Investigational ER degrader safe, with early signs of antitumor activity against advanced ER-positive breast cancer

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The new investigational estrogen receptor (ER) degrader GDC-0810 was safe and tolerable in postmenopausal women with advanced ER-positive breast cancer, and a subset of the women, all of whom were previously treated with standard endocrine therapy, gained clinical benefit from the drug, according to data from a first-in-human phase I/IIa clinical trial presented here at the AACR Annual Meeting 2015, April 18-22.

"Most breast cancers diagnosed in the United States are ER-positive, and their growth is fueled by the hormone estrogen," said Maura N. Dickler, MD, associate member of the Breast Medicine Service at Memorial Sloan Kettering Cancer Center and Weill Medical College of Cornell University in New York. "Resistance to currently available therapies targeting estrogen and the estrogen receptor causes morbidity and mortality for women with metastatic ER-positive breast cancer and new therapies that have activity against tumors resistant to currently available treatments are urgently needed.

"The phase I dose-escalation portion of the study enrolled heavily pretreated patients, and the observed antitumor activity is promising for GDC-0810, which is demonstrating clinical benefit in these patients who have developed resistance to other endocrine therapies for ER-positive breast cancer patients," continued Dickler. "The phase IIa dose-expansion portion of the study is ongoing. It is evaluating GDC-0810 efficacy in more defined patient subpopulations and will provide more

information about how effective this estrogen receptor degrader is."

Dickler explained that GDC-0810 is a selective ER degrader and that it works in a number of ways to prevent estrogen fueling tumor growth. She said that it not only targets the ER, like the antiestrogen tamoxifen, but also causes ER degradation.

The researchers enrolled 41 postmenopausal women with advanced or metastatic ER-positive breast cancer in the phase I dose-escalation portion of the clinical trial. Patients were assigned GDC-0810 either once or twice daily, with or without food. The most commonly observed side effects were diarrhea, nausea, fatigue, vomiting, flatulence, decreased appetite, and anemia. Based on tolerability, the researchers established that the recommended phase II dose was 600 milligrams of GDC-0810 once a day with food.

Using a technique called fluoroestradiol positron emission tomography, GDC-0810 was shown to occupy the ER at all doses of the antiestrogen tested in the clinical trial. Using this approach, it was found that GDC-0810 could occupy the ER in patients with ESR1 mutations. Dickler explained that this is important because ESR1 mutations can cause resistance to standard endocrine therapies like tamoxifen.

According to Dickler, the most recent data show that of the 37 patients who have been followed for 24 or more weeks, 14 achieved stable disease for six or more months. She went on to say that the team is very interested in analyzing whether GDC-0810 can benefit patients with ESR1 gene mutations in their tumors and that they are encouraged by the observation that one patient with such a mutation had shrinkage of liver metastases.

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