PIK3CA gene mutations make HER2- and hormone receptor-positive breast cancers treatment-resistant

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Women with breast cancer characterized by high levels of the protein HER2 and hormone receptors gained much less benefit from presurgery treatment with chemotherapy and HER2-targeted therapies if their cancer had one or more mutations in the PIK3CA gene, according to results presented here at the 2013 San Antonio Breast Cancer Symposium, held Dec. 10-14.

Treatment given to shrink or eliminate a tumor before surgery is called neoadjuvant therapy. In some women with breast cancer treated with neoadjuvant therapy, no residual invasive cancer can be detected in breast tissue samples and lymph nodes removed during surgery. Emerging data suggest that these women, who are said to have had a pathologic complete response, have a greater chance of long-term survival compared with women who do not have a pathologic complete response.

"Mutations in the PIK3CA gene are among the most common genetic aberrations in breast cancer," said Sibylle Loibl, M.D., professor at the German Breast Group in Neu-Isenburg, Germany. "We found that very few women with HER2- and hormone receptor-positive breast cancer with a PIK3CA mutation experienced a pathologic complete response after receiving neoadjuvant therapy.

"We need to identify new treatment options for this group of patients

and evaluate them in clinical trials," continued Loibl. "We also need to integrate PIK3CA mutation analysis of breast tumors into routine practice so that we can ensure women receive the most appropriate neoadjuvant therapy for their tumor type."

Loibl and colleagues investigated whether the presence of a PIK3CA mutation affected patients enrolled in the GeparSixto (G6) clinical trial in experiencing a pathologic complete response after neoadjuvant therapy. There were 595 participants in the G6 clinical trial, and information on the presence or absence of PIK3CA gene mutations was available for 512,240 with HER2-postive breast cancer and 272 with triple-negative breast cancer.

Participants in the G6 clinical trial received neoadjuvant chemotherapy (paclitaxel and nonpegylated-liposomal doxorubicin) and were randomly assigned the chemotherapy carboplatin or no additional chemotherapy. Patients with HER2-positive disease also received neoadjuvant trastuzumab and lapatinib, two HER2-targeted therapies, while patients with triple-negative disease also received neoadjuvant bevacizumab.

Loibl and colleagues found that patients with HER2-postive breast cancer were more likely to have at least one PIK3CA mutation in their tumor compared with women with triple-negative breast cancer. Overall, the pathologic complete response rate was lower among women with at least one PIK3CA mutation in their tumor compared with women without a PIK3CA mutation, but the effect was only significant among the group of women with HER2- and hormone receptor-positive breast cancer. Among these women, patients with a PIK3CA mutation had a pathologic complete response rate of only 6.5 percent compared with 30.8 percent for those without a PIK3CA mutation.

"To evaluate these findings in a group with only one HER2 treatment, we are currently analyzing data from another clinical trial, the

GeparQuinto clinical trial, which is a randomized, phase III clinical trial evaluating two different neoadjuvant therapy regimens with a single anti-HER2 treatment [trastuzumab or lapatinib] for women with HER2-positive breast cancer," said Loibl. "We hope to present these results together with those from the G6 clinical trial in San Antonio."

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