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How Do Brain Metastases Affect Your Choice of Systemic Treatment in a Patient with HR+/HER2-low MBC?

Announcer:
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Dr. Sammons:

Hello, my name is Dr. Sarah Sammons, and I am Associate Director of the Metastatic Breast Cancer Program at Dana Farber Cancer Institute in Boston, Massachusetts. And today we're going to learn a little bit about antibody drug conjugates in HER2-expressing breast cancer to brain metastases.

Breast cancer to brain metastases are a very common complication of metastatic breast cancer. Their prevalence is about 30 to 50% in HER2-positive and triple-negative breast cancer, and about 14% of patients that have hormone receptor-positive HER2-negative breast cancer will ultimately develop brain metastases. Therapies are very limited for patients that experience brain metastases, and newer therapies are always needed. Trastuzumab deruxtecan is an antibody drug conjugate targeting HER2-expressing breast cancers that has changed the standard of care in patients with low-expressing and over-expressing HER2-positive breast cancer.

While chemotherapy has very limited activity in breast cancer brain metastases, antibody drug conjugates such as trastuzumab deruxtecan, are showing very promising and somewhat surprising results in this critical unmet need trastuzumab deruxtecan has shown impressive activity in both stable and active HER2-positive brain metastases. And we will review some of this data today.

The first antibody drug conjugate to show intracranial activity in breast cancer brain metastases was trastuzumab emtansine, or T-DM1. In the KAMILLA clinical trial, where 2,000 patients were enrolled, approximately 400 of them had stable brain metastases at baseline, 126 of those patients had measurable brain metastases, evaluable for intracranial overall response. The intracranial response rate of T-DM1 in these patients was about 21%, which is much higher than historically seen with systemic chemotherapies in the brain. This was the first data to challenge historical thinking that large molecules such as antibody drug conjugates, could not penetrate the blood brain barrier. Sacituzumab govitecan is a TROP2 antibody drug conjugate that is currently approved in both triple-negative and hormone receptor-positive metastatic breast cancer. In both preclinical and clinical studies, sacituzumab has shown therapeutic levels in resected brain tumors in a small study. In a preoperative window study, a sacituzumab in patients with breast cancer brain metastases, or glioblastoma multiforme, patients who received at least 1 dose of sacituzumab and then went to brain resection had therapeutic levels of SG in their resected brain tumors, showing that ADCs can in fact penetrate the blood-brain barrier.

Trastuzumab deruxtecan is now approved in the second-line setting for HER2-positive metastatic breast cancer, given the results of the DESTINY-Breast03 clinical trial and the first results of the DESTINY-Breast01 clinical trial. In the DESTINY-Breast01 subgroup analysis of stable - of patients that had previous stable brain metastases, the median progression-free survival was the same, regardless of whether or not patients had brain metastases, showing that the drug had efficacy in those that had prior CNS disease.

We also have several small studies including DEBBRAH, a real-life cohort of patients with active brain metastases treated with T-DXd,

and TUXEDO, showing excellent activity of trastuzumab deruxtecan in patients that have active brain metastases. Active brain metastases are those defined as those that have brain mets that are either untreated or are growing or progressing, despite having prior radiation therapy. There are very limited treatment opportunities for these patients. Trastuzumab deruxtecan in these small studies, has shown CNS overall response rates of 73% in two cohorts and 50% and another, which is quite striking compared to previous studies.

Trastuzumab deruxtecan has only been studied in very small retrospective cohorts of patients with HER2-low breast cancer, and it's showing somewhat promising activity. We await further studies to understand the efficacy of trastuzumab deruxtecan in HER2-low brain metastases but given the promising efficacy and HER2-positive brain metastases, we do think ADCs in general are very promising in this space.

Here is a table of the ongoing research looking at antibody drug conjugates in patients with breast cancer brain metastases, so very promising space for this highly unmet need.

Thank you so much for joining me today to understand the data to date on antibody drug conjugates in breast cancer brain metastases.

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