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Acquired HER2 mutations confer resistance to hormone therapy in ER-positive metastatic breast cancer

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Mutations in human epidermal growth factor receptor 2 (HER2) were found to confer resistance to hormone therapy in some estrogen receptor (ER)-positive metastatic breast cancer cases, and resistance could be reversed by dual treatment with the hormone therapy fulvestrant and the HER2 kinase inhibitor neratinib, according to data presented during a media preview for the AACR Annual Meeting 2018, April 14-18, in Chicago, Illinois.

"Despite the reduction in breast cancer recurrence and mortality provided by ER-targeted therapies, resistant ER-positive metastatic breast cancer remains the most common cause of breast cancer death because patients invariably develop resistance and stop responding to these drugs," said Utthara Nayar, Ph.D., co-lead author and a research fellow in medicine at Dana-Farber Cancer Institute, Harvard Medical School, Boston.

Prior research has identified activating mutations in the ER in approximately 25-30 percent of patients with ER-positive metastatic breast cancer, Nayar explained. "The goal of our study was to identify additional mechanisms of resistance to help us understand how ER-positive breast cancer develops resistance to commonly used therapeutics, thereby aiding the development of new biomarkers for response as well as novel therapeutic strategies for metastatic breast cancer patients."

As part of an ongoing project at Dana-Farber, Nayar and Ofir Cohen, Ph.D., co-lead author, postdoctoral researcher and computational biologist at the Broad Institute and Dana-Farber, and colleagues used whole-exome sequencing to study metastatic tumor biopsies from patients with ER-positive metastatic breast cancer with resistance to hormone therapies. Out of the 168 patients examined, the researchers found HER2 mutations in 12 patients. Of these, eight patients had mutations previously identified to be activating. Nayar and colleagues then examined the available pre-treatment primary biopsies and found that four out of five patients with activating mutations had no evidence of pre-existing HER2 mutations, suggesting the acquisition of these HER2 mutations was a result of hormone therapy.

"It was surprising to discover that HER2 mutations can be acquired in the metastatic setting, suggesting that these tumors evolve," said Nikhil Wagle, MD, senior author, deputy director of the Center for Cancer Precision Medicine at Dana-Farber and assistant professor of medicine at Harvard Medical School, Boston. "These HER2 mutations seem to be a mechanism of resistance to therapies that target the estrogen receptor, which explains the context in which they are acquired."

With further analysis, the researchers found that resistance to hormone therapy mediated by HER2 mutations could be overcome with the combination of neratinib and the selective ER degrader fulvestrant in vitro. This dual treatment may be an effective therapeutic strategy for breast cancer patients who are resistant to ER-directed therapies with acquired HER2 mutations, noted Nayar.

"The discovery of the acquired HER2 mutation in one patient's metastatic biopsy prompted enrollment into a phase II trial of fulvestrant plus neratinib, resulting in a partial response lasting six months, consistent with our in vitro findings showing neratinib-induced resensitization to ER-directed therapy," said Nayar.

"Our study highlights how important it is to profile resistant metastatic tumors, since these tumors may harbor targetable mechanisms of resistance that were not present in the original tumor biopsy," said Wagle. "Repeated sequencing of tumors can pinpoint new genetic changes that cause resistance to therapies. This in turn can enable physicians to personalize therapy depending on the specific genetic changes in a patient's tumor over time."

Limitations of the study include the small number of patients identified with HER2 mutations and the heterogeneity of the tumor biopsies. "These are real-world samples, so the patients had different stages of cancer initially, received different treatments, and had different tumor features," noted Wagle. Additionally, because treatment-naïve biopsies for all patients were not available, the researchers need to study additional patients to more accurately determine the percentage of patients with HER2 mutations who have acquired or pre-existing mutations.

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