Study confirms everolimus can overcome trastuzumab resistance in HER-2 positive early breast cancer

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A study that aimed to understand how the cancer drug everolimus helps overcome the resistance breast cancers can develop to trastuzumab has left researchers contemplating a puzzle.

The study showed a statistically non-significant benefit in clinical response rates for some patients with early breast cancer when everolimus was added to treatment with trastuzumab. Yet the results suggest this benefit is achieved independently of the molecular pathways researchers expected would be involved.

Prof Mario Campone, Principal Investigator at Institut Cancerologie de l'Ouest in Nantes, France, presented the findings at the 5th IMPAKT Breast Cancer Conference in Brussels, Belgium. The IMPAKT meeting presents cutting edge, 'translational' breast cancer research that is beginning to have an impact for patients.

"As more targeted cancer drugs are developed, the challenge is to identify which patients will benefit from individual agents," Prof Campone said. "One of the objectives of this study was to determine molecular biomarkers that predict whether a patient's cancer is sensitive to the combination of everolimus and trastuzumab compared to trastuzumab alone."

Trastuzumab is a monoclonal antibody targeted against the HER2

tyrosine kinase receptor. Many patients who initially respond to trastuzumab develop resistance.

In preclinical studies, everolimus, an oral inhibitor of an important molecule called mammalian target of rapamycin (mTOR), has demonstrated an ability to reverse trastuzumab resistance. However, the mechanisms of action involved in the reversion of trastuzumab resistance are not completely understood.

"Resistance to trastuzumab may result from several molecular alterations occurring at different levels of the downstream effectors in the PI3K/AKT pathway, all of them resulting in maintenance of signal transduction," Prof Campone explains. "Therefore, using everolimus to inhibit mTOR, a major downstream effector of this pathway, can restore sensitivity to trastuzumab. In a pre-clinical model, everolimus also reverses trastuzumab resistance caused by upregulation of IGF-1R expression, an alternative signaling pathway, allowing IGF-1 to drive cell growth and proliferation."

At the IMPAKT meeting, Prof Campone's group report the first results of a clinical study and analysis of seven biomarkers in patients with early HER2-overexpressing cancers who were receiving treatment with trastuzumab alone, or everolimus plus trastuzumab.

Among the 80 patients (40 per arm), the clinical response rate was 35% in the trastuzumab arm and 45% in the patients who received both drugs. On the other hand, the pathological response rate was 43.5% among patients in the monotherapy arm, and 47.5% in the combination arm of the study.

"The conclusion of this paper in clinical practice is that the addition of everolimus to trastuzumab seems to improve the clinical response rate but not the pathologic response," Prof Campone said.

The researchers also studied a group of seven molecular markers to explore whether they could be used to predict which patients would respond to the combination of everolimus and trastuzumab. The biomarkers were p4EBP1, pS6, eIF4E, Ki67, pAKT, LKB1, and caspase 3, all of which are involved in pathways that lead to the activation of mTOR.

"None of these biomarkers was able to predict which patients would see the benefit of the two drugs," Prof Campone said. "It appears the combination of everolimus and trastuzumab is effective independently of the activation of the PI3K/AKT/mTOR pathway and without any anti-proliferative and pro-apoptotic effect."

The study provides important confirmation of the benefit of adding everolimus in this clinical setting, comments Prof Christoph Zielinski, Chairman of the Department of Medicine I at Medical University Vienna, Austria.

"This is a rather small trial with a limited number of patients, although it quite unequivocally shows that the addition of everolimus to trastuzumab leads to an increase in clinical responses in Her-2/neu overexpressing breast cancer, as compared to trastuzumab alone," he said.

"Thus, it not only adds to clinical possibilities which can be offered to patients, but also further explains the modalities of molecularly directed therapeutic manipulation in breast cancer," said Prof Zielinski. However, the limited pathologic response constitutes a clear drawback from clinical observations.

"Nevertheless this study contributes to our assumptions on the application of molecularly targeted therapies in breast cancer in particular and in malignancies in general. It also helps to move to an era where the targeting of multiple molecular structures (like here with

trastuzumab and everolimus) leads to ameliorated results by 'hitting' multiple growth-regulating mechanisms, but also avoiding treatment resistance which continues to be a major challenge in cancer treatment."

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