

Liquid biopsies in SOLAR-1 trial predict benefit of Alpelisib in PIK3CA-mutant breast cancer

December 6 2018

Liquid biopsy-based assessment of PIK3CA mutational status served as a better indicator of progression-free survival compared with analysis of tissue biopsy in breast cancer patients enrolled in the phase III clinical trial SOLAR-1, according to data presented at the 2018 San Antonio Breast Cancer Symposium, held Dec. 4-8.

"While the primary endpoint of the SOLAR-1 trial was determined based on PIK3CA [mutations](#) in any available tumor tissue, such as archival or fresh tissue, liquid biopsy analysis can be performed on a plasma sample obtained just prior to the initiation of [treatment](#)," said Dejan Juric, MD, director of the Termeer Center for Targeted Therapies at the Massachusetts General Hospital Cancer Center. "Our analysis reveals that advanced breast cancer patients with detectable PIK3CA mutations in their blood have a more impressive benefit when alpelisib [a selective PI3K-alpha inhibitor] is added to fulvestrant for their treatment compared to patients with PIK3CA mutations detected in their tissue."

Utilizing information from the SOLAR-1 trial, Juric and colleagues analyzed data from 341 hormone positive, HER2-negative advanced [breast cancer patients](#) with PIK3CA mutations, as determined by tissue biopsy, who had received prior endocrine therapy. Patients were randomized to receive either fulvestrant and alpelisib or fulvestrant and placebo. The median follow-up time was 20 months.

In addition to tissue-based analysis, the researchers evaluated progression-free survival (PFS) by PIK3CA mutational status as measured in circulating tumor DNA (ctDNA). PFS was also analyzed by line of metastatic treatment, and by prior exposure to cyclin-dependent kinase 4/6 (CDK4/6) inhibitors.

While patients with PIK3CA mutations as evaluated in tissue samples had a 35 percent reduction in risk for disease progression, the risk reduction was 45 percent for patients with PIK3CA mutations as evaluated in ctDNA.

"Compared to tissue DNA, circulating tumor DNA is a very easily accessible source of material for mutation profiling," said Juric. "The finding that assessing mutational status via [liquid biopsy](#) resulted in even larger clinical benefit compared to [tissue](#) biopsy, with improvement of median PFS from 3.7 months to 10.9 months, further highlights the clinical utility of this biospecimen."

Compared with patients in the placebo arm, those who received alpelisib as second line of treatment in the metastatic setting had a 39 percent reduction in risk for disease progression; the risk reduction was 33 percent for those who did not receive prior treatment with CDK4/6 inhibitors. There was also a 52 percent (nonsignificant) reduction in risk for participants who received prior treatment with CDK4/6 inhibitors.

Patients enrolled in the alpelisib arm experienced increased incidences of hyperglycemia, diarrhea, nausea, and rash compared to the placebo arm (65 percent versus 9 percent; 54 percent versus 11 percent; 46 percent versus 20 percent; and 40 percent versus six percent, respectively).

"PI3K-alpha is important for insulin signaling and PI3K-alpha inhibition results in insulin resistance; hyperglycemia is therefore an on-target effect inextricably linked with the activity of alpelisib," said Juric.

"Early detection and serial monitoring of elevated glucose, initiation of appropriate dietary measures, as well as early initiation of metformin and other insulin sensitizers is essential for adequate management of these patients."

Limitations of this study include a small number of patients who received prior treatment with CDK4/6 inhibitors. "Larger studies specifically focused on post-CDK4/6 [patients](#) are needed to further characterize the role of alpelisib in this setting," Juric noted.

Provided by American Association for Cancer Research

Citation: Liquid biopsies in SOLAR-1 trial predict benefit of Alpelisib in PIK3CA-mutant breast cancer (2018, December 6) retrieved 20 September 2024 from <https://medicalxpress.com/news/2018-12-liquid-biopsies-solar-trial-benefit.html>

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