Published in final edited form as:

Hosp Pract (1995). 2012 October ; 40(4): 7–15. doi:10.3810/hp.2012.10.997.

Targeting the Human Epidermal Growth Factor Receptor 2 Pathway in Breast Cancer

Senthilkumar Damodaran, MD, PhD¹ and Erin M. Olson, MD¹

¹James Cancer Hospital and Solove Research Institute, The Ohio State University Comprehensive Cancer Center, Columbus, OH

Abstract

The discovery of amplification of human epidermal growth factor receptor 2 (HER2), a member of the epidermal growth factor receptor family, was an important milestone in our understanding of the biology of breast cancers. This heralded the discovery of trastuzumab, a humanized monoclonal antibody targeting HER2. Trastuzumab is the foundation of treatment of HER2-positive breast cancers, demonstrating dramatic responses in patients with metastatic disease. Unfortunately, most tumors will inevitably develop resistance to trastuzumab, necessitating the need for alternate HER2-directed therapeutic approaches. Recent advances in our understanding of the interaction between HER2 and other members of the epidermal growth factor receptor family have led to identification of newer agents, resulting in the expansion of the clinical armamentarium of available agents for the treatment of HER2-positive tumors. In this article, we review the molecular biology of the ERbb receptor family, the use of HER2-targeted agents in early and advanced breast cancer, and the next-generation anti-HER2 agents that are currently in clinical evaluation.

Keywords

HER2; trastuzumab; breast cancer; pertuzumab; T-DM1

Introduction

The human epidermal growth factor receptor 2 (HER2) ERbb2 gene is amplified in approximately 25% of breast cancers, and encodes a 185-kDa transmembrane protein with tyrosine kinase activity.^{1,2}

Overexpression of HER2 results in augmented signaling through downstream phosphatidylinositol-3 kinase (PI3K) mitogen-activated protein kinase (MAPK) pathways. This results in activation of proto-oncogenes and transcriptional factors, such as fos, jun, myc, and SP1, leading to increased cell survival and proliferation.² Characteristics of HER2-amplified tumors include increased proliferation rates and a propensity for central nervous system (CNS) and visceral metastasis.^{3–5} Trastuzumab, the humanized monoclonal antibody targeting the extracellular domain of the HER2 receptor, has revolutionized the treatment of HER2-positive breast cancer by improving overall survival (OS) rates for patients with local-regional and advanced disease. Previously considered to have a worse prognosis, the

© Hospital Practice

Correspondence: Erin M. Olson, MD, B407 Starling Loving Hall, 320W. 10th Ave., Columbus, OH 43210. Tel: 614-366-8541, erin.olson@osumc.edu.

Conflict of Interest Statement

Senthilkumar Damodaran, MD, PhD and Erin M. Olson, MD disclose no conflicts of interest.

clinical outcomes of patients with HER2-amplified breast cancer in the post-trastuzumab era now resemble those of patients with HER2-negative disease.^{6,7}

HER2 belongs to the ERbb group of the protein kinase superfamily, which also includes epidermal growth factor receptor (EGFR [ERbb1]), HER3 (ERbb3), and HER4 (ERbb4).^{2,8} Although these receptors are important mediators of normal cell growth and development of various tissues, their activation has been associated with the development and progression of several malignancies.¹ Members of the ERbb family of receptors contain 3 functional domains: an extracellular domain for ligand binding, a transmembrane domain, and an intracellular tyrosine kinase domain (Figure 1). Unlike other ERbb family members that require ligand binding for activation, signaling through the HER2 network occurs in the absence of a known ligand.^{2,9} The HER2 monomer exists in activated conformation and is the preferred dimerization partner for the other members of the ERbb family, especially HER3.^{1,9} Receptor dimerization is an essential first step to propagate an intracellular signal and occurs through homodimerization (between 2 HER2 molecules) or heterodimerization (between HER2 and other ERbb receptors). When the HER2 gene is amplified, dimerization results in activation of a potent cell signaling cascade predominantly through the PI3K and MAPK pathways, leading to cell proliferation, angiogenesis, and tumor growth.²

HER2-amplified breast cancer is a classic example of oncogene addiction, as tumors that overexpress HER2 continue to demonstrate dependency on this signaling pathway despite evidence of tumor growth on a HER2-targeted therapy.¹⁰ In the contemporary oncology clinic, the therapeutic paradigm for this disease should always include some derivation of HER2 inhibition, and recent data suggest that targeting the HER2 protein via a dual anti-HER2 approach may be superior to monotherapy alone.^{11,12} Recently, the clinician's armamentarium of US Food and Drug Administration (FDA)-approved drugs has increased, allowing for multiple therapeutic choices in both the first-line setting and at the time of tumor progression. Additionally, the HER2 pipeline is filled with novel agents that target both the HER2 molecule and known resistance mechanisms. While oncologists and patients alike are hopeful regarding these therapeutic advances, the optimal order and duration of each regimen are not well studied and may vary between patients. Better understanding of the mechanisms of action, the clinical applications, and the potential toxicities associated with each of these agents may assist clinicians in navigating through the plethora of anti-HER2 treatment options.

Trastuzumab

Originally approved by the FDA in 1998 for metastatic disease, trastuzumab is the cornerstone of treatment for HER2-positive breast cancer and is a recombinant humanized monoclonal antibody that binds with high affinity to the extracellular juxtamembrane domain IV of HER2 (Figure 1). Trastuzumab is the standard of care for both localized and metastatic disease, demonstrating improvements in disease-free survival and overall survival.^{13,14} Multiple mechanisms underlying the antitumor activity of trastuzumab have been proposed and include antibody-dependent cell-mediated cytotoxicity, inhibition of HER2 receptor dimerization, blockade of HER2 receptor extracellular domain cleavage, decrease in angiogenesis, inhibition of DNA repair, induction of cell-cycle arrest, and apoptosis.^{15,16}

For patients with local–regional disease, the current standard of care is 1 year of adjuvant trastuzumab therapy.¹⁷ Trastuzumab may be administered after the completion of doxorubicin and cyclophosphamide in combination with paclitaxel or docetaxel, or may be concurrently administered with carboplatin and docetaxel (Table 1)^{13,18} In the metastatic setting, Slamon et al¹⁴ demonstrated in a pivotal phase 3 trial that trastuzumab in

combination with chemotherapy significantly improved tumor response (50% vs 32%; $P < 0.001$) and median OS rate (25.1 vs 20.3 months; $P = 0.046$) when compared with chemotherapy alone as first-line treatment. Further studies highlighted the dependency of these tumors on the HER2 pathway, as administration of trastuzumab-based regimens after progression on trastuzumab continued to induce durable responses.¹⁹ Extended obstruction of HER2 signaling with sequential trastuzumab-based therapy is critical to blocking the tumor's primary mechanism of growth and survival, and removing anti-HER2 therapy at progression results in an inferior patient outcome.^{19,20}

Overall, trastuzumab is well tolerated with minimal acute side effects. Although no significant differences in clinical efficacy between the anthracycline and nonanthracycline regimens can be discerned, the lower risk of cardiotoxicity and leukemia favors the use of a nonanthracycline-based regimen (docetaxel and carboplatin) with trastuzumab.²¹ The reported incidence of cardiotoxicity ranges from 2% to 4% of exposed patients, particularly when used in conjunction with an anthracycline-containing regimen.²¹ Left ventricular dysfunction secondary to trastuzumab is thought to be mediated through inhibition of HER2 signaling and angiotensin 2–induced activation of reactive oxygen species in cardiac myocytes.²² Recognized risk factors for trastuzumab-induced cardiotoxicity include hypertension, age > 60 years, and an ejection fraction of < 55% at baseline.²³ In most cases, cardiac dysfunction related to trastuzumab is asymptomatic and decreases in ejection fraction are reversible.

HER2 overexpression has been shown to confer intrinsic resistance to endocrine therapy, signifying the interaction between hormone receptors and the EGFR family.²⁴ Plasma membrane–associated estrogen receptors (ERs) can activate HER2 through an increase in second messengers, such as cyclic adenosine monophosphate. Conversely, members of the MAPK pathway and Akt, a downstream target of HER2, can phosphorylate ERs, leading to ligand-independent activation.⁴ This understanding of HER2–ER cross-talk has led to combined use of targeted agents.²⁵ The Trastuzumab and Anastrozole Directed Against ER-Positive HER2-Positive Mammary Carcinoma (TANDEM) phase 3 trial evaluated the combination of trastuzumab and anastrozole, an aromatase inhibitor (AI), in the treatment of HER2- and ER-positive metastatic breast cancers.²⁶ Combined therapy provided an improvement in progression-free survival (PFS), albeit with an increase in adverse effects.²⁶ Moreover, the response achieved was inferior to what would be expected with trastuzumab and chemotherapy.⁴ An indirect approach, using a downstream target of HER2, mammalian target of rapamycin (mTOR), was validated by the recently published Breast Cancer Trials of Oral Everolimus (BOLERO-2).²⁷ This multicenter phase 3 trial evaluated everolimus, an mTOR inhibitor, in combination with exemestane, a steroidal AI, and showed an improvement in PFS in patients with ER-positive metastatic breast cancers, previously treated with a nonsteroidal AI. Therefore, combined targeting of ER and HER2 signaling pathways has the potential to ameliorate resistance to endocrine therapy.²⁸

Although trastuzumab remains one of the most effective therapies for metastatic HER2-amplified patients, a subset will present with primary refractory disease and most initial responders will develop progression. Several mechanisms for inherent or acquired resistance have been proposed, including inefficient trastuzumab binding, compensatory cross-talk with other ERbb receptors, as well as altered expression of downstream mediators of signaling pathways.^{29,30} For example, proteolysis of the extracellular domain of HER2 by metalloproteases can lead to expression of the truncated and constitutively active form, p95HER2. This protein lacks the binding site for trastuzumab but retains the intracellular kinase activity.³¹ Other methods that decrease trastuzumab efficacy include interactions with other ERbb family members (eg, HER3) or their ligands and decreased levels of the tumor suppressor PTEN molecule.^{32,33} A better understanding of these mechanisms has led

to the development of next-generation anti-HER2 agents that are specifically designed to ameliorate or bypass tumor resistance to trastuzumab.

Lapatinib

Lapatinib is an oral, small-molecule, reversible tyrosine kinase inhibitor that targets the adenosine triphosphate binding site located on the intracellular kinase domains of both EGFR and HER2. Preclinical data suggest that elevated neuregulin-1 expression and activation of HER3 may predict response to lapatinib.³⁴ The activity of lapatinib is distinctly different from the mechanisms of action of trastuzumab and does not appear to be dependent on known mechanisms of trastuzumab resistance, including PTEN, p95HER2, or IGF1R status, providing preclinical rationale for the use of this agent in patients with disease progression on trastuzumab-based therapy.¹¹

The single-agent activity of lapatinib is modest in the trastuzumab-refractory setting,³⁵ and results in a shorter PFS compared with trastuzumab when administered with taxane-based chemotherapy as first-line treatment for metastatic disease (median PFS, 8.8 months for lapatinib vs 11.4 months for trastuzumab; hazard ratio [HR], 1.48; 95% CI, 1.15–1.92; $P = 0.003$).³⁶ Lapatinib received FDA approval when it improved PFS in combination with capecitabine compared with chemotherapy alone in patients previously treated with anthracycline-, taxane-, and trastuzumab-containing regimens (median PFS, 8.4 months with lapatinib/capecitabine vs 4.4 months with capecitabine alone; HR, 0.49; 95% CI, 0.34–0.71; $P < 0.001$).²⁰

Importantly, the effect of lapatinib is amplified when administered concurrently with trastuzumab. Based on preclinical data demonstrating that dual HER2 blockade produces a synergistic antitumor effect in the absence of cytotoxic chemotherapy,³⁷ a large phase 2 trial testing lapatinib and trastuzumab improved survival in patients with progression on trastuzumab (median OS rate, 14 vs 9.5 months; HR, 0.74; 95% CI, 0.57–0.97; $P < 0.026$).^{11,38} The main toxicities associated with this therapy are grade 3 diarrhea^{38,39} and alteration of liver enzymes³⁹; however, an increased risk of cardiac disease was not observed despite similar mechanisms of action.^{40,41} The biologic basis for the enhanced benefit and suitable toxicity profile of dual HER2 therapy is likely related to the distinct and complementary mechanisms of action of each HER2-targeted agent. Interestingly, lapatinib has been shown to retain activity in tumors that overexpress p95HER2, the truncated form of HER2, expression of which has been associated with resistance to trastuzumab.³¹ Clinical data from a targeted approach (in the absence of a cytotoxic agent) corroborates the reliance of HER2-amplified breast cancer on this oncogenic pathway and supports the hypothesis that dual HER2-targeted therapy leads to synergistic crippling of the primary oncologic driver in this disease.

Combined lapatinib and trastuzumab was the first dual anti-HER2 regimen tested in the trastuzumab-refractory population, resulting in a critical paradigm shift in the treatment of HER2-positive breast cancer. Prior to this novel discovery, HER2-based therapy required a chemotherapy backbone to cause cancer regression. With ongoing studies, it is hypothesized that lapatinib and trastuzumab will produce similar results in patients with metastatic cancer who are trastuzumab naïve.⁴² Given the promising data provided in patients with advanced disease, dual HER2 inhibition was tested and further validated in patients with local-regional HER2-positive breast cancer. The recently reported Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (Neo ALTTO) study has shown that use of lapatinib in combination with trastuzumab and paclitaxel in the neoadjuvant setting resulted in a significant improvement in the pathological response rate (51.3% vs 29.5%; $P = 0.0001$).³⁹ Comparably, the NSABP-41 trial evaluated doxorubicin and cyclophosphamide followed by

paclitaxel plus trastuzumab or lapatinib or both given prior to surgery. Preliminary findings showed a nonsignificant increase in the pathological response rate compared with trastuzumab plus chemotherapy in patients with operable HER2-positive breast cancer (62.0% vs 52.5%; $P = 0.095$).⁴³ Data from these studies suggest that dual inhibition may be superior to trastuzumab alone in patients with local disease; however, the impact of this regimen on breast cancer recurrence or survival remains unclear.

Pertuzumab

HER3 has recently sparked the attention of the breast cancer community, as blockade of HER2:HER3 heterodimer formation with pertuzumab has dramatically impacted the clinical outcome of patients with HER2-positive metastatic breast cancer. The HER2:HER3 complex transmits pro-malignant signals through the MAPK, protein kinase C, and Akt pathways, resulting in increased cell growth and survival.² Pertuzumab is the recombinant monoclonal antibody that binds to the dimerization arm (extracellular domain II) of HER2, resulting in the disruption of HER2:HER3 heterodimer and diminished downstream signaling.⁴⁴ In preclinical models, this novel antibody impedes tumor growth as significantly as trastuzumab,⁴⁵ and the combination of pertuzumab with trastuzumab produces enhanced antitumor activity compared with either agent alone.⁴⁵

Similar to other HER2-targeted agents, pertuzumab demonstrates only modest activity as a single agent.⁴⁶ Emphasizing the impact of dual HER2 inhibition, pertuzumab combined with trastuzumab in the clinical setting results in dramatically superior outcomes when compared with trastuzumab-based regimens alone. When studied as first-line therapy in the phase 3 Study to Evaluate Pertuzumab + Trastuzumab + Docetaxel vs Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-Positive Metastatic Breast Cancer (CLEOPATRA), the addition of pertuzumab to trastuzumab and docetaxel significantly prolonged PFS (18.5 vs 12.4 months; HR, 0.62; 95% CI, 0.51–0.75; $P < 0.001$) compared with trastuzumab and docetaxel.⁴⁶ Results from this trial led to FDA approval of pertuzumab (Perjeta™, Genentech). Although the OS data are not mature, the interim analysis (after 43% of pre-specified events, with a median follow-up of 19.3 months) showed a strong trend in favor of the combination, with more deaths in the control group (HR, 0.64; 95% CI, 0.47–0.88; $P = 0.005$).¹² Given the strength of the results of CLEOPATRA, pertuzumab administered with trastuzumab and chemotherapy is the new standard of care for first-line treatment of patients with HER2-positive metastatic breast cancer.

Mirroring the results of dual HER2-targeted therapy with trastuzumab and lapatinib, the combination of pertuzumab and trastuzumab in the absence of chemotherapy appears to cause similar tumor regression. Pertuzumab as monotherapy produced unimpressive results, with an objective response rate (ORR) of 3.4% and a clinical benefit rate (CBR) of 10.3%; however, after the addition of trastuzumab, the ORR and CBR improved to 17.6% and 41.2%, respectively.⁴⁶ The pertuzumab and trastuzumab regimen was relatively well tolerated, with the most common adverse events being diarrhea and nausea, without any increase in cardiac dysfunction.⁴⁶ The absolute numbers from this study are small; nevertheless, the data are consistent with the hypothesis that in most HER2-positive tumors, the HER2 protein itself continues to represent the cancer's major point of vulnerability. Larger studies examining the efficacy of this "all-targeted approach" are necessary to understand the extent to which these tumors are addicted to the HER2 oncogene, and the definitive point at which chemotherapy can be further eliminated.

In early-stage HER2-amplified breast cancer, combining traditional chemotherapy with dual HER2 inhibition using pertuzumab and trastuzumab engenders similar responses

demonstrated by lapatinib and trastuzumab. In the Efficacy and Safety of Neoadjuvant Pertuzumab and Trastuzumab in Women with Locally Advanced, Inflammatory, or Early HER2-Positive Breast Cancer (NeoSPHERE) trial, patients given pertuzumab and trastuzumab plus docetaxel as neoadjuvant therapy had a significantly improved pathological complete response compared with trastuzumab plus docetaxel (46% vs 29%; $P = 0.0141$).⁴⁷ The Study of Pertuzumab in Addition to Chemotherapy and Herceptin (Trastuzumab) as Adjuvant Therapy in Patients with HER2-Positive Primary Breast Cancer (APHINITY) is currently underway to study the addition of pertuzumab to trastuzumab and chemotherapy for adjuvant treatment.⁴⁸ One year of adjuvant trastuzumab in preventing breast cancer recurrence is well defined, but long-term follow-up is necessary to determine the role and duration of pertuzumab in this population.

Trastuzumab DM-1

Trastuzumab DM-1 (T-DM1), or trastuzumab emtansine, is an antibody-drug conjugate (ADC) consisting of the anti-body trastuzumab linked to the cytotoxic microtubule inhibitor DM-1.⁴⁹ The ADC approach allows selective delivery of chemotherapy to tumor cells that express HER2 receptors, attenuating the adverse effects associated with traditional chemotherapeutic agents. T-DM1 is often given as a single agent; however, the ADC mechanism likely makes this drug more similar to combination treatment than to monotherapy.

In the recently reported Open-Label Study of Trastuzumab Emtansine (T-DM1) vs Capecitabine + Lapatinib in Patients with HER2-Positive Locally Advanced or Meta-static Breast Cancer (EMILIA), T-DM1 was effective in the refractory HER2 population with minimal toxicity. This international phase 3 study compared T-DM1 with lapatinib with capecitabine in patients whose disease had progressed on trastuzumab and a taxane. T-DM1 significantly improved PFS (9.6 vs 6.4 months; HR, 0.65; 95% CI, 0.55–0.77; $P < 0.0001$), and while the data are not yet mature, there was a trend toward improvement in OS (HR, 0.62; 95% CI, 0.46–0.81; $P = 0.0005$).⁵⁰ T-DM1 was well tolerated with a better toxicity profile and improved quality-of-life outcome measures when compared with lapatinib and capecitabine. Thrombocytopenia was the major side effect, observed in 12.9% of patients compared with 0.2% of patients in the lapatinib and capecitabine arm.⁵⁰

Given the presented data, T-DM1 will likely receive accelerated approval from the FDA in the refractory setting, and will be the new standard of care for metastatic HER2-positive breast cancer after disease progression on trastuzumab. As previously discussed, pertuzumab will now be routinely administered with trastuzumab as first-line therapy, and it is unknown what effect, if any, T-DM1 will have on patients who are pertuzumab refractory. Although there are some data to suggest that patients respond to HER2-based therapy after exposure to pertuzumab,⁴⁶ the role of T-DM1 after administration of non-trastuzumab anti-HER2 agents requires additional investigation.

Further study of T-DM1 will include evaluation in early-stage breast cancer and in combination studies with next-generation HER2-targeted therapy. For patients with local-regional disease, the efficacy of T-DM1 is being tested after completion of anthracycline-based adjuvant and neoadjuvant treatment.⁵¹ The real benefit of T-DM1 lies in the potential to eliminate chemotherapy from therapeutic regimens, and prospective adjuvant trials using single-agent T-DM1 are in development for patients with small, HER2-positive, node-negative tumors. To assess the impact of T-DM1 when administered with other non-trastuzumab anti-HER2 drugs, the Study of Trastuzumab Emtansine (T-DM1) Plus Pertuzumab/Pertuzumab Placebo Versus Trastuzumab [Herceptin] Plus a Taxane in Patients with Metastatic Breast Cancer (MARIANNE) is designed to randomize patients to T-DM1

combined with pertuzumab or T-DM1 with placebo, versus the combination of trastuzumab plus a taxane in patients with advanced HER2-amplified breast cancer.⁵² With multiple HER2-targeted agents currently in clinical use, T-DM1 will likely play a prominent role, and these upcoming trials will assist in determining the optimal drug combination and duration of therapy.

Future Directions

The aforementioned anti-HER2 therapies interact directly with the transmembrane HER2 protein causing obstruction with pro-oncogenic signaling. Other possible avenues of interfering with HER2-mediated signaling include pan-ERbb inhibition, as well as disruption of downstream mediators. For example, irreversible pan-ERbb tyrosine kinase inhibitors, such as neratinib, have activity in both trastuzumab- and lapatinib-resistant breast cancers.^{53,54} The combination of neratinib with trastuzumab produced an ORR of 27% in a trastuzumab-refractory population,⁵⁵ suggesting that targeting ERbb-mediated resistance with neratinib may be a viable option in patients with advanced disease.

Deregulation of PI3K pathway has also been implicated in resistance to HER-2 targeted therapies.³² Currently, multiple phase 1 and 2 clinical trials are evaluating the use of pan-PI3K inhibitors in combination with HER2-targeted agents and are showing promising results.⁵⁶ Likewise, inhibition of mTOR (a molecule downstream of PI3K) with everolimus is efficacious when given with trastuzumab,⁵⁷ and 2 large, placebo-controlled, phase 3 trials are currently underway to confirm these initial findings. The BOLERO-1 trial will test the ability of everolimus to overcome inherent resistance to trastuzumab-based therapy in the first-line setting,⁵⁸ and the BOLERO-3 trial will determine the antitumor effect of everolimus plus trastuzumab in patients with prior disease progression on trastuzumab.⁵⁹

Other means of resistance to anti-HER2 drugs may not be directly within the HER2 pathway itself. For instance, heat-shock protein 90 (HSP90), a molecular chaperone, is commonly overexpressed in malignancies. HSP90 blockade induces proteasome-mediated breakdown of target proteins, including HER2.⁶⁰ Therefore, HSP90 inhibition increases HER2 degradation and can potentiate trastuzumab-induced apoptosis.⁶⁰ Currently, the therapeutic role of HSP90 inhibitors is under investigation in trastuzumab-resistant HER2-positive breast cancers.⁶¹

Finally, the rapidly emerging interest in immunotherapy across solid tumor malignancies has led to the development of clinical trials investigating the role of immune modulation in HER2-positive disease. Clinical trials evaluating immuno-therapy in this population are actively recruiting patients and include studies using immunopeptides derived from HER2, as well as cancer vaccines targeting the trastuzumab and pertuzumab epitopes of HER2.^{62,63} HER2-targeted vaccines are presumed to cause delayed-type hypersensitivity and expansion of cytotoxic CD8+T lymphocytes, resulting in development of an immune response against HER2-positive tumors.⁶⁴

Conclusion

Breast medical oncology has once again moved into a new era of targeted therapy as we continue to increase the number of agents available to patients with HER2-positive disease. The post-trastuzumab era has dramatically changed the natural course of HER2-amplified breast cancer for the better, and it is likely that these next-generation HER2-targeted therapies will have a similar impact on disease-free longevity. With the wealth of anti-HER2 agents available to treating physicians, secondary questions regarding the order and duration of therapy are raised. It is likely that agents such as T-DM1 and pertuzumab will be administered in off-label indications; however, the efficacy of these practices is not well

understood and physicians should proceed with caution. There is preliminary evidence to suggest that patients who experience disease progression on next-generation HER2-targeted therapy may respond to additional HER2 inhibition^{12,65}; however, these observations will need to be studied in larger prospective trials. Further investigation into the order and timing of each anti-HER2 agent is essential in achieving maximum benefit for most patients.

Distinct populations of HER2-positive patients will need to be the target of active investigation in future clinical studies. First, CNS disease increased dramatically after the widespread use of trastuzumab due to lack of effective anti-HER2 therapy to cross the blood-brain barrier. With T-DM1 and pertuzumab increasing extracranial disease control and OS rate, it is likely that the CNS will continue to be a sanctuary site for HER2-positive cancer cells, leading to further neurologic morbidity. Second, adjuvant trastuzumab has decreased the amount of distant recurrences; however, there remains a subset of patients with locally advanced tumors who will inevitably relapse. Patients with recurrent cancer after exposure to adjuvant trastuzumab are not well studied. Data on effective therapies in this population are limited and it is unknown if these patients will have a similar response to next-generation HER2-targeted therapies.

Moving forward, it is likely that the role of dual HER2-targeted regimens will increase and become more prevalent. Most evidence to date suggests that continuous HER2 blockade, despite prior disease progression, is necessary to engender durable responses. The proper identification of patients who may respond to therapy is critical, and investigators are encouraged to incorporate access to primary and metastatic tissues into clinical trials for biomarker development.⁶⁶ Future studies will continue to use a trastuzumab-based backbone with the addition of other agents that target HER2 or downstream effectors. It is plausible that as we move to a new paradigm of targeted therapy, the use of cytotoxic chemotherapy (and the associated toxicities) will decline.

References

1. Hynes NE, Lane HA. ERBB receptors and cancer; the complexity of targeted inhibitors. *Nat Rev Cancer*. 2005; 5(5):341–354. [PubMed: 15864276]
2. Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. *Nat Rev Mol Cell Biol*. 2001; 2(2):127–137. [PubMed: 11252954]
3. Arpino G, Wiechmann L, Osborne CK, Schiff R. Crosstalk between the estrogen receptor and the HER tyrosine kinase receptor family: molecular mechanism and clinical implications for endocrine therapy resistance. *Endocr Rev*. 2008; 29(2):217–233. [PubMed: 18216219]
4. Prat A, Baselga J. The role of hormonal therapy in the management of hormonal-receptor-positive breast cancer with co-expression of HER2. *Nat Clin Pract Oncol*. 2008; 5(9):531–542. [PubMed: 18607391]
5. Musgrove EA, Sutherland RL. Biological determinants of endocrine resistance in breast cancer. *Nat Rev Cancer*. 2009; 9(9):631–643. [PubMed: 19701242]
6. Papaldo P, Fabi A, Ferretti G, et al. A phase II study on metastatic breast cancer patients treated with weekly vinorelbine with or without trastuzumab according to HER2 expression: changing the natural history of HER2-positive disease. *Ann Oncol*. 2006; 17(4):630–636. [PubMed: 16410363]
7. Dawood S, Broglio K, Buzdar AU, Hortobagyi GN, Giordano SH. Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: an institutional-based review. *J Clin Oncol*. 2010; 28(1):92–98. [PubMed: 19933921]
8. Gutierrez C, Schiff R. HER2: biology, detection, and clinical implications. *Arch Pathol Lab Med*. 2011; 135(1):55–62. [PubMed: 21204711]
9. Tzahar E, Waterman H, Chen X, et al. A hierarchical network of interreceptor interactions determines signal transduction by Neu differentiation factor/neuregulin and epidermal growth factor. *Mol Cell Biol*. 1996; 16(10):5276–5287. [PubMed: 8816440]

10. Olson EM. Maximizing human epidermal growth factor receptor 2 inhibition: a new oncologic paradigm in the era of targeted therapy. *J Clin Oncol.* 2012; 30(14):1712–1714. [PubMed: 22393085]
11. Blackwell KL, Burstein HJ, Storniolo AM, et al. Randomized study of lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. *J Clin Oncol.* 2010; 28(7):1124–1130. [PubMed: 20124187]
12. Baselga J, Cortes J, Kim SB, et al. CLEOPATRA Study Group. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med.* 2012; 366(2):109–119. [PubMed: 22149875]
13. Yin W, Jiang Y, Shen Z, Shao Z, Lu J. Trastuzumab in the adjuvant treatment of HER2-positive early breast cancer patients: a meta-analysis of published randomized controlled trials. *PloS One.* 2011; 6(6):e21030. [PubMed: 21695277]
14. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med.* 2001; 344(11):783–792. [PubMed: 11248153]
15. Baselga J, Albanell J, Molina MA, Arribas J. Mechanism of action of trastuzumab and scientific update. *Semin Oncol.* 2001; 28(5 suppl 16):4–11. [PubMed: 11706390]
16. Spector NL, Blackwell KL. Understanding the mechanisms behind trastuzumab therapy for human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol.* 2009; 27(34):5838–5847. [PubMed: 19884552]
17. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med.* 2005; 353(16):1673–1684. [PubMed: 16236738]
18. Valero V, Forbes J, Pegram MD, et al. Multicenter phase III randomized trial comparing docetaxel and trastuzumab with docetaxel, carboplatin, and trastuzumab as first-line chemotherapy for patients with HER2-gene-amplified metastatic breast cancer (BCIRG 007 study): two highly active therapeutic regimens. *J Clin Oncol.* 2011; 29(2):149–156. [PubMed: 21115860]
19. von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/ breast international group 03–05 study. *J Clin Oncol.* 2009; 27(12):1999–2006. [PubMed: 19289619]
20. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med.* 2006; 355(26):2733–2743. [PubMed: 17192538]
21. Slamon D, Eiermann W, Robert N, et al. Breast Cancer International Research Group. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med.* 2011; 365(14):1273–1283. [PubMed: 21991949]
22. Zeglinski M, Ludke A, Jassal DS, Singal PK. Trastuzumab-induced cardiac dysfunction: a ‘dual-hit’. *Exp Clin Cardiol.* 2011; 16(3):70–74. [PubMed: 22065936]
23. Perez EA, Suman VJ, Davidson NE, et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. *J Clin Oncol.* 2008; 26(8):1231–1238. [PubMed: 18250349]
24. Pietras RJ, Arboleda J, Reese DM, et al. HER-2 tyrosine kinase pathway targets estrogen receptor and promotes hormone-independent growth in human breast cancer cells. *Oncogene.* 1995; 10(12):2435–2446. [PubMed: 7784095]
25. Gutierrez MC, Detre S, Johnston S, et al. Molecular changes in tamoxifen-resistant breast cancer: relationship between estrogen receptor, HER-2, and p38 mitogen-activated protein kinase. *J Clin Oncol.* 2005; 23(11):2469–2476. [PubMed: 15753463]
26. Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TANDEM study. *J Clin Oncol.* 2009; 27(33):5529–5537. [PubMed: 19786670]
27. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med.* 2012; 366(6):520–529. [PubMed: 22149876]

28. Gluck S, Arteaga CL, Osborne CK. Optimizing chemotherapy-free survival for the ER/HER2-positive metastatic breast cancer patient. *Clin Cancer Res.* 2011; 17(17):5559–5561. [PubMed: 21764887]
29. Vu T, Claret FX. Trastuzumab: updated mechanisms of action and resistance in breast cancer. *Front Oncol.* 2012; 2:62. [PubMed: 22720269]
30. Wong AL, Lee SC. Mechanisms of resistance to trastuzumab and novel therapeutic strategies in HER2-positive breast cancer. *Int J Breast Cancer.* 2012:415170.
31. Scaltriti M, Rojo F, Ocaña A, et al. Expression of p95HER2, a truncated form of the HER2 receptor, and response to anti-HER2 therapies in breast cancer. *J Natl Cancer Inst.* 2007; 99(8): 628–638. [PubMed: 17440164]
32. Arteaga CL, Sliwkowski MX, Osborne CK, Perez EA, Puglisi F, Gianni L. Treatment of HER2-positive breast cancer: current status and future perspectives. *Nat Rev Clin Oncol.* 2012; 9(1):16–32. [PubMed: 22124364]
33. Holbro T, Beerli RR, Maurer F, Koziczak M, Barbas CF 3rd, Hynes NE. The ErbB2/ErbB3 heterodimer functions as an oncogenic unit: ErbB2 requires ErbB3 to drive breast tumor cell proliferation. *Proc Natl Acad Sci U S A.* 2003; 100(15):8933–8938. [PubMed: 12853564]
34. Wilson TR, Lee DY, Berry L, Shames DS, Settleman J. Neuregulin-1-mediated autocrine signaling underlies sensitivity to HER2 kinase inhibitors in a subset of human cancers. *Cancer Cell.* 2011; 20(2):158–172. [PubMed: 21840482]
35. Blackwell KL, Pegram MD, Tan-Chiu E, et al. Single-agent lapatinib for HER2-overexpressing advanced or metastatic breast cancer that progressed on first- or second-line trastuzumab-containing regimens. *Ann Oncol.* 2009; 20(6):1026–1031. [PubMed: 19179558]
36. Gelmon KA, Boyle F, Kaufman B, et al. Open-label phase III randomized controlled trial comparing taxane-based chemotherapy (Tax) with lapatinib (L) or trastuzumab (T) as first-line therapy for women with HER2+ metastatic breast cancer: interim analysis (IA) of NCIC CTG MA.31/GSK EGF 108919. Presented at: American Society of Clinical Oncology Annual Meeting; June 2012; Chicago, IL.
37. Konecny GE, Pegram MD, Venkatesan N, et al. Activity of the dual kinase inhibitor lapatinib (GW572016) against HER-2-over-expressing and trastuzumab-treated breast cancer cells. *Cancer Research.* 2006; 66(3):1630–1639. [PubMed: 16452222]
38. Blackwell KL, Burstein HJ, Storniolo AM, et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF 104900 Study. *J Clin Oncol.* 2012; 30(21): 2585–2592. [PubMed: 22689807]
39. Baselga J, Bradbury I, Eidtmann H, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. *Lancet.* 2012; 379(9816):633–640. [PubMed: 22257673]
40. Azim H, Azim HA Jr, Escudier B. Trastuzumab versus lapatinib: the cardiac side of the story. *Cancer Treat Rev.* 2009; 35(7):633–638. [PubMed: 19640652]
41. Perez EA, Koehler M, Byrne J, Preston AJ, Rappold E, Ewer MS. Cardiac safety of lapatinib: pooled analysis of 3689 patients enrolled in clinical trials. *Mayo Clin Proc.* 2008; 83(6):679–686. [PubMed: 18533085]
42. www.ClinicalTrials.gov. Lapatinib in Combination with Trastuzumab in Patients with HER2-Positive, Metastatic Breast Cancer. NCT00470704. <http://clinicaltrials.gov/ct2/show/NCT00470704?term=NCT00470704&rank==1>. Accessed December 5, 2012
43. Robidoux, A. Evaluation of lapatinib as a component of neoadjuvant therapy for HER2+ operable breast cancer: NSABP protocol B-41; Presented at: American Society of Clinical Oncology Annual Meeting; Chicago, IL. Jun. 2012
44. Olson EM. Maximizing human epidermal growth factor receptor 2 inhibition: a new oncologic paradigm in the era of targeted therapy. *J Clin Oncol.* 2012; 30(14):1712–1714. [PubMed: 22393085]
45. Scheuer W, Friess T, Bartscher H, Bossenmaier B, Endl J, Hasmann M. Strongly enhanced antitumor activity of trastuzumab and pertuzumab combination treatment on HER2-positive human xenograft tumor models. *Cancer Res.* 2009; 69(24):9330–9336. [PubMed: 19934333]

46. Cortés J, Fumoleau P, Bianchi GV, et al. Pertuzumab monotherapy after trastuzumab-based treatment and subsequent reintroduction of trastuzumab: activity and tolerability in patients with advanced human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol*. 2012; 30(14):1594–1600. [PubMed: 22393084]
47. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012; 13(1):25–32. [PubMed: 22153890]
48. www.ClinicalTrials.gov. A Study of Pertuzumab in Addition to Chemo-therapy and Herceptin (Trastuzumab) as Adjuvant Therapy in Patients with HER2-Positive Primary Breast Cancer. NCT01358877. <http://clinicaltrials.gov/ct2/show/NCT01358877?term=NCT01358877&rank=1>. Accessed December 5, 2012
49. Niculescu-Duvaz I. Trastuzumab emtansine, an antibody-drug conjugate for the treatment of HER2+ metastatic breast cancer. *Curr Opin Mol Ther*. 2010; 12(3):350–360. [PubMed: 20521224]
50. Blackwell KL, Miles D, Gianni L, et al. Primary results from EMILIA, a phase III study of trastuzumab emtansine (T-DM1) versus capecitabine (X) and lapatinib (L) in HER2-positive locally advanced or metastatic breast cancer (MBC) previously treated with trastuzumab (T) and a taxane. Presented at: American Society of Clinical Oncology Annual Meeting; June 2012; Chicago, IL.
51. www.ClinicalTrials.gov. A Study of Trastuzumab Emtansine (T-DM1) Sequentially with Anthracycline-Based Chemotherapy, as Adjuvant or Neoadjuvant Therapy for Patients with Early Stage HER2-Positive Breast Cancer. NCT01196052. <http://clinicaltrials.gov/ct2/show/NCT01196052?term=NCT01196052&rank=1>. Accessed December 5, 2012
52. www.ClinicalTrials.gov. A Study of Trastuzumab Emtansine (T-DM1) Plus Pertuzumab/ Pertuzumab Placebo Versus Trastuzumab [Herceptin] Plus aTaxane in Patients with Metastatic Breast Cancer(MARIANNE). NCT01120184. <http://clinicaltrials.gov/ct2/show/NCT01120184?term=NCT01120184&rank=1>. Accessed December 5, 2012
53. Burstein HJ, Sun Y, Dirix LY, et al. Neratinib, an irreversible ErbB receptor tyrosine kinase inhibitor, in patients with advanced ErbB2-positive breast cancer. *J Clin Oncol*. 2010; 28(8):1301–1307. [PubMed: 20142587]
54. Ocaña A, Amir E. Irreversible pan-ErbB tyrosine kinase inhibitors and breast cancer; current status and future directions. *Cancer Treat Rev*. 2009; 35(8):685–691. [PubMed: 19733440]
55. Swaby, R.; Blackwell, K.; Jiang, Z., et al. Neratinib in combination with trastuzumab for the treatment of advanced breast cancer: a phase I/II study; Presented at: American Society of Clinical Oncology Annual Meeting; Orlando, FL. Jun. 2009
56. Krop, I.; Saura, C.; Ahnert, JR., et al. A phase I/IB dose-escalation study of BEZ235 in combination with trastuzumab in patients with PI3- kinase or PTEN altered HER2+ metastatic breast cancer; Presented at American Society of Clinical Oncology Annual Meeting; Chicago, IL. Jun. 2012
57. Jerusalem G, Fasolo A, Dieras V, et al. Phase I trial of oral mTOR inhibitor everolimus in combination with trastuzumab and vinorelbine in pre-treated patients with HER2-overexpressing metastatic breast cancer. *Breast Cancer Res Treat*. 2011; 125(2):447–455. [PubMed: 21107682]
58. www.ClinicalTrials.gov. Everolimus in Combination with Trastuzumab and Paclitaxel in the Treatment of HER2 Positive Locally Advanced or Metastatic Breast Cancer (BOLERO-1). NCT00876395. <http://clinicaltrials.gov/ct2/show/NCT00876395?term=NCT00876395&rank=1>. Accessed December 5, 2012
59. www.ClinicalTrials.gov. Daily Everolimus in Combination with Trastuzumab and Vinorelbine in HER2/Neu Positive Women with Locally Advanced or Metastatic Breast Cancer (BOLERO-3). NCT01007942. <http://clinicaltrials.gov/ct2/show/NCT01007942?term=NCT01007942&rank=1>. Accessed December 5, 2012
60. Puglisi F, Minisini AM, DeAngelis C, Arpino G. Overcoming treatment resistance in HER2-positive breast cancer: potential strategies. *Drugs*. 2012; 72(9):1175–1193. [PubMed: 22686613]
61. www.ClinicalTrials.gov. Phase I-II Study to Determine the Maximum Tolerated Dose (MTD) of AUY922 in Advanced Solid Malignancies. and Efficacy in HER2+ or ER+ Locally Advanced or

- Metastatic Breast Cancer Patients. NCT00526045. <http://clinicaltrials.gov/ct2/show/NCT00526045?term=NCT00526045&rank=1>. Accessed December 5, 2012
62. www.ClinicalTrials.gov. Vaccine Therapy in Treating Patients with Metastatic Solid Tumors. NCT01376505. <http://clinicaltrials.gov/ct2/show/NCT01376505?term=NCT01376505&rank=1>. Accessed December 5, 2012
 63. www.ClinicalTrials.gov. Combination Immunotherapy with Herceptin and the HER2 Vaccine NeuVax. NCT01570036. <http://clinicaltrials.gov/ct2/show/NCT01570036?term=NCT01570036&rank=1>. Accessed December 5, 2012
 64. Ladjemi MZ, Jacot W, Chardes T, Pelegrin A, Navarro-Teulon I. Anti-HER2 vaccines: new prospects for breast cancer therapy. *Cancer Immunol Immunother*. 2010; 59(9):1295–1312.
 65. Olson EM, Lin NU, Dipiro PJ, et al. Responses to subsequent anti-HER2 therapy after treatment with trastuzumab-DM1 in women with HER2-positive metastatic breast cancer. *Ann Oncol*. 2012; 23(1):93–97. [PubMed: 21531783]
 66. Olson EM, Lin NU, Krop I, Winer EP. The ethical use of research biopsies. *Nat Rev Clin Oncol*. 2011; 8(10):620–625. [PubMed: 21808265]
 67. www.ClinicalTrials.gov. Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation. NCT00490139. <http://clinicaltrials.gov/ct2/show/NCT00490139?term=NCT00490139&rank=1>. Accessed December 5, 2012
 68. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet*. 2010; 375(9712):377–384. [PubMed: 20113825]
 69. Untch M, Fasching PA, Konecny GE, et al. Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-over-expressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. *J Clin Oncol*. 2011; 29(25):3351–3357. [PubMed: 21788566]
 70. www.ClinicalTrials.gov. A Study of Trastuzumab Emtansine in Comparison with Treatment of Physician's Choice in Patients with HER2-Positive Breast Cancer Who Have Received at Least Two Prior Regimens of HER2-Directed Therapy. NCT01419197. <http://clinicaltrials.gov/ct2/show/NCT01419197?term=NCT01419197&rank=1>. Accessed December 5, 2012

Figure 1.

Epidermal growth factor receptor family and targeted agents. HER2 does not have a known ligand. HER3 does not have tyrosine kinase activity. Humanized monoclonal antibodies, trastuzumab and pertuzumab, as well as lapatinib, a small-molecule tyrosine kinase inhibitor, are FDA-approved agents. T-DM1 is an antibody drug conjugate.

Abbreviations: AR, amphiregulin; BTC betacellulin; EGFR, epidermal growth factor receptor; EPG, epigen; EPR, epiregulin; HB-EGF, heparin-binding EGF-like ligand; HER, human epidermal growth factor receptor; FDA, US Food and Drug Administration; NRG, neuregulin; TGF, transforming growth factor; T-DM1, trastuzumab DM-1.

Table 1

Completed or Ongoing Phase 3 Clinical Trials of HER2-Targeted Agents in the Adjuvant, Neoadjuvant, and Metastatic Settings

Setting	Regimen	Study	FDA Approval
Adjuvant			
Standard	Trastuzumab plus chemotherapy ^{13,17,21}	Phase 3	Yes
	Pertuzumab plus trastuzumab plus chemotherapy (APHINITY) ⁴⁸	Phase 3 (in progress)	No
	Trastuzumab plus lapatinib plus chemotherapy (ALTTO) ⁶⁷	Phase 3 (in progress)	No
Neoadjuvant			
Standard	Trastuzumab plus chemotherapy ^{68,69}	Phase 3	No
	Trastuzumab plus lapatinib plus chemotherapy (Neo ALTTO) ³⁹	Phase 3	No
	Pertuzumab plus trastuzumab plus chemotherapy (NeoSPHERE) ⁴⁷	Phase 3 (in progress)	No
Metastatic			
First line	Trastuzumab plus pertuzumab plus chemotherapy (CLEOPATRA) ⁴⁶	Phase 3	Yes
	Trastuzumab plus chemotherapy ¹⁴	Phase 3	Yes
	T-DM1 plus pertuzumab (MARIANNE) ⁵²	Phase 3 (in progress)	No
Second line (progression on trastuzumab)	Lapatinib plus capecitabine ²⁰	Phase 3	yes
	Lapatinib plus trastuzumab ¹¹	Phase 3	No
	T-DM1 (EMILIA) ⁵⁰	Phase 3 (in progress)	Application pending
Salvage	T-DM1 (TH3RESA) ⁷⁰	Phase 3 (in progress)	No

Abbreviations: ALTTO, Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation; APHINITY, A Study of Pertuzumab in Addition to Chemotherapy and Herceptin (Trastuzumab) as Adjuvant Therapy in Patients with HER2-Positive Primary Breast Cancer; CLEOPATRA, A Study to Evaluate Pertuzumab + Trastuzumab + Docetaxel vs Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-Positive Metastatic Breast Cancer; EMILIA An Open-Label Study of Trastuzumab Emtansine (T-DM1) vs Capecitabine + Lapatinib in Patients with HER2-Positive Locally Advanced or Metastatic Breast Cancer; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; MARIANNE, A Study of Trastuzumab Emtansine (T-DM1) Plus Pertuzumab/Pertuzumab Placebo Versus Trastuzumab [Herceptin] Plus aTaxane in Patients with Metastatic Breast Cancer; Neo ALTTO, Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation; NeoSPHERE, Efficacy and Safety of Neoadjuvant Pertuzumab and Trastuzumab in Women with Locally Advanced, Inflammatory, or Early HER2-Positive Breast Cancer; T-DM1, trastuzumab DM-1; TH3RESA, A Study of Trastuzumab Emtansine in Comparison with Treatment of Physician's Choice in Patients with HER2-Positive Breast Cancer Who Have Received at Least Two Prior Regimens of HER2-Directed Therapy.