Elacestrant may improve outcomes for patients whose metastatic breast cancers progressed on prior endocrine therapy

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The investigational oral selective estrogen receptor degrader (SERD) elacestrant significantly decreased the risk of death or disease

progression and increased progression-free survival compared with standard-of-care endocrine therapy for postmenopausal patients with estrogen receptor (ER)-positive/HER2-negative metastatic breast cancers that progressed on prior endocrine and targeted therapies, according to results from the phase III EMERALD trial, which were presented at the San Antonio Breast Cancer Symposium, held December 7-10, 2021.

Patients with metastatic ER-positive breast cancer are typically treated with endocrine therapy, such as aromatase inhibitors or fulvestrant (Faslodex); however, resistance to these treatments commonly develops, in some cases due to mutation of the ESR1 gene. Fulvestrant, which is delivered through intramuscular injections, is currently the only SERD approved for patients with breast cancer.

"There is an urgent unmet need for alternative SERDs that are effective against ER-positive metastatic breast cancer, including those with ESR1 mutations," said Aditya Bardia, MD, MPH, director of the breast cancer research program at Mass General Cancer Center, and associate professor at Harvard Medical School.

Elacestrant is an investigational SERD that, unlike fulvestrant, is administered orally. Bardia explained that elacestrant has greater absorption, improved pharmokinetics, and enhanced inhibition of ER compared with fulvestrant. In addition, elacestrant has demonstrated greater antitumor activity in mouse xenograft models of ER-positive breast cancer. A phase I clinical trial found that elacestrant treatment had an acceptable safety profile and led to responses in heavily pretreated postmenopausal patients with ER-positive/HER2-negative metastatic breast cancer.

To understand how elacestrant compares to the current standard –of care, Bardia and colleagues initiated the phase III EMERALD trial,

making elacestrant the first oral SERD to be studied in a randomized phase III clinical trial.

The trial enrolled 477 postmenopausal patients with ER-positive/HER2-negative metastatic breast cancer who had received one or two prior lines of endocrine therapy without chemotherapy in the metastatic setting, and who had progressed on prior treatment with a CDK4/6 inhibitor. Patients were randomly assigned to receive either elacestrant or standard of care (investigator's choice of fulvestrant or an aromatase inhibitor). Among the enrolled patients, 228 had tumors with mutated ESR1 (115 in elacestrant arm and 113 in standard-of-care arm).

Bardia and colleagues found that patients in the elacestrant arm had a 30 percent lower risk of death or disease progression compared with those in the standard-of-care arm. Among patients whose tumors had ESR1 mutations, those in the elacestrant arm had a 45 percent reduced risk of death or disease progression. Subgroup analyses showed that elacestrant improved outcomes regardless of the presence of visceral metastases, the number of prior lines of therapy, pretreatment with fulvestrant, or geographic region.

At 12 months, patients in the elacestrant arm had a significantly higher rate of progression-free survival than those who received the standard of care (22.32 percent vs. 9.42). Among patients with ESR1-mutated tumors, 26.76 percent of those treated with elacestrant had progression-free survival at 12 months compared with 8.19 percent of patients treated with standard of care. An interim analysis of overall survival showed a trend in favor of elacestrant, including in patients with ESR1-mutated tumors, according to Bardia.

Certain grade 1 or 2 treatment-related adverse events were more common among patients treated with elacestrant compared with standard of care, including nausea (25.3 percent vs. 8.7 percent), vomiting (11

percent vs. 2.6 percent), and fatigue (11 percent vs 7.9 percent). Grade 3 or higher treatment-related adverse events were observed among 7.2 percent of patients in the elacestrant arm and 3.1 percent of those in the standard-of-care arm. There were no treatment-related deaths in either arm.

"Elacestrant is the first oral SERD to demonstrate a statistically significant and clinically meaningful improvement of progression-free survival in patients with ER-positive/HER2-negative metastatic breast cancer in the second- and third-line settings, including for patients whose tumors harbor ESR1 mutations," said Bardia. "Elacestrant was well tolerated with manageable and reversible side effects. This therapy has the potential to become the new standard of care for patients with this cancer."

Bardia noted that future studies will aim to understand the efficacy of elacestrant during earlier lines of treatment and in combination with other therapies. A planned phase II trial will examine the impact of elacestrant in combination with abemaciclib specifically for patients with brain metastases.

A limitation of this study was that all enrolled patients had received prior treatment with a CDK4/6 inhibitor; thus, the efficacy of elacestrant in patients without prior CDK4/6 inhibitor treatment remains unknown.

More information: Abstract: GS2-02. Elacestrant, an oral selective estrogen receptor degrader (SERD), vs investigator's choice of endocrine monotherapy for ER+/HER2- advanced/metastatic breast cancer (mBC) following progression on prior endocrine and CDK4/6 inhibitor therapy: Results of EMERALD phase 3 trial