Hit multiple targets for maximum benefit in HER2-positive breast cancer, studies suggest

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Combining targeted therapies might be required for maximum anti-tumor activity when treating HER2-positive breast cancers, according to two new studies by Vanderbilt-Ingram Cancer Center (VICC) investigators.

The findings, reported in two papers in the Proceedings of the National Academy of Sciences (*PNAS*), suggest that upregulation of the HER3 receptor limits the effectiveness of two classes of targeted therapies (HER2- and PI3 kinase-targeted therapies). Therefore targeting HER3 together with these agents should improve their clinical utility.

Around 25 percent of breast cancers have increased expression of the HER2 receptor, which is associated with more aggressive tumors and a poorer prognosis. HER2-targeted therapies like trastuzumab (Herceptin) and lapatinib (Tykerb) are effective in many women with HER2-positive breast tumors.

"But even in patients who respond to HER2-targeted therapies, the clinical response tends to be short-lived and tumors become resistant," said Carlos Arteaga, M.D., professor of Medicine and Cancer Biology, and director of the VICC Breast Cancer Research Program.

HER2 is a member of the EGF receptor family involved in signaling pathways that promote cell growth. HER2 must interact and form complexes with other members of the EGF receptor family, and its main partner in activating pathways that promote tumor growth is HER3. This complex of HER2/HER3 is a potent activator of the PI3K/Akt pathway, the key survival pathway in HER2-positive cancers.

"Based on this evidence, we hypothesized that, for these therapies to have maximum effect, HER3 and its output to the PI3K/Akt pathway must be completely shut down," Arteaga said.

A postdoctoral fellow in Arteaga's laboratory, Joan Garrett, Ph.D., led experiments to examine the effect of the HER2 tyrosine kinase inhibitor, lapatinib, on HER3 expression and activity.

She found that inhibiting HER2 with lapatinib led to an increase in HER3 expression and activation in both HER2-positive human breast tumors and cell lines. Inhibiting HER3 in HER2-positive breast cancers growing in mice made tumor cells markedly more sensitive to lapatinib. Additionally, blocking both HER2 and HER3 was more effective at inhibiting the activity of PI3K/Akt pathway than either inhibitor alone.

Those results, published March 7 in *PNAS*, show that upregulation of HER3 limits the effectiveness of HER2-targeted therapies and that a combination of drugs that target both HER2 and HER3 should be considered for optimal clinical benefit.

Since PI3K/Akt is the key pro-survival signaling pathway downstream of HER2, the investigators also examined the utility of inhibitors of PI3K in HER2-positive breast cancer cells.

Those experiments, led by postdoctoral fellow Anindita Chakrabarty, Ph.D., and published Feb. 28 also in *PNAS*, showed a similar upregulation of HER3 in response to treatment with a PI3K inhibitor currently in clinical development. In turn, this compensatory upregulation of HER3 partially reactivated the PI3K/Akt pathway and limited the action of the PI3K inhibitor.

"This shows that therapeutic use of PI3K inhibitors would be limited if used as single agents in HER2-positive cancers. These results have

implications for other cancers treated with this class of drugs," Arteaga said. However, he notes PI3K inhibitors might have clinical merit when used in combination with HER2-HER3 antagonists.

Since both HER3 inhibitors and PI3K inhibitors are now in clinical development, "these studies provide a scientific rationale for how a combination of the new drugs with HER2-targeted therapies might be used to provide better results for many patients with breast cancer," Arteaga said.

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