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The Role of HER2-Directed Therapy for Second-Line Treatment of HER2+ Metastatic Breast Cancer

Announcer:
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Dr. Schmid:
Hello. I'm Dr. Peter Schmid, and this is CME on ReachMD. In this episode, we'll look at second-line therapy for HER2-positive metastatic breast cancer.

HER2-positive metastatic breast cancer is really interesting. For many years we thought we reached a plateau, and it would be very difficult to improve the outcome for patients with metastatic HER2-positive breast cancer. We had a very clear standard of care in the first-line setting, which remains the standard of care, and this is a taxane-based chemotherapy in combination with dual HER2 blockade with trastuzumab/pertuzumab. And that led to a progression-free survival of approximately 18 months. It's helpful to remember that number when we talk about the other data of new agents.

Again, in the past, second-line treatment patients would receive therapy with an antibody-drug conjugate called T-DM1 and a randomized trial that showed a progression-free survival of around 7 to 9 months. Now, this has now been replaced with a new antibody-drug conjugate called trastuzumab deruxtecan. And this is a novel form of ADC, a third-generation antibody-drug conjugate. These third-generation ADCs have a pretty pronounced bystander effect and, therefore, have a substantially increased activity to some of the compounds we saw with second-line ADCs.

T-DXd has been explored in two phase 3 trials in patients with HER2-positive disease. The DB-02 trial was a trial for patients who had already received another ADC, T-DM1. And in this trial, about 47% of patients received T-DXd as second-line therapy. Most of the other patients are third- and subsequent-line therapy, and was compared to treatment of physicians, such as standard chemotherapy with HER2-targeted agents.

The hazard ratio in terms of progression-free survival was 0.35 in favor of trastuzumab deruxtecan, with a median progression-free survival of 70.8 months versus 6.9 months for treatment of physician's choice. So a dramatic improvement in progression-free survival.

The second trial in this setting, DB-03, was a randomized trial where the 2 ADCs, trastuzumab deruxtecan and T-DM1, were compared head-to-head. Again, it was a trial predominately in the second- and third-line setting. 39% received the treatment as second line, about 10% as first line, and the rest of patients in third- and subsequent-line therapy. The hazard ratio was again significant with a hazard ratio of 0.33. The median progression-free survival was nearly 29 months with trastuzumab deruxtecan.

If you think about 29 months in a second- and third-line setting, comparing to the 18 months we currently achieve with taxanes and dual HER2 blockade in a first-line setting, this is a very, very significant step forward. And the control arm was only at 6.8 months, demonstrating how powerful the second-line treatment with trastuzumab deruxtecan was. The duration of response was just over 3

years, but again, one of the, for me, clinically really important characteristics of treatment with trastuzumab deruxtecan in the second-line setting were the very high responses of nearly 80%, compared to around 34% with T-DM1. And not surprisingly, this led to, on the one hand, an improvement in overall survival, but also to an improvement in quality of life of patients with the shrinkage of the tumor.

One of the questions that has been open and discussed is whether we should make a difference in our strategy depending on whether patients have brain metastases or not. And in this context, it was really interesting to see the data of the DB-11 trial fairly recently, which compared patients with and without brain mets who receive treatment with trastuzumab deruxtecan. And it showed that the response rate of active brain metastases was more than 60% and even higher in patients who had untreated active brain metastasis where the responses were close to 80%. The progression-free survival for patients with brain metastases was about 17 months. And what I found really striking was the overall survival of patients with or without brain metastases appeared relatively similar.

So we have a compound that's highly active with trastuzumab deruxtecan as a second-line treatment, not just for extracranial disease, but also now for intracranial disease, and is therefore recommended as the standard of care for patients in second-line metastatic HER2-positive breast cancer.

I hope you find this interesting. Thank you for your attention, and I look forward to discussing this in the future.

Announcer:
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