# Major Strides in HER2 Blockade for Metastatic Breast Cancer

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Breast cancer that is characterized by amplification or overexpression of human epidermal growth factor receptor 2 (HER2) accounts for 15 to 20% of all forms of the disease. The advent of HER2-targeted drugs, such as trastuzumab, pertuzumab, lapatinib, and the antibody-drug conjugate trastuzumab emtansine, has revolutionized the treatment of both early-stage and metastatic HER2-positive breast cancer.[1-4] The increasing availability of HER2-targeted agents has led to improved outcomes for patients with HER2-positive metastatic breast cancer, as reported in a study in which overall survival rose from a median of 38.7 months to 51.1 months from 2008 through 2012.[5]

The standard first-line systemic treatment for HER2-positive metastatic breast cancer consists of trastuzumab plus pertuzumab combined with a taxane, and trastuzumab emtansine is the recommended second-line therapy. However, there is no single accepted standard for third-line therapy and beyond, and currently available options provide only modest efficacy. In addition, as survival of patients with HER2-positive metastatic breast cancer is improving with the clinical adoption of effective systemic therapies, the central nervous system (CNS) is increasingly becoming a sanctuary site, with brain metastasis occurring in almost 50% of patients.[6] Although HER2-targeted systemic therapies have led to great strides in the treatment of extracranial disease, currently available agents have shown very limited activity against CNS disease.

In this issue of the *Journal*, investigators present the results of two clinical trials that evaluated new anti-HER2 agents as third-line or later therapy for HER2-positive metastatic breast cancer.[7,8] In the first article, Murthy et al. report the results of the HER2CLIMB trial, in which 612 patients with HER2-positive metastatic breast cancer who had been previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine were randomly assigned to receive trastuzumab and capecitabine with or without tucatinib. Tucatinib is an oral HER2 tyrosine kinase inhibitor that is highly selective for the kinase domain and, unlike other HER2 tyrosine kinase inhibitors, has minimal inhibition of epidermal growth factor receptor, which may lead to a more favorable safety profile. According to the trial design, HER2CLIMB enrolled a large proportion of patients with brain metastases (47%, which included 28% who had treated brain metastases and 19% who had progressive or untreated brain metastases).

The median duration of progression-free survival was 7.8 months in the tucatinib-combination group and 5.6 months in the placebo-combination group, corresponding to 46% lower risk of disease progression or death in the tucatinib-combination group (hazard ratio, 0.54; $P<0.001$). The median duration of overall survival was 21.9 months in the tucatinib-combination group and 17.4 months in the placebo-combination group, corresponding to 34% lower risk of death in the tucatinib-combination group (hazard ratio, 0.66; $P=0.005$). In an important finding, the benefit of tucatinib was maintained in patients with brain metastases, with a median duration of progression-free survival of 7.6 months in the tucatinib-combination group and 5.4 months in the placebo-combination group (hazard ratio for disease progression or death, 0.48; $P<0.001$). Whether the observed CNS efficacy is a result of intracranial response in progressive or untreated disease, a delay in or prevention of new brain lesions in patients with treated disease, or both remains to be seen. Unlike the experience with previous tyrosine kinase inhibitor combinations, in which unacceptable side effects have been a concern, only 5.7% of the patients discontinued tucatinib because of adverse events. The remarkable results of the HER2CLIMB trial are bound to be practice changing for patients with HER2-positive metastatic breast cancer who have undergone previous therapy with trastuzumab, pertuzumab, and trastuzumab emtansine, and additional details regarding CNS activity will further refine the placement of tucatinib in treatment algorithms.

In the second article, Modi et al. report the results of DESTINY-Breast01, an open-label, single-group, phase 2 study of trastuzumab deruxtecan

(DS-8201). Trastuzumab deruxtecan is an antibody drug conjugate with a potent topoisomerase I inhibitor as the payload. It has a higher drug-to-antibody ratio than trastuzumab emtansine (8 to 1 vs. 3 to 1) and a highly permeable payload that potentially allows bystander cytotoxic effects on neighboring tumor cells. The patients who were enrolled in the DESTINY-Breast01 study had undergone a median of six lines of prior therapy for advanced HER2-positive breast cancer. Trastuzumab deruxtecan monotherapy led to an impressive objective response rate of 60.9% and a median duration of progression-free survival of 16.4 months in a heavily pretreated population in which 100% of the patients had received a previous antibody-drug conjugate (trastuzumab emtansine). The trial included 13% of patients with treated brain metastases who had a median duration of progression-free survival similar to that of the entire trial population (18.1 months). Enthusiasm for this tremendous antitumor activity was dampened somewhat by the substantial risk (13.6%) of interstitial lung disease, which led to death in 2.2% of the patients. The exact mechanism leading to pulmonary toxicity is not clear. It is hoped that close monitoring, thorough assessment of potential risk factors, and the early initiation of appropriate diagnostic and treatment measures in future trials will provide further guidance on ways to reduce the incidence and severity of this toxic effect.

Another recent study of a new anti-HER2 therapy in a heavily pretreated population is the SOPHIA trial, in which the substitution of trastuzumab with margetuximab (a novel Fc-engineered HER2 antibody with increased affinity for the Fc gamma receptor CD16A) in a chemotherapy backbone led to a modest improvement in progression-free survival at the time of the September 2019 data cutoff (5.7 months vs. 4.4 months; hazard ratio, 0.71; P<0.001), with exploratory analyses suggesting that the Fc receptor CD16A genotype may influence the efficacy of margetuximab.[9]

In summary, the HER2CLIMB and DESTINY-Breast01 trials represent major advances in the treatment of HER2-positive metastatic breast cancer and mark the beginning of the next frontier of highly effective HER2-targeted agents. On December 20, 2019, the Food and Drug Administration (FDA) approved the use of trastuzumab deruxtecan in patients with unresectable or metastatic HER2-positive breast cancer who have undergone at least two anti-HER2 regimens.[10] The submission to the FDA of a biologics license application for tucatinib is expected this year. In the near future, as the oncology community and patients are able to take advantage of these novel drugs, the selection of the most effective agent or combination in the clinic will be based on the status of CNS disease, the toxicity profile, prior treatment, the preference and coexisting illnesses of the patients (including risk factors for interstitial lung disease and the choice of single vs. multiple drugs), and perhaps genotype. Furthermore, important consideration will also have to be given to cost and access. There are several countries in the world where trastuzumab emtansine is not yet available, and efforts are needed to improve access to newer, presumably more expensive HER2-targeted drugs. In ongoing trials (ClinicalTrials.gov numbers, NCT03523585, NCT03529110, and NCT03975647), investigators are evaluating the initiation of tucatinib and trastuzumab deruxtecan in earlier lines of therapy, when these agents may have an even greater effect on the lives and disease course of patients with HER2-positive breast cancer.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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# ANCA-Associated Vasculitis — Refining Therapy with Plasma Exchange and Glucocorticoids

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Plasma exchange has been a mainstay of induction therapy for patients with antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis who have rapidly progressive glomerulonephritis or diffuse alveolar hemorrhage.[1-3] Clinical data, in vitro data, and data from studies in animals have shown that ANCAs are pathogenic.[4] Plasma exchange rapidly depletes pathogenic ANCAs and theoretically should diminish vascular injury and end-organ damage and hasten resolution of disease.

In this issue of the *Journal*, Walsh et al. report the results of the PEXIVAS trial, a very large randomized clinical trial involving patients with ANCA-associated vasculitis (704 patients with a median follow-up of 2.9 years).[5] The trial assessed the efficacy of plasma exchange when added to current standard induction therapy in patients with kidney injury (an estimated glomerular filtration rate of <50 ml per minute per 1.73 $m^2$ of body-surface area) or pulmonary hemorrhage. A secondary aim was to assess the noninferiority of a reduced-dose regimen of oral glucocorticoids to a standard-dose regimen. The use of plasma exchange did not result in a lower incidence of the primary composite outcome of end-stage kidney disease or death from any cause. Reduced glucocorticoid dosing was noninferior to standard dosing and resulted in fewer complications related to infections.

Previous studies have suggested that plasma exchange reduces the risk of end-stage kidney disease but does not necessarily reduce the risk of death.[6] A previous study that compared plasma exchange with intravenous pulse methylprednisolone as induction therapy in patients with ANCA-associated vasculitis who had severe kidney injury showed that plasma exchange reduced the risk of dependence on dialysis by 50% at 12 months.[2] The PEXIVAS trial included patients with a broader range of severity of kidney injury than those in previous studies of plasma exchange, and plasma exchange had no significant effect on the primary composite outcome. The trial has limitations that are potentially of clinical importance. A kidney biopsy was not required for entry into the trial. Patients with ANCA-associated vasculitis frequently have a relapsing and remitting course; thus, diffuse tubulointerstitial and glomerular scarring can occur before initial diagnosis. At the time of entry, severe ANCA-induced kidney disease that caused an estimated glomerular filtration rate of less than 50 ml per minute per 1.73 $m^2$ could have resulted from active inflammatory injury, chronic sclerotic injury, or both. Without baseline biopsy data, the proportion of patients who had kidney dysfunction caused by active inflammation, which may respond to immunomodulatory therapy, as compared with chronic sclerosis, which would not respond to this therapy, is unknown. A subgroup of patients with aggressive kidney disease with minimal scarring may benefit from plasma exchange. Aside from this caveat, the results of the PEXIVAS trial show that plasma exchange should not be included in standard induction therapy for patients with ANCA-associated vasculitis who have kidney dysfunction.

Another major current indication for plasma exchange in patients with ANCA-associated vasculitis is pulmonary hemorrhage.[3] In the current trial, 191 patients had pulmonary hemorrhage;