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Applying Data Into Practice: Sequencing Strategies for HER2-Targeted Breast Cancer

Dr Sammons:
This is CME on ReachMD. I'm Dr. Sarah Sammons. With me today is my friend and colleague, Dr. Carey Anders. Today, we'll discuss recent data regarding sequencing considerations for metastatic breast cancer with brain metastasis in HER2-positive disease. We'll start with a case.

A 48-year-old woman was diagnosed 4 years ago with HER2-positive IHC 3+ stage IIB invasive ductal carcinoma of the left breast. She was treated neoadjuvantly with TCHP. She then had a left mastectomy with negative margins, followed by adjuvant radiation and a year of HER2-targeted maintenance with trastuzumab and pertuzumab. She was estrogen negative and did not require any endocrine therapy.

Eighteen months ago, the patient developed metastatic disease in the liver and bone, and she was treated with first-line trastuzumab, pertuzumab, and docetaxel. She achieved a partial response lasting 9 months before developing progressive disease in the liver, liver enlargement that was symptomatic, and new asymptomatic brain lesions. Her brain lesions were treated with stereotactic radiosurgery, and then she went on to receive second-line trastuzumab deruxtecan, or T-DXd. She experienced disease control for 8 months before she had further progression in the brain and, unfortunately, her systemic sites as well.

This is a really challenging case, Dr. Anders. Tell me what you would be thinking about for this patient and what you would offer her in the next-line setting.

Dr. Anders:
This is, unfortunately, quite common in our practice. I will say, this case is a little unusual. The patient's disease-free intervals, or progression-free intervals, are quite short. Typically, in the first-line setting, we're going to achieve at least 20-plus months of disease stability. In this patient's case, there was less than a year before progressive disease in the liver and brain.

I do agree with the second-line therapy with trastuzumab/deruxtecan, based on prior knowledge of the DESTINY-Breast03 study. Of course, we do now have additional data supporting the selection of T-DXd and pertuzumab in frontline.

In this particular case, the patient had progression 8 months after initiation of T-DXd, which, again, is shorter than what we have seen historically in clinical trials with regards to median time to progression, usually on the order of more than 18, 20, 20-plus months. So I would be pretty concerned about this tempo of disease or velocity of disease. I think one of the things we might consider here is, is this tumor truly HER2 driven, or have we seen receptor discordance, and this particular breast cancer has lost expression of HER2?So that might be something I would be thinking about. And since there is systemic progression, a biopsy could help with that.

Now, presuming that the tumor remains HER2 positive in third-line metastatic HER2-positive breast cancer, particularly with brain and extracranial disease progression sites, I would be considering the HER2CLIMB regimen. This is the combination of the oral

chemotherapeutic capecitabine with the brain-permeable selective HER2-targeted tyrosine kinase inhibitor tucatinib and trastuzumab. That should help with both intracranial and extracranial sites of progression, hopefully in a way that is consistent with good quality of life.

Dr. Sammons:
Yes, I agree, Carey. Those are really interesting insights. This patient has not behaved in the classic way for a patient with HER2-positive metastatic breast cancer. She has had only 9 months of disease control on first-line therapy, which is far below the median, and only 8 months on second-line therapy, which is also far below the median. So I would actually be thinking about re-biopsying this patient to double-check that they were truly HER2-positive. And I'd also send next-generation sequencing to understand her mutational profiles. If she truly, in fact, was still HER2 positive. I agree that I would give her the HER2CLIMB regimen with tucatinib, capecitabine, and trastuzumab, likely after local therapy to the brain.

Dr. Anders:
All very good points. And I think this really is a changing landscape. We've learned a tremendous amount at ASCO 2025 about how we'll sequence all of these fantastic HER2-directed therapies to improve our patients' survival and ensure that they are experiencing excellent quality of life.

Dr. Sammons:
Thank you so much for joining today, and we hope that you learned a lot.