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What Are the Data for HER2-Targeted ADCs in HR+/HER2-Low Metastatic Breast Cancer?

Announcer:
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Dr. Mayer:
Hi there. I'm Erica Mayer from Dana Farber. And we're going to review the data or HER2 targeted antibody drug conjugates in hormone receptor-positive HER2-low metastatic breast cancer.

So I want to talk about trastuzumab deruxtecan, also known as T-DXd. T-DXd is a HER2-targeted antibody that's covalently linked to a payload, which is a highly potent topoisomerase 1 inhibitor. When an ADC reaches a cancer cell, it reaches its receptor here, it's a HER2 receptor, it's internalized, the ADC is degraded, and this allows release of that potent payload into the cancer cell, leading to apoptosis. Something important about T-DXd is that not only does it kill the targeted cancer cell, but there's also what's called the bystander effect, where surrounding cells, hopefully cancer cells, are also killed and affected by the medication.

T-DXd was first evaluated in HER2-low metastatic breast cancer in a phase 1 study. HER2-low means that HER2 is IHC 1+ or 2+, but FISH negative. In this study of about 50 patients who were heavily pretreated, there was an overall response rate of 37% and a progression-free survival of 11 months. Both of those are quite favorable in a heavily pretreated population. If you look at the waterfall plot, you can see that the vast majority of patients experienced an element of response to therapy, and how much they responded does not appear to be linked to whether they were IHC 1+ or IHC 2+. This data formed the basis of the DESTINY-Breast04 study, which was a registrational phase 3 study of T-DXd for HER2-low metastatic disease. This was presented in a plenary session at ASCO 2022. In this study, patients who had HER2 low-risk disease who had had previously 1 to 2 prior lines of chemotherapy in the metastatic setting, and prior endocrine therapy exposure were randomized to receive T-DXd monotherapy or treatment provider choice. And the choices are listed here. You can see the vast majority of patients received either eribulin or capecitabine for TPC. Most of the patients on the study were hormone receptor-positive, close to 500. There was also a small exploratory cohort of hormone receptor-negative disease. The primary endpoint of the study was progression-free survival.

Results from DESTINY-Breast04 showed us that the use of T-DXd led to significant improvements in progression-free and overall survival in the hormone receptor-positive population. PFS was improved by about 5 months, from 5 months with TPC to about 10 months for T-DXd. And there was also a significant 6-month improvement in overall survival. In the hormone receptor-negative subgroup, which was more exploratory, similar benefits were seen as well with about a 6-month improvement in progression-free survival, and about a 10-month improvement in overall survival.

In terms of response rate, patients who receive the T-DXd had a significantly higher response rate compared to those who got treatment provider choice with response rates about 50% for the HER2-low hormone receptor-positive or negative groups, compared to about 16% in patients who receive treatment of provider choice.

In terms of side effects seen in patients, those who received T-DXd did have more GI toxicity, notably more nausea and vomiting compared to those who received treatment provider choice. Other notable side effects included fatigue and alopecia. But importantly,

the patients who received T-DXd had less hematologic toxicity compared to the patients who received the treatment provider choice chemotherapy. The most common side effects associated with dose reduction were nausea and fatigue. And with treatment discontinuation, was interstitial lung disease. Notably, about 12% of patients experienced any-grade interstitial lung disease. And importantly, a small percentage, 0.8%, experienced grade 5 or fatal interstitial lung disease, which is a very important toxicity signal with this agent.

So when we think about how we treat our patients with hormone receptor-positive HER2-negative or HER2-low advanced disease, we now have the addition of T-DXd. Based on DESTINY-Breast04, this is available in the second-line setting or beyond. So we might think about this as an option for a patient who perhaps has had capecitabine as their first-line chemotherapy or taxane. And then think about using T-DXd in the second-line setting as a preferred choice versus other chemotherapy options.

Thank you very much for listening, and I hope this presentation was helpful.

Announcer:
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