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Guideline Recommendations for the Definition and Treatment of HER2-Low Breast Cancer

Announcer:
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Dr. Mayer:
Hello. I'm Erica Mayer from Dana-Farber Cancer Institute in Boston. Our discussion today will focus on guideline recommendations for the definition and treatment of HER2-low breast cancer.

So, first, what is the definition of HER2-low? When HER2 testing was first developed, it was primarily designed to distinguish between positive and negative, and specifically, immunohistochemistry was positive, IHC 3+, or negative, IHC 2+, 1+, or zero. It was not designed to look at low levels of HER2 or distinguish low levels from completely negative.

However, in recent years we are now beginning to understand that there may be subtle gradations in HER2 testing, and being HER2 negative may not actually be negative. It's been demonstrated that there may be an intermediate category, HER2-low, and this comprises about 60% to 65% of what we think of as HER2-negative disease. This includes patients with HER2 2+ and HER2 1+ disease. This is important because in the realm of drug development, there are agents being developed for patients who have this intermediate HER2 staining. The most notable drug in this category would be trastuzumab deruxtecan, or T-DXd. This is an antibody-drug conjugate, which is targeted towards the HER2 receptor. This agent has been demonstrated to be highly active in HER2-positive breast cancer, so clearly HER2 positive, and approved in that setting. More recently, though, we've seen some very exciting data looking at this drug in patients who have HER2-low breast cancer. We first saw data from the DESTINY-Breast04 study. This was a very important study in patients who had HER2-low breast cancer, so HER2 2+, HER2 1+, who could be hormone receptor positive or even hormone receptor negative, essentially triple negative.

These patients had received 1 to 2 prior lines of chemotherapy and were randomized to receive T-DXd or treatment of provider choice. The results from this study were quite striking, presented at ASCO Plenary and demonstrated substantial improvements in not only progression-free survival but also overall survival. Very exciting data for the breast cancer community. And this did lead to FDA approval of T-DXd in HER2-low metastatic breast cancer that's been pretreated.

In thinking about HER2-low, that had still left the category of HER2-zero. But if one examines that category, one could determine there is actually a HER2 ultra-low feature there, and that's about 20% to 25% of what we think of as HER2-low. This includes cancers that have a faint, incomplete membrane staining, 10% or less of tumor cells. So just a whisper of HER2 staining.

This is relevant in the design of the DESTINY-Breast06 study. This is a study that we saw presented this year at ASCO 2024, a study that enrolled patients with hormone receptor-positive breast cancer, that could be HER2-low or HER2 ultra-low, who had not had prior chemotherapy in the metastatic setting. Patients were randomized to receive up-front T-DXd versus treatment of provider choice, which for the majority of patients included capecitabine or a taxane. Results from this study were also quite impressive, demonstrating a

significant improvement in progression-free survival for patients who received T-DXd over the treatment of provider choice. And now one might say, should every patient receive T-DXd in the first-line setting? Certainly, this data is very impressive. However, our practice patterns prior to DESTINY-Breast06 often included offering patients capecitabine in the first-line setting, which is an oral and well-tolerated drug, and makes a nice bridge between endocrine therapy and chemotherapy. I think, that one can consider in patients who are symptomatic and need an objective response, it is very appropriate to offer T-DXd in this setting. But for patients who are asymptomatic, have a low burden of disease, and have had long intervals of disease control on prior therapies, this would still be patient preference, and capecitabine may be an appropriate choice in that setting, reserving T-DXd for later lines.

Now, what about the pure HER2-zero patients? There has been a small study called DAISY, which has looked at the activity of T-DXd in HER2-low, HER2 positive, and even HER2-zero, showing that the small population of patients there did actually have some responses to T-DXd. And this provides support for an ongoing study called DESTINY-Breast15, which is enrolling patients with HER2-low, HER2 ultra-low, and HER2-zero disease, offering T-DXd in this setting. And this will hopefully help us best understand if T-DXd has activity across the entire spectrum of HER2 disease.

So in summary, T-DXd is available in the first-line setting for hormone receptor-positive, HER2-low, and ultra-low, based on DESTINY-Breast06, and available in the second-line setting based on DESTINY-Breast04.

The small DAISY study suggests the activity may be continuous across the spectrum, but I think, importantly, determining HER2 status beyond the binary positive/negative is really important nowadays. This requires good communication with your pathologist and asking them, is my patient HER2 ultra-low, and really digging into the HER2 testing. And ultimately, we probably need better HER2 testing in the future to help us best understand with greatest precision who are the right candidates for our therapies.

Unfortunately, time's up. Thank you very much for watching.

Announcer:
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