Analysis of blood samples finds ESR1 gene mutations are prevalent and associated with reduced survival

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Among patients with estrogen receptor (ER)-positive, metastatic breast cancer, those who had a D538G and/or a Y537S mutation in the estrogen receptor 1 (ESR1) gene, as detected in cell-free DNA obtained from patient blood samples, had significantly worse median overall survival, according to data presented at the 2015 San Antonio Breast Cancer Symposium, held Dec. 8–12.

"Even though patients with ER-positive, metastatic breast cancer are all generally given treatments targeting the estrogen receptor, there is a real diversity in how their tumors respond to these drugs, and, therefore, a real diversity in patient outcomes," said Sarat Chandarlapaty, MD, PhD, a breast medical oncologist at Memorial Sloan Kettering Cancer Center in New York. "Our goal was to determine if changes in the estrogen receptor itself might explain these differences. Specifically, we wanted to know: Are mutations in the estrogen receptor common in patients with advanced breast cancer? And do they have an effect on outcomes?

"Using a simple blood test, we found that the D538G and Y537S mutations in the estrogen receptor are more common in patients with advanced, ER-positive breast cancer than previously appreciated and that patients with these mutations don't respond as well to currently used therapies and die from their disease sooner than patients who do not have these mutations," added Chandarlapaty. "The data also suggest that there appear to be differences in how these two mutations affect

response to everolimus, but there is more work needed to confirm this. Finding out which cancers respond best to which treatments is key to directing clinical and research efforts and will help breast cancer care become more precise and effective in the future."

Previously published results from the phase III BOLERO-2 clinical trial showed that adding everolimus to the standard hormonal therapy exemestane improved outcomes for postmenopausal women with ER-positive, locally advanced or metastatic breast cancer that has progressed after treatment with an aromatase inhibitor, and led to the U.S. Food and Drug Administration approving everolimus for this use in July 2012.

In this analysis, Chandarlapaty and colleagues evaluated blood samples from 541 of the 724 patients enrolled in BOLERO-2. They detected the D538G ESR1 mutation in samples from 83 patients, the Y537S ESR1 mutation in samples from 42 patients, and both mutations in samples from 30 patients.

Median overall survival was 32.1 months for patients with neither a D538G nor a Y537S ESR1 mutation, 26 months for those with only a D538G mutation, 20 months for those with only a Y537S mutation, and 15.2 months for those with both mutations. Exploratory analyses showed that adding everolimus to exemestane more than doubled progression-free survival for patients with neither ESR1 mutation and for those with a D538G mutation. However, the treatment combination did not appear to increase progression-free survival for patients with a Y537S mutation.

Chandarlapaty stated, "These data show clearly that the D538G and Y537S ESR1 mutations are prevalent among patients with advanced, ER-positive breast cancer that has progressed after treatment with an aromatase inhibitor and that they are associated with worse outcomes. However, the number of patients with the Y537S ESR1 mutation was small so further studies are needed before we can consider bypassing

everolimus treatment for this patient population."