treatment response. According to Baselga, patients with PIK3CA-mutated, HER2-positive breast cancer normally do not respond as well to treatment with conventional HER2-targeted therapies such as trastuzumab compared with patients without PIK3CA mutations in their tumors.

However, for patients treated with T-DM1, PIK3CA mutation status did not significantly decrease progression-free survival.

"Our findings are an important step toward identifying the best therapy for individual patients with HER2-positive breast cancer," said Baselga. "HER2-positive breast cancer is not a uniform disease; each patient is different. These data help us as we look to identify a panel of molecular features that we can use to make informed treatment decisions."

Kadcyla (ado-trastuzumab emtansine or T-DM1) is a trademark of Genentech, a member of the Roche Group.

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