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MSK studies highlight potential of liquid biopsy

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Information gleaned from a liquid biopsy may help predict how individual women with advanced breast cancer will respond to certain therapies as well as reveal genetic mutations that can impact prognosis, according to two new studies led by Memorial Sloan Kettering Cancer Center (MSK) Physician-in-Chief José Baselga and physician-scientist Sarat Chandarlapaty. The studies were presented this week at the San Antonio Breast Cancer Symposium.

Liquid biopsies rely on blood samples drawn from cancer patients to analyze trace amounts of free-floating tumor DNA in the blood. The minimally invasive test offers several advantages over conventional tumor biopsies. Since surgery is not needed, patients can be tested more frequently. And liquid biopsies may actually provide a more accurate picture of cancer in the body, as genetic sequencing of free-floating tumor DNA may better capture the diversity of genetic alterations found in cancer cells in different parts of the body, including the primary tumor and metastases.

"Testing for mutations in the blood can help identify the population of patients who may benefit most from certain drugs or combinations," Dr. Baselga said. "The liquid biopsy analyses in these two studies gave us incredibly important information. Going forward, liquid biopsy will become standard practice for testing new drugs and monitoring response to current therapies."

Liquid Biopsy in BELLE-2: Presence of Mutation Predicts Success of Treatment

A team led by Dr. Baselga found that detecting a mutated PIK3CA gene in a blood sample can predict how well some advanced breast cancer patients may respond to the experimental drug buparlisib. A mutated PIK3CA gene can activate the PI3K disease pathway, which promotes resistance to hormone therapies. Buparlisib blocks the PI3K pathway, and thus may increase a woman's sensitivity to hormone therapy.

The researchers analyzed blood samples from 587 patients entering the phase III BELLE-2 trial, which is testing the safety and effectiveness of adding buparlisib to the standard hormone drug fulvestrant to treat women with estrogen receptor (ER)-positive breast cancer who have grown resistant to aromatase inhibitors.

The entire study population benefited from the combination therapy, but the presence of a PIK3CA mutation in 34 percent (200 out of 587) of the patients' liquid biopsies had a striking effect: Those that received buparlisib plus fulvestrant had 7 months of progression-free survival (PFS)—the length of time after the treatment during which the patient lived with the cancer and it did not get worse—compared with only 3.2 months for those receiving fulvestrant plus a placebo.

"These effects are quite dramatic in patients with the PIK3CA mutation—an increase from three months to seven months is huge," Dr. Baselga said. "For the first time, we show that inhibiting the PI3K pathway may be a viable option for patients with hormone therapy-resistant breast cancer."

Among those who did not have the PIK3CA mutation—a total of 387 patients—there was no difference in PFS, suggesting that adding

buparlisib did not provide any advantage. Being able to identify patients who will not benefit from the new drug combination is also important, as the side effects proved to be significant, with 25 percent of patients having serious adverse events such as high blood sugar and potential early signs of liver damage.

Liquid Biopsy in BOLERO-2: Mutations Are Common, Lead to Worse Outcomes

In the second study, Dr. Chandarlapaty and colleagues found that women with advanced ER-positive breast cancer had significantly worse overall survival if tumor cell DNA in their liquid biopsy carried one or both of two specific mutations that occur in the gene that makes the estrogen receptor: D538G and Y537S.

The researchers analyzed liquid biopsies from 541 patients enrolled in the phase III BOLERO-2 clinical trial, which previously found that adding the drug everolimus to the aromatase inhibitor exemestane improved outcomes for most patients. They detected the D538G mutation in 83 patients, the Y537S mutation in 42 patients, and both mutations in 30 patients.

There were differences in outcomes based on the mutations, regardless of treatment received in the trial. In patients without either mutation, median overall survival was about 32.1 months. Patients carrying a D538G mutation had a median overall survival of 26 months. For patients with the Y537S mutation it was 20 months, and for those with both mutations, it was only 15.2 months.

"There is a real diversity in how tumors respond to drugs targeting the ER receptor, and therefore a real diversity in patient outcomes," Dr. Chandarlapaty explained. "We wanted to find out whether mutations in

this receptor are common in patients with advanced breast cancer—and if so, whether that affects how well the patients respond to treatment. This study shows us that women with the mutations don't respond to the currently used therapies as well and die from their disease sooner."

Dr. Chandarlapaty's team was surprised by how common the D538G and Y537S mutations were in this patient group—and also by how often the mutations were detected in the blood samples compared with samples from the primary tumors.

"This is a vital point for the medical community—a simple blood test proves to be quite sensitive in detecting very important genetic alterations and has the potential to help make breast cancer care more precise and effective," he said.

Provided by Memorial Sloan Kettering Cancer Center

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