

Treatment targeting PI3K may delay resistance to anti-HER2 therapy in breast cancer patients

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Patients with HER2-positive breast cancer being treated with anti-HER2 therapy may be able to prevent or delay resistance to the therapy with the addition of a phosphatidylinositol-3 kinase inhibitor to their treatment regimens.

The data, published in *Cancer Research*, a journal of the American Association for [Cancer Research](#), indicated that failure of the anti-HER2 antibody trastuzumab to block HER2 from activating the phosphatidylinositol-3 kinase (PI3K) signaling pathway can lead to resistance to treatment. Therefore, dual simultaneous inhibition of both HER2 and PI3K may prolong the use of anti-HER2 therapies in women with [breast cancer](#).

"HER2 breast cancer is a subtype of breast cancer for which we have an increasing number of effective treatments, including trastuzumab, an antibody that targets HER2," said Carlos L. Arteaga, M.D., director of the Breast Cancer Program at Vanderbilt-Ingram [Cancer Center](#) in Nashville, Tenn. "Unfortunately, many breast cancer tumors learn how to resist this therapy."

Arteaga and colleagues explored the possibility that aberrant signaling through the PI3K pathway was a mechanism of resistance to trastuzumab. They used breast cancer models of trastuzumab resistance with different modes of aberrant PI3K pathway activation, and treated

the cells with a PI3K inhibitor with or without trastuzumab.

Inhibiting PI3K reduced [cancer cells](#)' ability to proliferate and induced the death of trastuzumab-resistant cells. In addition, combining PI3K inhibitors with trastuzumab resulted in superior anti-tumor effects against trastuzumab-resistant, HER2-positive cells in xenografts compared with the PI3K inhibitor alone.

The investigators also conducted analyses to determine how the [drug combination](#) decreased resistance to trastuzumab.

"We found that the trastuzumab-[resistant cells](#) in which the PI3K pathway was activated had high levels of an anti-death protein called survivin," Arteaga said. "This implied that if we could get levels of survivin to decrease, these cells would become sensitive to treatment."

They also measured pretreatment levels of survivin in HER2-positive breast cancer tumors and found that higher pretreatment levels of the protein correlated with a poor response to therapy.

"This suggests that we could measure levels of survivin in tumors, and if they are high or do not decrease with treatment, we could predict that the tumor is resistant to anti-HER2 therapy and try to find alternative treatments," Arteaga said.

Arteaga and colleagues plan to continue testing PI3K inhibitors, which are already in early clinical development, in combination with other HER2 drugs in breast cancer. They also plan to measure survivin levels in HER2-overexpressing breast cancer tumors to determine if levels can predict tumors that will benefit from combination treatment.

Provided by American Association for Cancer Research

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