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Genomic Sequencing of Treatment-resistant Metastatic Breast Cancer Reveals Clinically Relevant Genetic Alterations

SAN ANTONIO — Genomic sequencing of estrogen receptor (ER)-positive metastatic breast cancer that had become resistant to therapies revealed multiple genomic and molecular alterations that were not present in the primary tumor samples, with implications for choice of next therapy, clinical trial eligibility, and novel drug targets, according to data presented at the 2016 San Antonio Breast Cancer Symposium, held Dec. 6–10.

"In spite of tremendous advances in the treatment of ER-positive breast cancer using therapies directed against the estrogen receptor, patients frequently develop resistance to these therapies," said senior investigator of the study Nikhil Wagle, MD, deputy director of the Center for Cancer Precision Medicine at Dana-Farber Cancer Institute (DFCI); assistant professor of medicine at Harvard Medical School; and an associate member of the Broad Institute of MIT and Harvard.

"These resistant tumors remain the most common cause of breast cancer death, yet mechanisms by which this resistance develops are poorly understood," Wagle added.

In contrast to the published studies of primary, treatment-naïve breast tumors, this research focuses on metastatic tumor samples from patients with resistant disease, explained lead author of the study Ofir Cohen, PhD, a postdoctoral researcher and computational biologist at the Broad Institute and DFCI. This represents a clinically important population of patients that is largely uncharacterized by comprehensive exome and transcriptome sequencing, he added.

"Our current research is part of a growing effort by many researchers to start closing the gap by better understanding the genomic underpinning of the metastatic and resistance states," Cohen said.

Wagle, Cohen, and colleagues analyzed treatment-resistant metastatic breast tumor samples collected from 130 patients who were treated at the Susan F. Smith Center for Women's Cancers at DFCI. Pretreatment samples of the primary tumors were analyzed from 34 of these patients. The investigators performed massively parallel sequencing (also known as "next-generation sequencing") to sequence the whole exome (the genes encoding all of the proteins in the cancer

cell) and transcriptome (all of the genetic messages in the cell that direct the expressions of proteins) of these breast cancer samples.

"We found that the genomic landscape of drug resistant ER-positive metastatic breast cancer is significantly different from that of primary ER-positive breast cancer. Moreover, we were able to identify multiple clinically relevant genomic and molecular alterations in the metastatic biopsies with implications for choice of next therapy, clinical trial eligibility, and novel drug targets," said Cohen.

Briefly, whole exome sequencing showed metastatic breast cancer samples to have more frequent alterations in the genes ESR1, ERBB2, PIK3CA, PTEN, RB1, AKT1, among others. Transcriptomic sequencing helped identify several types of resistance that are likely to be clinically relevant.

"With increasing numbers of patients from whom we were able to obtain and sequence the original primary tumor, we have been able to distinguish between pre-existing events [found in both the primary and the metastatic samples] and evolutionary, acquired events [found only in the metastatic sample]," said Cohen.

"Pre-existing events may highlight events that predispose to metastasis, supporting the idea that comprehensive characterization of primary tumors might help predict metastatic potential, while acquired events may suggest novel therapeutic approaches to overcome or prevent resistance, and highlight the idea of periodic monitoring with technologies such as cell-free DNA from blood [liquid biopsies]," Cohen added.

Clinically relevant results that are identified by next-generation sequencing in these tumors have been returned to the clinicians and patients and are being used for clinical decision making, Wagle noted.

Ultimately, the goal of this collaborative effort is to integrate the functional and clinical findings into a unified "Resistance Atlas" for ER-positive metastatic breast cancer, which should help inform treatment decisions for individual patients as well as propel the development of new combination treatment strategies for ER-positive metastatic breast cancer, Wagle said.

A limitation of the study is that most of the samples were both metastatic and treatment-resistant and therefore, potential "drivers" of metastasis were interwoven with that of drug resistance. The investigators are using several functional assays to help untangle metastasis-driving events from resistance-conferring events, Cohen said.

This study was funded by the National Cancer Institute, the National Human Genome Research Institute, the Department of Defense Breast Cancer Research Program, Susan G. Komen, The V Foundation, The Breast Cancer Alliance, the AACR-Landon Foundation, the Friends of Dana-Farber Cancer Institute, and the Breast Cancer Research Foundation. Cohen declares no conflicts of interest. Wagle is an equity holder in Foundation Medicine, a consultant to Novartis, and a recipient of sponsored research support from Novartis, Genentech, and Merck.

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The mission of the 2016 San Antonio Breast Cancer Symposium is to produce a unique and comprehensive scientific meeting that encompasses the full spectrum of breast cancer research, facilitating the rapid translation of new knowledge into better care for patients with breast cancer. The Cancer Therapy & Research Center (CTRC) at The University of Texas Health Science Center at San Antonio, the American Association for Cancer Research (AACR), and Baylor College of Medicine are joint sponsors of the San Antonio Breast Cancer Symposium. This collaboration utilizes the clinical strengths of the CTRC and Baylor and the AACR's scientific prestige in basic, translational, and clinical cancer research to expedite the delivery of the latest scientific advances to the clinic. For more information about the symposium, please visit www.sabcs.org.