Targeted agent addition to herceptin has positive effect on metastatic HER-2 breast cancer

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Adding Afinitor to Herceptin, the main treatment for HER2-positive metastatic breast cancer, helps some women with disease that has been resistant to previous Herceptin-based therapies, according to a study led by researchers at The University of Texas MD Anderson Cancer Center and published in the *Journal of Clinical Oncology*.

The Phase I/II study demonstrated that a combination of the targeted therapies, which play different roles in cancer, offers a personalized therapy approach that can help some patients with advanced disease. Thirty-four percent of the women in the study benefited from the regimen.

About one in four breast cancer tumors is HER2-positive, which means it makes too much of the protein HER2, a human epidermal growth factor. This type of breast cancer often is more aggressive and difficult to treat.

"Herceptin (trastuzumab) works well for many patients, but about 30 percent of those with advanced disease do not respond to the drug, even combined with chemotherapy," said PK Morrow, M.D., assistant professor in the Department of Breast Medical Oncology and lead co-author of the study. "Even if metastatic HER2-positive breast cancer initially responds to Herceptin, the disease usually eventually progresses on standard Herceptin-based therapy."

Resistance to Herceptin has been linked to activation of the PI3K/mTOR cancer pathway. PTEN, a protein that acts as a tumor suppressor, can counteract P13K. However in the absence of PTEN, the mTOR cancer pathway may be activated. Afinitor (everolimus) overcomes resistance by inhibiting the mTOR pathway.

Bench-to-Bedside Research

"Combining these two agents offers patients with metastatic HER2-positive breast cancer a chemotherapy-free option," Morrow said. "Despite the fact that most of these women had received multiple chemotherapy regimens, this regimen offered additional clinical benefit and less toxicity for many of patients."

Built on preclinical studies at MD Anderson that showed mTOR inhibition makes mice with HER2-positive and PTEN-deficient breast tumors more sensitive to Herceptin, the study was part of MD Anderson's and Dana- Farber Cancer Institute's breast cancer SPORE (Specialized Program of Research Excellence) grant from the National Cancer Institute.

"This study is important to breast cancer treatment, and it represents a crucial step toward personalized cancer therapy by increasing our understanding of cancer pathways," said Francisco J. Esteva, M.D., Ph.D., professor in MD Anderson's Department of Breast Medical Oncology and corresponding author. "It's the culmination of more than five years, starting with basic research and animal studies, and an excellent example of bench-to-bedside research."

Approach Shows Promise

Presented in part at the 2010 annual meeting of the American Society of

Clinical Oncology, the study stemmed from two concurrent trials at MD Anderson and Dana-Farber. Forty-seven women with HER2-positive metastatic breast cancer that had progressed on Herceptin-based therapy were given Herceptin every three weeks and Afinitor daily. Almost half the women had previously received two or more chemotherapy regimens.

The combination therapy resulted in partial responses in 15 percent of patients and persistent stable disease in 19 percent of patients, resulting in a clinical benefit rate of 34 percent. Median progression-free survival was four months. Treatment was well tolerated, and side effects, which included fatigue, infection and mouth sores, were manageable.

Patients with PTEN loss had lower rates of overall survival, but progression-free survival was not affected, suggesting that PTEN loss enables activation of pathways that promote cancer growth. However, PIK3 mutations did not significantly affect progression-free survival or overall survival. The finding that progression-free survival was not significantly affected by PTEN loss or PIK3 mutation suggests that the addition of Afinitor may slow tumor progression through inhibition of mTOR.

Provided by University of Texas M. D. Anderson Cancer Center