HER2-Positive Breast Cancer: Update on New and Emerging Agents

Alexandra Drakaki, MD, and Sara A. Hurvitz, MD

Abstract

The most common malignancy and second leading cause of cancer-related death in women is breast cancer. An improved understanding of breast cancer pathobiology has led to the development of novel therapies that are directed at proteins uniquely expressed on tumor cells. One such targeted approach is trastuzumab for HER2-amplified/overexpressing breast cancer. Since the approval of trastuzumab for HER2-positive metastatic breast cancer in 1998, outcomes for patients diagnosed with this innately aggressive form of cancer have vastly improved. Subsequently, several new therapies have been developed for HER2-positive breast cancer, including lapatinib (a small-molecule inhibitor of HER1 and HER2 tyrosine kinase), pertuzumab (a HER2-directed monoclonal antibody), and trastuzumab emtansine (T-DM1; the first antibody-drug conjugate approved for breast cancer). In addition, several emerging agents are currently being evaluated in clinical trials for HER2-positive breast cancer. In this review, the current available therapies for HER2-positive breast cancer will be described, and innovative HER2-directed approaches that are currently under investigation will be explored.

Key words: Breast cancer, HER2-targeted therapy, trastuzumab, pertuzumab, lapatinib, T-DM1, trastuzumab emtansine

Introduction

Breast cancer remains the most common cancer diagnosed in women, and in spite of significant improvements in treatment, it is still the second leading cause of cancer-related deaths.[1] Research in the last several decades has led to a better understanding of the complex molecular heterogeneity of this malignancy. One such discovery was the identification of the *HER2* gene, which encodes a tyrosine kinase receptor that is a potent mediator of cellular growth and proliferation in normal and malignant epithelial cells. Amplification of this gene is observed in up to 25% of breast cancers and has been shown to be a driving force of tumor biology.[2,3]

This discovery led to the development and approval of the first HER2-targeted therapy, trastuzumab.[4] Since that time, several other HER2-targeted therapeutics have been successfully designed and approved for the treatment of HER2-positive breast cancer. It is now clear that the routine use of trastuzumab and other HER2-targeted agents has dramatically improved the prognosis associated with HER2-driven breast cancer. This article will briefly review the current available therapies for HER2-positive breast cancer, describe several newly approved agents, and provide a concise consideration of novel therapies currently under investigation.

Trastuzumab or Lapatinib in the Early- and Late-Stage Settings

Trastuzumab is a recombinant humanized monoclonal antibody (mAb) that inhibits ligand-independent HER2 and HER3 signaling[5] and may trigger antibody-dependent cellular cytotoxicity.[6,7] Multiple trials have studied its role in the adjuvant, neoadjuvant, and metastatic settings. The addition of trastuzumab to chemotherapy in patients with previously untreated metastatic breast cancer (MBC) led to a significantly higher objective response rate, prolonged time to progression (TTP; 7.4 vs 4.6 months; P <.001), and improved overall survival (OS; 25 vs 20 months; P = .01) compared with chemotherapy alone.[4] Furthermore, in patients with early-stage breast cancer, the addition of trastuzumab to chemotherapy significantly improved disease-free survival (DFS) and OS in multiple clinical trials in the early and locally advanced settings.[8-12]

While evidence consistently shows that in the absence of HER2-directed therapy, HER2-positive disease has a poorer prognosis compared with HER2-normal cancer, recent studies are now indicating that the prognosis associated with trastuzumab-treated HER2-positive breast cancer is better than that for HER2-normal breast cancer, thus indicating that trastuzumab has altered the natural history of HER2-driven cancer.[13,14]

Lapatinib is a dual tyrosine kinase inhibitor (TKI) of HER2 and epidermal growth factor receptor (EGFR or HER1). Patients with advanced breast cancer or MBC who have already progressed on regimens that included trastuzumab, an anthracycline, and a taxane had a better TTP (8.4 vs 4.4 months; P <.001) when they received lapatinib in combination with capecitabine compared with those who received capecitabine alone.[15] These were the first results to show that continuing HER2-targeted therapy after progression on a HER2-targeted regimen improves outcomes. Moreover, these data led to the FDA approval of lapatinib in 2007.

Trastuzumab and lapatinib have each been combined with chemotherapy[16] or endocrine therapy[17,18] in clinical trials for HER2-positive MBC, and have demonstrated acceptable safety profiles and improved outcomes compared with single-agent chemotherapy or endocrine therapy. While data support the use of trastuzumab- or lapatinib-based therapy in the trastuzumab-pretreated advanced disease setting,[19] a head-to-head study of paclitaxel plus trastuzumab or lapatinib in the frontline setting showed improved progression-free survival (PFS) in the trastuzumab arm.[20] Thus, trastuzumab-based therapy remains the optimal choice in the first-line setting.

Trastuzumab has been evaluated in several studies in the neoadjuvant setting and has been shown to improve outcomes compared with chemotherapy alone.[11,12] However, when lapatinib was compared with trastuzumab in combination with neoadjuvant anthracycline-taxane–based chemotherapy in the GeparQuinto trial,[21] the pathologic complete response (pCR) rate at the time of surgery was significantly lower in the lapatinib group (93 of 307 patients [30.3%] in the trastuzumab group and 70 of 308 patients [22.7%] in the lapatinib group; P =.04). Therefore, the use of lapatinib alone or in combination with chemotherapy is not supported by evidence in the neoadjuvant setting.

Dual Receptor Blockade: Lapatinib Plus Trastuzumab

Preclinical studies have demonstrated synergy in vitro and in vivo by combining lapatinib with trastuzumab.[22,23] Based on these data, clinical evaluation of dual HER2 targeting was undertaken, and ultimately showed that in heavily pretreated, trastuzumab-resistant HER2-positive MBC, PFS and OS were improved with trastuzumab plus lapatinib compared with lapatinib alone.[24,25] These data therefore support the use of trastuzumab in combination with lapatinib in trastuzumab-pretreated MBC.

Dual HER2 targeting with lapatinib and trastuzumab has also been evaluated in the early-stage setting but has demonstrated conflicting results. In the phase II CHER LOB trial,[26] paclitaxel was combined with trastuzumab, lapatinib, or their combination, followed by an anthracycline-based regimen. Patients in the lapatinib-trastuzumab combination arm had a 46.7% pCR rate compared with 25% in the trastuzumab arm and 26.3% in the lapatinib arm.

Similarly, in the phase III NeoALTTO study,[27] paclitaxel was given in combination with lapatinib or trastuzumab or both. While the pCR rate (with *pCR* defined as no invasive cancer in breast and no cancer metastases in lymph nodes, or American Joint Committee on Cancer stage ypT0/is ypN0) was significantly higher in the group receiving both HER2-targeted drugs (46.8% for lapatinib plus trastuzumab vs 27.6% for trastuzumab vs 20.0% for lapatinib; P = .007), the event-free survival (EFS) and OS were no different in the combination arm compared with single-agent HER2-targeted therapy.[28] In contrast to these 2 studies, the phase III NSABP B-41 trial,[29] in which patients received paclitaxel plus lapatinib and/or trastuzumab after doxorubicin/cyclophosphamide, showed no significant difference between treatment arms in terms of pCR.

In addition to these data in the neoadjuvant setting, the ALTTO study[30] revealed that adjuvant lapatinib plus trastuzumab did not improve DFS compared with trastuzumab alone, underscoring the lack of data to support the use of lapatinib in the curative setting.

What's *Neu* With HER (HER2/*neu*): Pertuzumab and T-DM1

Pertuzumab is a novel humanized mAb directed at the dimerization domain (domain 2) of HER2. Specifically, it inhibits ligand-dependent signaling between HER2 and HER3, which is known to activate a potent cell-survival signal. Because of the different binding sites, trastuzumab and pertuzumab have different but similar and complementary mechanisms of action.[31]

The combination of pertuzumab with trastuzumab was evaluated in a large phase III randomized trial in the first-line HER2-positive MBC setting.[32,33] The results of this study showed that the addition of pertuzumab to trastuzumab and docetaxel significantly prolonged both PFS and OS compared with trastuzumab and docetaxel alone. Based on these data, in 2012 the FDA approved pertuzumab in combination with trastuzumab and docetaxel for HER2-positive MBC in patients who had received no prior HER2-directed therapy.

Two phase II trials have evaluated pertuzumab-plus-trastuzumab–based therapy in the neoadjuvant setting. In the randomized, multicenter phase II NeoSphere trial,[34] pertuzumab and/or trastuzumab with or without docetaxel were given for 4 cycles prior

to surgery. In this trial, the use of dual HER2-targeted therapy with pertuzumab and trastuzumab combined with docetaxel was associated with a significantly improved pCR (45.8%) compared with pertuzumab or trastuzumab plus docetaxel (24% and 29%, respectively).[34]

The cardiac safety of pertuzumab plus trastuzumab combined with chemotherapy was evaluated in the phase II, randomized neoadjuvant TRYPHAENA study.[35] In 2 of the treatment arms, trastuzumab (H) and pertuzumab (P) were given concurrently or sequentially with an anthracycline-based (5-fluorouracil, epirubicin, cyclophosphamide [FEC] followed by docetaxel [T]) chemotherapy regimen (FECHP-THP and FEC-THP). A third arm evaluated the safety of concurrent docetaxel and carboplatin with trastuzumab and pertuzumab (TCHP). Low rates of symptomatic systolic dysfunction were noted in all 3 arms in this relatively small study, and there was no evidence that pertuzumab increased the rate of cardiac dysfunction. Although the primary endpoint of this trial was cardiac safety, the secondary endpoint was pCR. The pCR rates were high in all 3 treatment arms (61.6% vs 57.3% vs 66.2%).

Based on the results of these 2 studies, in September 2013 the FDA approved 3 neoadjuvant regimens for HER2-positive breast cancer (THP x 4 cycles; FEC x 3 cycles followed by THP x 3 cycles; and TCHP x 6 cycles). Subsequently, National Comprehensive Cancer Network (NCCN) guidelines supported the use of pertuzumab with trastuzumab in the adjuvant setting; however, the use of pertuzumab in the adjuvant setting is still being evaluated in the APHINITY trial (NCT01358877), in which patients with HER2-positive breast cancer are randomized to receive adjuvant chemotherapy and trastuzumab with or without pertuzumab for 1 year.

Ado-trastuzumab emtansine (T-DM1) is another novel anti-HER2 therapy. Specifically, it is an antibody-drug conjugate (ADC) in which trastuzumab is stably linked to a potent microtubule inhibitor, which is a derivative of maytansine (DM1). T-DM1 was compared with lapatinib and capecitabine in the second-line, advanced-disease setting in the EMILIA study.[36] Patients with HER2-positive MBC whose disease progressed on trastuzumab and taxane-based therapy had an OS of 30.9 months in the T-DM1 arm compared with 25.1 months in the control group. Importantly, T-DM1 is associated with improved tolerability compared with standard therapy.

In the TH3RESA trial,[37] a heavily pretreated patient population with advanced HER2-positive breast cancer was randomized to receive T-DM1 compared with physician's choice therapy. The PFS was significantly improved with T-DM1 compared with physician's choice (median, 6.2 months vs 3.3 months; P <.001), providing further evidence of the relative activity and tolerability of this agent against the current standard therapy.

These findings led to the FDA approval of the first ADC for breast cancer in 2013. T-DM1 has been compared with docetaxel plus trastuzumab in first-line MBC in a phase II study, and demonstrated a significant 5-month improvement in PFS compared with the control arm.[38] The use of T-DM1 in the front-line setting is being more definitively evaluated in the phase III MARIANNE study (NCT01120184), the results of which are pending. In that study, patients with MBC or recurrent, locally advanced HER2-positive breast cancer receive T-DM1 with or without pertuzumab compared with a taxane and trastuzumab. A global press release on December 18, 2014, indicated that the MARIANNE study met the noninferiority endpoint, showing similar PFS among the 3 arms; however, it did not meet the PFS superiority endpoint for T-DM1–containing regimens. The full results have not been presented publicly as of the date of this publication.

As an adjuvant treatment, T-DM1 is being compared with trastuzumab in the phase III KATHERINE trial (NCT01772472), while in the KAITLIN trial (NCT01966471), taxanes will be given postoperatively with either T-DM1 plus pertuzumab or trastuzumab plus pertuzumab in patients who have already received anthracycline-based chemotherapy. In the neoadjuvant setting, KRISTINE (TRIO-021; NCT02131064) is an ongoing trial in which patients are randomized to receive T-DM1 with pertuzumab compared with TCHP.

Emerging Agents for HER2-Positive Breast Cancer

Neratinib is a potent pan-TKI that irreversibly inhibits HER2. An ongoing phase III study (NALA; NCT 01808573) is comparing neratinib plus capecitabine to lapatinib plus capecitabine for patients with HER2-positive MBC that progressed on 2 prior HER2-targeted regimens. In the ExteNET trial (NCT00878709), patients with early-stage HER2-positive breast cancer who received adjuvant trastuzumab for a year were randomized to receive neratinib or placebo for an additional year. A press release in 2014 indicated that neratinib was associated with a 33% improvement in DFS compared with placebo; however, these results have not been peer-reviewed or publicly presented to date. Given the increased rate of diarrhea from neratinib, preemptive use of antidiarrheal drugs is being evaluated in ongoing clinical trials.

MM-302 is a novel ADC that offers targeted delivery of pegylated liposomal doxorubicin to cancer cells overexpressing the HER2 protein. Based on a phase I monotherapy study, MM-302 is well tolerated with promising activity, especially in patients with anthracycline-naïve breast cancer.[39] In the phase II randomized HERMIONE trial (NCT02213744), the investigational drug MM-302 plus trastuzumab will be compared with chemotherapy of physician's choice plus trastuzumab in anthracycline-naïve patients

with locally advanced breast cancer or MBC that has progressed on pertuzumab and T-DM1 in the advanced-disease setting.

ONT-380, also known as ARRY-380, is a small-molecule selective inhibitor of HER2. Given that it is associated with highly potent inhibition of HER2 without significant inhibition of HER1, ONT-380 may have a better side-effect profile with less skin rash and GI toxicity compared with other dual inhibitors. Currently, there are 2 ongoing phase Ib clinical trials with ONT-380 in women with HER2-amplified breast cancer. In the first trial, ONT-380 is given with capecitabine and/or trastuzumab in patients whose disease progressed after trastuzumab and T-DM1 (NCT02025192). In the second study, ONT-380 is given with T-DM1 in patients who were previously treated with trastuzumab and taxanes (NCT01983501). Results are eagerly awaited from these 2 studies.

Small HER2-Positive Tumors

The biological aggressiveness of HER2-positive breast cancer leads many clinicians to recommend trastuzumab-based chemotherapy even for tumors smaller than 2 cm in size. However, randomized studies evaluating the benefit of this approach for small, lymph node–negative tumors are lacking, and the proportion of patients with tumors smaller than 1 cm in size enrolled in the large adjuvant studies is very small. Moreover, trastuzumab-based regimens can lead to considerable side effects, owing mainly to the cytotoxic chemotherapy used. Therefore, given the efficacy and tolerability profile of T-DM1 in the metastatic and neoadjuvant settings, a phase II study is being conducted (the ATEMPT trial; NCT01853748) for patients with stage I HER2-positive tumors. In this randomized trial, patients will receive T-DM1 or paclitaxel in combination with trastuzumab, with both HER2-targeting drugs given for 1 full year, in the adjuvant setting in order to compare the effectiveness of the 2 treatment arms, and to assess symptoms and changes in quality of life.

Management of HER2-Positive Breast Cancer Brain Metastases

Treating patients with brain metastases is definitely more challenging due to the lack of effective therapies that cross the blood–brain barrier, as well as the poor prognosis associated with this condition. Although randomized studies to indicate the therapy or therapies associated with optimal outcomes are lacking, in 2014 the American Society of Clinical Oncology published clinical practice guidelines for the management of patients with HER2-positive breast cancer with brain metastases, indicating that patients should receive appropriate systemic therapy for extracranial disease as well as appropriate local therapy, which may include surgery, whole-brain radiotherapy, and/or stereotactic radiosurgery.[40] The major determinants of the choice of treatment are a patient's performance status, multifocality, and size of the lesions. The consensus indicates that patients should not undergo screening imaging of the brain unless they are symptomatic, because doing so has not been shown to improve long-term outcomes for patients.

What Obstacles Are We Facing With HER2 Targeting?

HER2-targeted approaches have revolutionized the treatment and outcomes associated with HER2-overexpressing breast cancer. However, de novo and acquired resistance to HER2-directed approaches remains a clinical challenge. Several resistance mechanisms have been described, including mutations in other signaling pathways, such as the insulin-like growth factor receptor, receptor crosstalk, and autophagy.[41]

Another mechanism of resistance is the presence of a short form of HER2 that is constitutively active and missing the p95 extracellular domain. This short-form HER2 does not respond to trastuzumab therapy because the trastuzumab-binding domain is lacking.[42] The presence of *PI3K* mutations may also play a role in resistance to anti-HER2 therapy, thus providing rationale for targeting the PI3K/mTOR pathway.[43] Interestingly, these preclinical data are confirmed by the findings of the BOLERO-3 trial,[44] in which the addition of everolimus (an mTOR inhibitor) to trastuzumab and vinorelbine significantly prolonged PFS in patients with trastuzumab- and taxane-resistant disease. In the BOLERO-1 trial, patients with HER2-positive MBC were randomized in the first-line setting to receive trastuzumab and paclitaxel with or without everolimus.

While uncommon in breast cancer, HER2 somatic mutations may also play a role in breast carcinogenesis in tumors lacking HER2 amplification. Therefore, tumors with those mutations may be resistant to reversible HER2 inhibitors but sensitive to irreversible ones.[45] More than 12 different HER2 mutations have been described, and identification and targeting of those mutations may prove to be beneficial in the treatment of this disease.

Conclusions

The discovery of the HER2 alteration as a driver of disease biology in up to one-quarter of breast cancers led to a paradigm shift in the way this malignancy was understood, such that it is now recognized and accepted that breast cancer comprises heterogeneous subtypes that are each best treated with molecularly targeted approaches. The successful development of trastuzumab, the first drug targeting HER2-positive cancer, validated the concept that we can improve disease biology by treating the underlying molecular driver. In the past decade, 3 more HER2-directed therapies—lapatinib, pertuzumab, and T-DM1—have earned regulatory approval based on data in the metastatic and early-stage settings. While the outcomes associated with this disease have been dramatically improved with the use of these agents, resistance to these approaches remains an unmet clinical need. Understanding the mechanism of resistance to HER2-directed therapy will hopefully lead to the development of novel therapeutic agents

aimed at preventing or circumventing resistance, thus turning an otherwise terminal disease into a chronic condition.

Acknowledgment: Both authors contributed equally to the writing of this article.

Affiliations: Drs Drakaki and Hurvitz are from the Division of Hematology/Oncology, University of California, Los Angeles.

Disclosures: Dr Hurvitz receives research funding relevant to the content of this article (paid to the University of California, Los Angeles) from Boehringer-Ingelheim, Genentech, GlaxoSmith-Kline, Merrimack Pharmaceuticals, Novartis, Puma Biotechnology, and Roche. Dr Drakaki reports no relevant conflicts of interest to disclose.

Source of funding: Dr Hurvitz receives support from the National Cancer Institute of the National Institutes of Health (NIH) under Award Number P30CA016042, and from the STOP CANCER Marni Levine Memorial Seed Grant. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Address correspondence to: Sara A. Hurvitz, MD, FACP, Associate Professor of Medicine, University of California, Los Angeles, Department of Medicine, Division of Hematology/Oncology, 2825 Santa Monica Blvd, Suite 211, Santa Monica, CA 90404; phone: 310-829-5471; fax: 310-829-6192; email: shurvitz@mednet.ucla.edu.

REFERENCES

1. Siegel R, Ma J, Zou Z, et al. Cancer statistics, 2014. *Cancer.* 2014;64:9-29.
2. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987;235:177-182.
3. Slamon DJ, Godolphin W, Jones LA, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science*. 1989;244:707-712.
4. 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;344:783-792.
5. Junttila TT, Akita RW, Parsons K, et al. Ligand-independent HER2/HER3/PI3K complex is disrupted by trastuzumab and is effectively inhibited by the PI3K inhibitor GDC-0941. *Cancer Cell.* 2009;15:429-440.
6. Clynes RA, Towers TL, Presta LG, et al. Inhibitory Fc receptors modulate in vivo cytoxicity against tumor targets. *Nat Med.* 2000;6:443-446.
7. Junttila TT, Parsons K, Olsson C, et al. Superior in vivo efficacy of afucosylated trastuzumab in the treatment of HER2-amplified breast cancer. *Cancer Res.* 2010;70:4481-4489.
8. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005;353:1673-1684.
9. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*. 2005;353:1659-1672.
10. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011;365:1273-1283.
11. 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;375:377-384.
12. Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. *J Clin Oncol.* 2005;23:3676-3685.
13. Dawood S, Broglio K, Buzdar AU, et al. Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: an institutional-based review. *J Clin Oncol.* 2010;28:92-98.
14. Musolino A, Ciccolallo L, Panebianco M, et al. Multifactorial central nervous system recurrence susceptibility in patients with HER2-positive breast cancer: epidemiological and clinical data from a population-based cancer registry study. *Cancer.* 2011;117:1837-1846.
15. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med.* 2006;355:2733-2743.
16. Hurvitz SA, Kakkar R. Role of lapatinib alone or in combination in the treatment of HER2-positive breast cancer. *Breast Cancer (Dove Med Press).* 2012;4:35-51.
17. 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;27:5529-5537.
18. Johnston S, Pippen J Jr, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J Clin Oncol.* 2009;27:5538-5546.
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. *J Clin Oncol.* 2009;27:1999-2006.

20. 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. *J Clin Oncol.* 2012;30. Abstract LBA671.
21. Untch M, Loibl S, Bischoff J, et al. Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy (GeparQuinto, GBG 44): a randomised phase 3 trial. *Lancet Oncol.* 2012;13:135-144.
22. Konecny GE, Pegram MD, Venkatesan N, et al. Activity of the dual kinase inhibitor lapatinib (GW572016) against HER-2-overexpressing and trastuzumab-treated breast cancer cells. *Cancer Res.* 2006;66:1630-1639.
23. Scaltriti M, Verma C, Guzman M, et al. Lapatinib, a HER2 tyrosine kinase inhibitor, induces stabilization and accumulation of HER2 and potentiates trastuzumab-dependent cell cytotoxicity. *Oncogene.* 2009;28:803-814.
24. 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;28:1124-1130.
25. 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 EGF104900 Study. *J Clin Oncol.* 2012;30:2585-2592.
26. Guarneri V, Frassoldati A, Bottini A, et al. Preoperative chemotherapy plus trastuzumab, lapatinib, or both in human epidermal growth factor receptor 2-positive operable breast cancer: results of the randomized phase II CHER LOB study. *J Clin Oncol.* 2012;30:1989-1995.
27. 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;379:633-640.
28. Piccart-Gebhart M, Holmes AP, de Azambuja E, et al. The association between event-free survival and pathological complete response to neoadjuvant lapatinib, trastuzumab, or their combination in HER2-positive breast cancer. Survival follow-up analysis of the NeoALTTO study. *Cancer Res.* 2013;73. Abstract S1-01.
29. Robidoux A, Tang G, Rastogi P, et al. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial. *Lancet Oncol.* 2013;14:1183-1192.
30. Piccart-Gebhart MJ, Holmes AP, Baselga J, et al. First results from the phase III ALTTO trial (BIG 2-06; NCCTG [Alliance] N063D) comparing one year of anti-HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T→L), or their combination (T+L) in the adjuvant treatment of HER2-positive early breast cancer (EBC). *J Clin Oncol.* 2014;32(suppl; abstr LBA4).
31. Nahta R, Hung MC, Esteva FJ. The HER-2-targeting antibodies trastuzumab and pertuzumab synergistically inhibit the survival of breast cancer cells. *Cancer Res.* 2004;64:2343-2246.
32. Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med.* 2012;366:109-119.
33. Swain SM, Kim SB, Cortes J, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol.* 2013;14:461-471.
34. 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;13:25-32.
35. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol.* 2013;24:2278-2284.
36. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med.* 2012;367:1783-1791.
37. Krop IE, Kim SB, Gonzalez-Martin A, et al. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2014;15:689-699.
38. Hurvitz SA, Dirix L, Kocsis J, et al. Phase II randomized study of trastuzumab emtansine versus trastuzumab plus docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. *J Clin Oncol.* 2013;31:1157-1163.
39. Munster P, Krop IE, Miller K, et al. Assessment of safety and activity in an expanded phase 1 study of MM-302, a HER2-targeted liposomal doxorubicin, in patients with advanced HER2-positive (HER2+) breast cancer. *Cancer Res.* 2013;73.Abstract PA-12-29.
40. Ramakrishna N, Temin S, Chandarlapaty S, et al. Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol.* 2014;32:2100-2108.
41. Hurvitz SA, Hu Y, O'Brien N, et al. Current approaches and future directions in the treatment of HER2-positive breast cancer. *Cancer Treat Rev.* 2013;39:219-229.
42. Arribas J, Baselga J, Pedersen K, et al. p95HER2 and breast

cancer. *Cancer Res.* 2011;71:1515-1519.
43. O'Brien NA, McDonald K, Tong L, et al. Targeting PI3K/mTOR overcomes resistance to HER2-targeted therapy independent of feedback activation of AKT. *Clin Cancer Res.* 2014;20:3507-3520.
44. Andre F, O'Regan R, Ozguroglu M, et al. Everolimus for women with trastuzumab-resistant, HER2-positive, advanced breast cancer (BOLERO-3): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Oncol.* 2014;15:580-591.
45. Bose R, Kavuri SM, Searleman AC, et al. Activating HER2 mutations in HER2 gene amplification negative breast cancer. *Cancer Discov.* 2013;3:224-237.