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Time needed to complete: 58m

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What Are the Clinical and Therapeutic Implications of the Evolving HER2 Testing Landscape?

Announcer:
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Dr. Sammons:
Hello, my name is Dr. Sarah Sammons, and I'm Associate Director of the EMBRACE Metastatic Breast Cancer Program at Dana Farber Cancer Institute in Boston, Massachusetts. Thank you so much for joining me today to talk about the clinical and therapeutic implications of evolving HER2 testing landscape in metastatic breast cancer.

Traditional HER2 testing followed a very binary paradigm; tumors were either considered HER2-positive or HER2-negative. And by these definitions, about 80 to 85% of breast cancer was considered HER2-negative, and did not benefit from HER2-targeted therapy. This treatment paradigm has rapidly evolved in the last year or 2 due to highly effective HER2-targeting agents that have activity in HER2 low expressing breast cancer. HER2-low is now considered a biomarker for the FDA approved drug, trastuzumab deruxtecan, and so the testing of this has evolved. Previously, HER2 testing was considered positive if immunohistochemistry was 3+, or 2+ but ISH positive. Now, HER2-low is considered positive if the tumor is HER2 2+, but ISH negative, or HER2 1+. HER2-0 is still considered HER2 negative. By these definitions, approximately two-thirds, or 65% of hormone receptor-positive breast cancer is considered HER2-low, and about one-third, or 36% of triple-negative breast cancer is considered HER2-low by these standards.

One of the problems with HER2 testing is that there is very low concordance amongst pathologists between HER2 and HER2-low testing by immunohistochemistry. In a recent study that included 18 experienced pathologists, there was only 26% concordance between a diagnosis of HER2-0 and HER2 1+ breast cancer. This is historically because pathologists are most used to identifying overexpressing or very highly expressing levels of HER2, and it can be very subjective. As HER2-low has emerged as a new biomarker for effective HER2-targeting drugs, there has been a lot of research to understand if HER2-low is a distinct biologic subtype of breast cancer. Many studies have looked at gene expression assays of HER2-low versus HER2-0 breast cancer. And what we have found is that HER2-low does not seem to be a distinct biologic subset. Amongst triple-negative breast cancer, PAM50, a basal-like breast cancer, is similar amongst HER2-low or HER-0. And amongst hormone receptor-positive, about 90% of HER2-low or HER2-0 breast cancers are luminal. HER2-low also does not appear to have prognostic implications.

In the last 2 years, there have been many studies to understand if HER2-low is prognostic. And what the abundance of data points to is that when you control for triple-negative or hormone receptor-positive amongst HER2-low, there are not prognostic implications.

HER2-low has emerged essentially as a biomarker for very effective HER2-targeting antibody drug conjugates. One called fam-trastuzumab is currently FDA approved to target HER2-low breast cancer and is the first drug to be approved in this space based on the DESTINY-Breast04 clinical trial, which we will talk more about in this series. The trastuzumab deruxtecan is approved for adult patients with metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or had a recurrence within 6 months of completing adjuvant therapy. There are many other clinical trials ongoing looking at new HER2-targeting drugs for HER2-low breast cancer, and you will only hear more about HER-low as a biomarker for therapies in metastatic breast cancer, and for that matter,

other tumor types.

Thank you so much for joining me today to understand more about this new entity of HER-low, which is a paradigm shift in HER2 testing.

Announcer:
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