

EDITORIALS



HER2 Therapy — An Abundance of Riches

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Human epidermal growth factor receptor 2 (HER2)-positive breast cancer is a distinct subset of breast cancer characterized by overexpression of the HER2 protein. Clinically, HER2-positive tumors are associated with a more aggressive phenotype and poor outcomes. With the introduction of trastuzumab, a humanized monoclonal antibody targeting HER2, significant improvements in survival were observed in patients with HER2-positive metastatic breast cancer and in patients with early-stage disease.^{1,2} Despite the practice-changing impact of trastuzumab and the substantial improvement in outcomes, patients with HER2-positive metastatic breast cancer ultimately die from the disease.

A number of strategies have been developed to deal with progressive HER2-positive metastatic breast cancer. In most cases, trastuzumab is administered with a chemotherapy agent. At the time of disease progression, clinicians frequently continue trastuzumab but change to an alternative chemotherapy agent. This strategy was widely adopted before there were data to prove its value.³ Lapatinib, an oral, small-molecule, tyrosine kinase inhibitor binding both HER1 and HER2, was the second anti-HER2 agent approved for clinical use. The combination of lapatinib and capecitabine, as compared with capecitabine alone, improved progression-free survival and the response rate.⁴ Finally, a dual targeting approach with a combination of trastuzumab and lapatinib improved progression-free survival as compared with lapatinib alone in patients with metastatic breast cancer who had not had a response to trastuzumab.⁵ Any of these therapeutic approaches would be considered to be appropriate for a patient with progressive disease, but there is not one approach that is convincingly superior

to another, and these options can be used in sequence. The clinical dogma is to leverage the HER2 status of the tumor and continue anti-HER2 therapy, in some form, indefinitely. Although these strategies can confer benefit to some patients after disease progression, none of these strategies are curative.

The human epidermal growth factor receptor (EGFR) family is composed of four members: HER1 or EGFR, HER2, HER3, and HER4. Signal transduction occurs as a result of receptor dimerization between members of the HER family either as heterodimerization (different receptors) or homodimerization (two of the same receptor). The HER2–HER3 heterodimer is particularly critical for activation of the phosphatidylinositol 3-kinase (PI3K)–Akt–mammalian target of rapamycin (mTOR) pathway, which in turn is able to influence other critical pathways driving angiogenesis, cell survival, migration, apoptosis, and proliferation^{2,6} (Fig. 1).

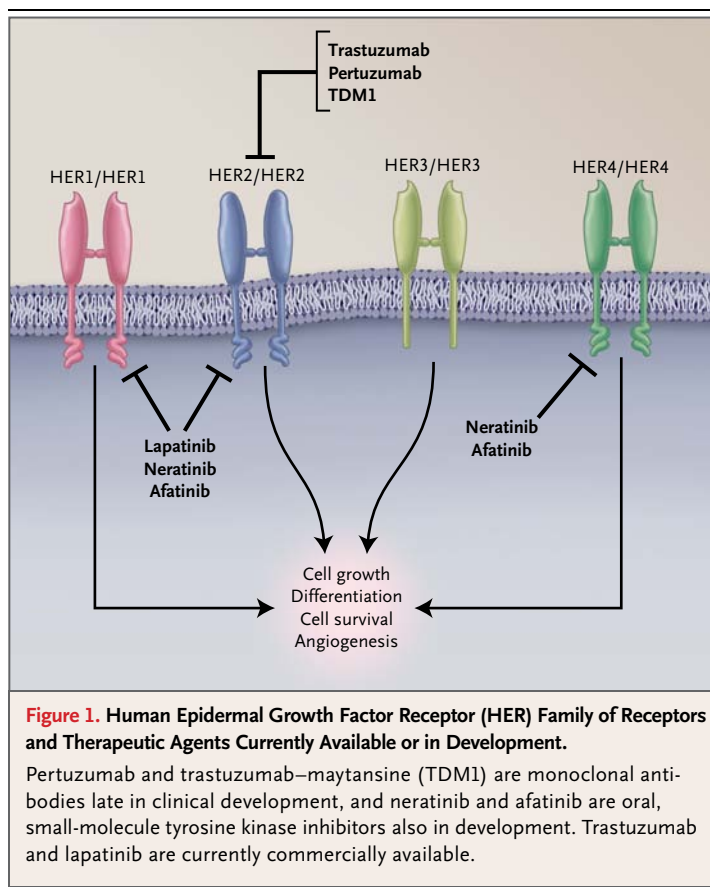
Pertuzumab is a humanized monoclonal antibody that binds to a distinct epitope of HER2 (domain II); trastuzumab binds to domain IV.⁶ The binding of pertuzumab to HER2 blocks dimerization with other potential HER receptor partners, resulting in decreased downstream signaling. As a single agent, pertuzumab is associated with minimal cardiac toxic effects but only modest antitumor activity.⁷ Preclinical studies showed that there was synergy between pertuzumab and trastuzumab. Phase 2 trials confirmed that the combination of trastuzumab and pertuzumab produced responses in patients who had previously had disease progression while receiving trastuzumab-based therapy.⁸ More recently, the Neoadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation (NEOSPHERE),

a study of neoadjuvant therapy in patients with newly diagnosed HER2-positive breast cancer, showed a markedly higher pathologic complete response rate with the triple therapy of docetaxel, pertuzumab, and trastuzumab than with docetaxel and trastuzumab or docetaxel and pertuzumab.⁹ Interestingly, a fourth treatment group in the NEOSPHERE study received combination therapy with pertuzumab and trastuzumab without any chemotherapy. The antibody combination produced a pathologic complete response rate of 17%,⁹ raising the prospect of effective, nonchemotherapy approaches to HER2-positive disease if predictive markers of pathologic complete response rate could be identified.

Baselga and colleagues now report the results of the Clinical Evaluation of Pertuzumab and Trastuzumab study (CLEOPATRA; ClinicalTrials.gov number, NCT00567190), a randomized, phase 3 trial in patients with HER2-positive metastatic breast cancer receiving first-line therapy with docetaxel and trastuzumab or docetaxel, trastuzumab, and pertuzumab.¹⁰ Integrating pertuzumab into the treatment regimen improved progression-free survival by 6 months. An overall survival advantage has not been confirmed (though a strong trend is suggested).

The challenge to clinicians going forward will be how best to use the many HER2 therapies that are in development. On the basis of the data from the CLEOPATRA trial, pertuzumab would logically be used in combination with trastuzumab and chemotherapy as first-line therapy of HER2-positive metastatic breast cancer. Trastuzumab–maytansine (DM1) (TDM1; Genentech) is an immunoconjugate agent that combines trastuzumab with DM1, an antimicrotubule cytotoxic agent. TDM1 has significant antitumor activity in patients with HER2-positive metastatic breast cancer who had progressive disease while they were receiving anti-HER2 therapy and chemotherapy.¹¹ A large, randomized, phase 3 clinical trial (EMILIA, NCT00829166) is comparing TDM1 with capecitabine–lapatinib in patients with HER2-positive metastatic breast cancer who have received pretreatment with trastuzumab. Smaller phase 2 trials have also shown the antitumor activity and acceptable side-effect profile of pertuzumab–TDM1 therapy (NCT00875979 and MARIANNE, NCT01120184).

Several oral, small-molecule, tyrosine kinase inhibitors are also in development. Afatinib (BIBW



2992; Boehringer Ingelheim) is an oral, irreversible HER family inhibitor targeting EGFR (HER1), HER2, and HER4. Initial reports confirm the antitumor activity of afatinib alone or with chemotherapy in patients who have had disease progression while they were receiving other anti-HER2 therapy.¹² Neratinib (HKI-272; Pfizer and Puma Biotech) is an oral, irreversible inhibitor of EGFR (HER1), HER2, and HER4 that has shown substantial single-agent activity in patients who have never received treatment with trastuzumab, as well as in patients who have already received trastuzumab therapy.¹³

Although HER2-positive breast cancer accounts for only 25 to 30% of breast cancers, the increasing therapeutic options provide hope to patients and considerable challenges for clinicians. For patients with metastatic breast cancer who have progressive disease, there may be numerous anti-HER2 agents available that could be used in combination or in sequence. In patients with early-stage breast cancer, more effec-

tive anti-HER2 agents as adjuvant therapies may translate into metastatic disease developing in fewer patients. Given the success of the pivotal trials of adjuvant trastuzumab therapy, clinical trials of adjuvant therapies, which are already large and expensive, will by necessity require even more subjects to detect small differences with a new agent. These are challenges that reflect the rewards of successful translational research, challenges we hope to face with other subsets of breast cancer.

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How Much Atrial Fibrillation Is Too Much Atrial Fibrillation?

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Modern cardiac pacemakers and defibrillators function as permanently implanted cardiac monitors, detecting atrial and ventricular arrhythmias. Although the principal purpose of collecting this information is to manage the patient's cardiac rhythm, these data can also be used to detect and study clinically inapparent arrhythmias and their consequences. In this issue of the *Journal*, Healey and coworkers¹ report the results of a prospective study involving patients in whom a pacemaker or defibrillator had recently been implanted (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial [ASSERT])^{1,2}; ClinicalTrials.

gov number, NCT00256152). This study had two purposes: to determine whether asymptomatic episodes of atrial fibrillation were associated with stroke and to determine whether a programmable algorithm to maintain a paced atrium reduced the risk of atrial fibrillation. The programming strategy did not reduce the risk of atrial fibrillation, possibly because atrial pacing may be arrhythmogenic.³ As a result, the report focuses on the first, and possibly more intriguing, question.

A total of 2580 patients 65 years of age or older with hypertension, in whom a pacemaker (95% of the patients) or defibrillator (5%) had recently been implanted, were enrolled in 23