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https://reachmd.com/programs/cme/recent-updates-in-her2-targeted-tkis-for-metastatic-breast-cancer/29951/

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

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Recent Updates in HER2-Targeted TKIs for Metastatic Breast Cancer

Dr. Sammons:
This is CME on ReachMD. I'm Dr. Sarah Sammons. Today, I will review some of the recent updates on HER2-targeted tyrosine kinase inhibitors for treating metastatic HER2-positive breast cancer, and then I'll discuss the implications for practice.

The first study that I want to discuss investigates real-world clinical outcomes on the use of tucatinib, a HER2-specific tyrosine kinase inhibitor, when added to capecitabine and trastuzumab after progression on at least 2 lines of HER2-targeted therapy. In the clinic, we're really using trastuzumab/pertuzumab in the first-line setting after induction with a taxane. Then in the second-line setting, for the vast majority of patients, we're using trastuzumab deruxtecan. After progression on trastuzumab deruxtecan, what are we using in the clinic? Well, we have a few options. We have tucatinib-based options, tucatinib with capecitabine and trastuzumab.

Well, how does that perform post-T-DXd? Because in the HER2CLIMB study, no patients had had prior T-DXd, so we're now reliant on real-world data. We have 2 studies that have looked at this. The first was published by Anders, et al., and it looked at 89 patients with metastatic HER2-positive breast cancer who received tucatinib in the metastatic setting; 30 of them had had prior trastuzumab deruxtecan. What they found was that the median real-world time to treatment discontinuation was 6 months, showing still pretty respectable efficacy. So that would tell us with a real-world time to next treatment of 8.4 months, a real-world time to treatment continuation of 6 months, that a tucatinib-based regimen still has efficacy when given after progression on T-DXd.

Also this year at ASCO 2025, just very recently, we saw a study by the UNICANCER group that looked at trastuzumab, tucatinib, and capecitabine when given in a French cohort after progression on T-DXd. They found a real-world median PFS of 4.7 months and a real-world time to next treatment of 5.2 months.

So in both of these studies, what we see with tucatinib-based regimens post-T-DXd is a PFS or time to treatment discontinuation between 5 and 6 months, showing some efficacy. So I do think that the HER2CLIMB tucatinib-based regimen can be an option for our patients after progression on T-DXd.

Other tyrosine kinase inhibitors that we have approved in metastatic HER2-positive breast cancer is a HER2 tyrosine kinase inhibitor called neratinib. Now, neratinib inhibits HER1, HER2, and HER4, so it's more of a pan-HER inhibitor. Because of that, it has slightly more diarrhea than tucatinib. Neratinib has been given with capecitabine, showing promising results. I would say that we favor tucatinib, capecitabine, and trastuzumab at this time as our third-line regimen, given the overall survival and PFS data and the safety/tolerability. So normally we wouldn't give neratinib anymore with capecitabine.

So in TBCRC 022, investigators looked at neratinib given with T-DM1, particularly in patients that had active brain metastasis.

Essentially, what they saw was a CNS objective response rate, depending on the arm, between 29% and 36%, showing pretty respectable efficacy. We also saw an intracranial response rate of about 30% in patients that had prior T-DM1, so still showing efficacy

in patients that had progressed previously on T-DM1.

And so our options for HER2-positive metastatic breast cancer get pretty slim at this juncture after patients have had progression on trastuzumab, pertuzumab, T-DXd, and tucatinib. Particularly for my patients with active CNS disease, I will consider giving them T-DM1 with neratinib.

Because of neratinib's issues with diarrhea, before prescribing it, I would familiarize yourself with the CONTROL trial, which looked at dose escalation of neratinib and also prophylaxis with anti-diarrheals, which really can help patients better tolerate it.

So essentially, what we're seeing in the post-T-DXd setting, we're still seeing activity of tucatinib-based regimens. After tucatinib, I do think neratinib and T-DM1 can be an option for our patients, particularly those who have active CNS disease.

Thank you so much for listening, and I hope this brief review will be useful in your practice.