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DESTINY-Breast04 Findings: T-DXd and Quality of Life in HER2-Low Metastatic Breast Cancer

You're listening to *On the Frontlines of Metastatic Breast Cancer* on ReachMD, and this is an *AudioAbstract*. I'm Dr. Mimi Maeusli, and today, I'll be taking a closer look at patient-reported outcomes from the DESTINY-Breast04 trial on trastuzumab deruxtecan, or T-DXd, in HER2-low metastatic breast cancer.

The FDA approval of T-DXd for HER2-low metastatic breast cancer demonstrated that tumors previously considered HER2-negative could, in fact, respond to targeted treatment. While clinical outcomes from DESTINY-Breast04 confirmed T-DXd's superiority over standard chemotherapy in extending survival, a new analysis published in *The Oncologist* shifts the focus to the patient experience in the trial.

DESTINY-Breast04 enrolled 557 patients with HER2-low unresectable or metastatic breast cancer who had received one or two prior chemotherapy regimens. Patients were randomized two to one to receive either T-DXd or physician's choice of chemotherapy, which included capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel.

Patient-reported outcomes were assessed throughout treatment using validated instruments, including the EORTC QLQ-C30 for global health and core symptoms, the QLQ-BR23 for breast cancer–specific domains, and the EQ-5D-5L for overall health status. The key measure was time to definitive deterioration, which was defined as any decline of 10 points or more from baseline in the symptom score without subsequent improvement.

Across multiple domains, patients receiving T-DXd showed a slower rate of decline and prolonged maintenance of function compared to those treated with chemotherapy.

Time to deterioration in global health status was significantly delayed with T-DXd, with a hazard ratio of 0.63 and a confidence interval of 0.48 to 0.84. Fatigue, physical functioning, and nausea and vomiting also declined more slowly with T-DXd, with hazard ratios between 0.60 and 0.64. And finally, in contrast to the progressive decline observed in the chemotherapy arm, T-DXd patients maintained more stable scores over time. These patterns were consistent across hormone receptor subgroups, supporting broad applicability within the HER2-low metastatic breast cancer population.

For patients with advanced breast cancer, treatment goals include not only extending survival, but doing so without accelerating symptom burden. These findings suggest that T-DXd offers a clinically meaningful advantage in this regard. Despite known risks—particularly nausea and interstitial lung disease—patients treated with T-DXd reported slower deterioration of quality-of-life metrics than those receiving standard chemotherapy.

The results support T-DXd as a therapeutic option that provides both disease control and improved tolerability, an important consideration in treatment selection and sequencing. The authors also emphasize the value of incorporating patient-reported outcomes into clinical trials as core evidence rather than adjunctive endpoints.

Notably, several limitations warrant consideration. Attrition over time, particularly among chemotherapy recipients, may introduce bias, as patients with worsening symptoms are more likely to discontinue treatment or fail to complete assessments. Additionally, while the tools used were validated, they may not fully capture T-DXd–specific toxicities such as interstitial lung disease. Future studies may benefit from a more tailored symptom assessment framework.

Additionally, generalizability may be constrained by the trial population, which excluded patients with ECOG performance status greater than one and included only those who were relatively fit. Outcomes may differ in older or more comorbid populations.

Lastly, the open-label design may contribute to reporting bias, though the use of threshold-based deterioration scores helps to mitigate this concern.

This analysis of patient-reported outcomes adds critical context to the established clinical efficacy of T-DXd. In a treatment setting where symptom progression can erode physical autonomy and emotional well-being, delaying deterioration in fatigue, physical function, and overall health status carries direct relevance to both patients and providers.

The findings help reinforce that T-DXd is not only associated with improved survival, but also with a more favorable symptom trajectory, reinforcing its value in treatment decisions for patients with HER2-low metastatic breast cancer.

This has been an *AudioAbstract* for *On the Frontlines of Metastatic Breast Cancer,* and I'm Dr. Mimi Maeusli. To access this and other episodes in our series, visit ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!