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https://reachmd.com/programs/cme/emerging-data-in-her2-targeted-adcs-for-metastatic-breast-cancer/29952/

Released: 02/06/2025
Valid until: 06/18/2026
Time needed to complete: 1h 15m

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Emerging Data in HER2-Targeted ADCs for Metastatic Breast Cancer

Dr. Anders:
This is CME on ReachMD and I'm Carey Anders. Today, I'll discuss emerging data on HER2-targeted antibody drug conjugates for treating patients with metastatic breast cancer. There were several exciting abstracts that were presented at the 2025 annual ASCO meeting on this topic, and I'll review some of these abstracts and their implications to practice.

The first was the late-breaking abstract, DESTINY-Breast09, that was presented by Dr. Sarah Tolaney. This included trastuzumab/deruxtecan with pertuzumab versus our traditional taxane/trastuzumab/pertuzumab, or THP, as per the CLEOPATRA study, for first-line treatment of patients with HER2-positive, advanced metastatic breast cancer. This was an interim analysis.

And what we learned from DESTINY-Breast09 is that the combination of trastuzumab/deruxtecan with pertuzumab, compared to THP, improved patients' progression-free survival. The patients who received T-DXd with pertuzumab had a progression-free survival of 40.7 months, versus those in the traditional THP CLEOPATRA arm at 26.9 months.

The hazard ratio, favoring T-DXd, was 0.56, and the P value was highly statistically significant.Dr. Tolaney indicated that this data may change our first-line standard of care for our patients who present with metastatic HER2-positive breast cancer.

The side effect profile from both arms was relatively similar to what we've seen in prior analysis. And I think one of the biggest questions that we're awaiting is how will this change in direction or sequencing of therapies impact our patients' long-term overall survival? Will patients have an improved survival for moving T-DXd and pertuzumab into first line, versus the current or the previous standard of care, which was THP followed by T-DXd?

The other very important component here is quality of life. And what is the quality of life for patients who are on T-DXd for such a long period of time compared to THP, where we do drop the taxane component after 6 to 8 cycles, and patients move forward with dual antibody therapy?

The other piece to consider are those for our patients with hormone receptor-positive HER2-positive breast cancer. This was about 50% of the patient population. We recently learned about the PATINA data, where patients who had a response to THP with hormone receptor-positive, HER2-positive breast cancer, after the taxane component, were able to continue with dual antibody therapy and add anti-estrogen therapy with an aromatase inhibitor and a CDK 4/6 inhibitor, namely palbociclib.

In patients in the PATINA study, the progression-free survival was on the order of 44 months, so I also think we're trying to determine what might be best for our patients with hormone receptor-positive, HER2-positive breast cancer, versus hormone receptor-negative, HER2-positive breast cancer.

A second abstract to note was the DESTINY-Breast06 exploratory biomarker analysis of trastuzumab/deruxtecan versus physician's

choice chemotherapy in HER2-low/-ultralow, hormone receptor-positive metastatic breast cancer that was presented by Dr. Rebecca Dent.

And in this analysis, the authors evaluated preferential response to T-DXd versus physician's choice chemotherapy by biomarkers PI3 kinase, ESR1 mutations, and BRCA mutations.

And the bottom line is that all biomarker subsets responded better and longer to T-DXd, but there was a more profound response in BRCA mutation carriers favoring T-DXd. And while we don't know the exact reason for this preferential response in BRCA mutation carriers, one could hypothesize that it's due to the chemotherapy payload of T-DXd with a topoisomerase inhibitor, which is a DNA-damaging agent, which might be more sensitive in a patient population with BRACA mutations that have deficient DNA damage repair.

So we are hopeful that this information will help guide you in your practice, and unfortunately, my time is up. Thanks for listening.