Recent advances in HER2 directed therapy in HER2 positive advanced breast cancer

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HER2 positive breast cancer is a unique subset of breast cancer driven by HER2 signaling and a key treatment strategy is HER2 inhibition. For the past decade, first-line dual anti-HER2 blockade with pertuzumab and trastuzumab combined with taxanes followed by second-line trastuzumab emtansine has been the conventional treatment algorithm for HER2 positive metastatic breast cancers. Following a long lag of almost 7 years with no new agents approved for HER2+ metastatic breast cancer after the approval of trastuzumab emtansine in 2013, 4 new HER2-directed therapies were approved by the US FDA for advanced HER2 positive breast cancer between December 2019 and December 2020, namely, antibody-drug conjugate trastuzumab deruxtecan, small molecule receptor tyrosine kinase inhibitors tucatinib and neratinib, and HER2 monoclonal antibody margetuximab. Among these, trastuzumab deruxtean is the shining star, trumping trastuzumab emtansine in the DESTINY Breast03 trial, prolonging median progression-free survival by almost 4-fold to ~25 months in patients receiving second-line and beyond treatment, compared to ~7 months with trastuzumab emtansine. This has been practice-changing, prompting both NCCN and ESMO to revise their guidelines to recommend trastuzumab deruxtecan as the preferred second line treatment regimen over trastuzumab emtansine. Tucatinib, on the other hand, stood out among the new agents as the preferred treatment for CNS disease. In the phase III randomized HER2Climb trial that compared trastuzumab + capecitabine with trastuzumab + tucatinib + capecitabine in patients receiving third-line and beyond treatment, patients with active brain metastases were enrolled. Impressive CNS objective response rates were observed in almost half the patients with active measurable brain metastases that was durable for at least 6 months in three-quarters of responders. As CNS progression is a common problem in HER2 positive metastatic breast cancer, tucatinib now offers a viable and effective systemic therapy option in patients with active CNS disease. The approval and availability of these new agents has expanded the treatment options for patients with HER2+ metastatic breast cancer with clinically meaningful impact on survival and quality of life.