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HER2-Targeted TKI Combinations in Second-Line and Beyond MBC

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Dr. Sammons:
Hello, everyone. This is CME on ReachMD. I'm Dr. Sarah Sammons. In this brief lecture, I will review the data for clinical trials in metastatic breast cancer that have included the drug tucatinib, which is a highly brain-penetrant tyrosine kinase inhibitor. These two trials are called HER2CLIMB and HER2CLIMB-02.

First, we'll review the HER2CLIMB study because this was the first one reported almost 5 years ago at this point. In the HER2CLIMB study, patients with metastatic HER2-positive breast cancer who had had a prior treatment and progression on trastuzumab, pertuzumab, and TDM1 were randomized to either tucatinib, trastuzumab, and capecitabine or placebo trastuzumab and capecitabine.

It was a positive clinical trial, and the addition of tucatinib to trastuzumab and capecitabine did prolong both progression-free survival and overall survival in the overall population. Now, there was a really modest improvement in progression-free survival of only about 2 months, 7.8 months with the addition of tucatinib versus 5.6 months with placebo.

However, this trial was ground-breaking for other reasons. This was really the first phase 3 trial to include such a large population of brain metastasis patients. So, HER2CLIMB included almost 50% of patients with brain metastasis, and they also included patients with active brain metastasis. So, either untreated with radiation or treated but progressive.

And this trial was also very important because tucatinib added to trastuzumab and capecitabine prolonged CNS progression-free survival. So, the amount of time until they relapsed in the brain, and overall survival and intracranial response rate in the brain metastasis population. So, really, in terms of clinical practice, it showed us that tucatinib, capecitabine, and trastuzumab is a very good option for our patients with HER2-positive brain metastasis. And also, even our patients with active brain metastasis, where we really never had a phase 3 trial including those patients before.

The HER2CLIMB-02 clinical trial, which resulted about 1 year ago, looked at the addition of tucatinib to TDM1 in the second-line setting. So, patients were either randomized to tucatinib plus TDM1 or placebo plus TDM1. And this was also a positive clinical trial yielding a modest improvement in progression-free survival. Patients who received tucatinib plus TDM1 had a progression-free survival of 9.5 months versus 7.4 months with TDM1 alone.

Now, we do still wait overall survival data from HER2CLIMB-02. We also still await sort of that nitty gritty intracranial response rate data. So, data on CNS overall response rates, data on CNS progression-free survival. We haven't seen any of that data yet, and we really hope to see that before we can really understand how to use that in clinical practice. And it is also not FDA-approved yet.

So, I would say, in terms of tucatinib-containing regimens that are FDA-approved, useable in the clinic, right now, we have capecitabine, tucatinib, and trastuzumab, which can be used after progression on trastuzumab and TDM1 in the second-line and beyond. I think most

of us are using it in the after T-DXd setting, and it's a very good option for our patients with brain metastasis.

Thank you so much for joining me.

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