Trastuzumab (Herceptin) has dramatically changed the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer. A phase III trial of firstline trastuzumab with various chemotherapy regimens compared with chemotherapy alone demonstrated a significant improvement in survival (25.1 vs 20.3 months) and overall response (50% vs 32%).

In their article, Dr. Murphy and Dr. Fornier point out that a large volume of preclinical and clinical research has focused on identifying mechanisms of resistance to trastuzumab. Targeting the HER-2 pathway and other approaches may enhance the clinical benefit from trastuzumab and overcome potential resistance. The authors present a detailed review of other novel agents that may provide further therapeutic options in patients with HER2-positive breast cancer.

The results of the pivotal phase III trial that investigated the addition of lapatinib (Tykerb) to capecitabine (Xeloda) in patients with HER2-positive advanced breast cancer are discussed by the authors. The results of this trial led to US Food and Drug Administration approval of lapatinib in combination with capecitabine for treatment of patients with metastatic HER2-positive breast cancer that progressed after treatment with trastuzumab, anthracyclines, and taxanes. Lapatinib in combination with trastuzumab has demonstrated an improvement in overall survival compared with lapatinib alone in patients who have progressed on prior trastuzumab-containing regimens for metastatic breast cancer. As the authors point out, this study confirms a role for combined HER2 blockade.

Other trials are evaluating lapatinib in the adjuvant and neoadjuvant settings. A phase III adjuvant trial is currently ongoing, ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation), in patients with HER2-positive, early breast cancer. In Design 1, all (neo)adjuvant chemotherapy is completed prior to administration of the study treatments. In Design 2, all anthracycline-based (neo)adjuvant chemotherapy is completed prior to administration of the study treatments, while taxane is given concurrently with the study treatments. Within each design, patients are randomized to one of four treatment arms: 1) trastuzumab alone; 2) lapatinib alone; 3) trastuzumab followed by lapatinib; or 4) lapatinib in combination with trastuzumab.

Neo ALTTO (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) is a companion trial to ALTTO that will evaluate the effectiveness of lapatinib as neoadjuvant therapy for HER2-positive breast cancer. This trial compares the efficacy of neoadjuvant lapatinib plus paclitaxel, vs trastuzumab plus paclitaxel, vs concomitant lapatinib and trastuzumab plus paclitaxel given as neoadjuvant treatment. After surgery, patients receive three courses of adjuvant FEC (fluorouracil [5-FU], epirubicin, and cyclophosphamide) followed by the same targeted therapy from randomization to complete 1 year of anti-HER2 therapy. NSABP B-41 is evaluating lapatinib in the neoadjuvant setting for HER2-positive breast cancer. This study compares the following regimens: AC (doxorubicin [Adriamycin] and cyclophosphamide) followed by paclitaxel plus trastuzumab and lapatinib, AC followed by paclitaxel plus lapatinib, and AC followed by paclitaxel plus trastuzumab given before surgery to patients with HER2-positive breast cancer. All patients will receive postoperative trastuzumab continuing until 1 year after administration of the first preoperative targeted therapy (trastuzumab and/or lapatinib) dose.

The authors note that the results of pertuzumab (Omnitarg) in combination with trastuzumab demonstrated an overall response rate of 24.2% in patients with metastatic breast cancer progressing after prior trastuzumab. A phase III study to evaluate first-line trastuzumab and docetaxel (Taxotere) with or without pertuzumab (CLEOPATRA trial) is ongoing. The authors also discuss the results from studies done with trastuzumab-DM1 (T-DM1). An ongoing
phase III trial is currently evaluating T-DM1 in comparison with the combination of capecitabine and lapatinib in patients with HER2-positive locally advanced or metastatic breast cancer who have received prior trastuzumab-based therapy.\(^\text{15}\)

A phase II study evaluating the combination of trastuzumab and bevacizumab (Avastin) as first-line therapy in HER2-positive breast cancer has demonstrated that this combination is active, with a clinical response rate of 48%.\(^\text{16}\) As the authors explain, this combination with chemotherapy is currently being evaluated in the adjuvant setting. A phase III adjuvant trial is examining whether regimens of chemotherapy plus trastuzumab plus bevacizumab improve outcomes relative to regimens of chemotherapy plus trastuzumab.\(^\text{17}\)

Trastuzumab is the foundation of treatment for women with HER2-positive breast cancer, and has been a success in the adjuvant and metastatic setting. The limitations of trastuzumab have also become apparent, however. Mechanisms of trastuzumab resistance have been discussed in this review article. Multifaceted strategies that target these alternative pathways are needed to overcome these mechanisms of resistance. The continued development of novel agents demonstrates promising treatment approaches for the future.

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