HER2-Directed Therapy for Metastatic Breast Cancer

By Danijela Jelovac, MD [5] and Leisha A. Emens, MD, PhD [6]

This article reviews clinical data informing the effective management of HER2-positive metastatic breast cancer, including the optimal sequence of HER2-targeted agents.

Introduction

The human epidermal growth factor receptor 2 (HER2) is a transmembrane tyrosine kinase that is overexpressed in approximately 20% of invasive breast cancers, primarily due to gene amplification.[1] HER2 overexpression is clearly associated with more aggressive disease and worse clinical outcomes.[2] Importantly, HER2 overexpression strongly predicts response to HER2-targeted therapies, highlighting the importance of accurately defining the level of HER2 expression in both primary and metastatic tumors. Multiple studies have shown discordance in HER2 expression levels in up to 25% of paired primary and metastatic breast cancers,[3-5] and a substantial proportion of women with HER2-negative primary tumors acquire HER2 protein overexpression in their tumors at the time of relapse.[6-8] In patients with metastatic breast cancer (MBC), accurate determination of HER2 status is thus critical for guiding treatment decisions. The National Comprehensive Cancer Network (NCCN) guidelines recommend HER2 testing at relapse, particularly if HER2 expression was originally unknown or negative.[9]

Over the last 15 years, several HER2-targeted therapies have been developed, including HER2-specific monoclonal antibodies that bind to the external domain of the molecule (trastuzumab [Herceptin] and pertuzumab [Perjeta]), small-molecule tyrosine kinase inhibitors that inhibit signaling within the cell (lapatinib [Tykerb], neratinib [HKI-272], and afatinib [BIBW 2992]), and HER2-specific monoclonal antibodies conjugated to cytotoxic molecules (trastuzumab emtansine [T-DM1, Kadcyla]). Currently, four of these HER2-targeted agents are approved by the US Food and Drug Administration (FDA) for use: trastuzumab, lapatinib, pertuzumab, and T-DM1, with the last approved in February of this year. Here we review these HER2-targeted therapies, and discuss novel, promising agents for treatment of HER2-positive MBC that may become available in the next few years.

Trastuzumab

The first HER2-targeted therapy approved by the FDA is trastuzumab, a humanized monoclonal antibody (IgG1) that binds to the external domain of HER2. It has preferential activity against breast cancers driven by HER2 homodimers.[10] Since receiving FDA approval in 1998, trastuzumab has become clearly established as the key component of treatment for HER2-positive breast cancer in both the adjuvant and metastatic settings.[11-17] The addition of trastuzumab to chemotherapy is associated with significant improvement in time to tumor progression (TTP), objective response rate (ORR), duration of response, and overall survival (OS) in patients with HER2-positive MBC.[15] Patients with metastatic HER2-positive tumors may derive benefit from treatment with trastuzumab as a single agent, or in combination with cytotoxic or endocrine therapy.

Trastuzumab as a single agent in metastatic disease

Two seminal trials of single agent trastuzumab in the metastatic setting tested a weekly schedule, demonstrating moderate clinical activity with response rates (RR) of 15% to 34%[16,17] (Table 1). The most common adverse events were infusion-related, and cardiac dysfunction was reported in 2% to 4.7% of patients in these early studies.[16,17] A third phase II study evaluated the administration of trastuzumab every 3 weeks for the first-line treatment of HER2-positive MBC in 105 patients. Here, the ORR was 23% and the clinical benefit rate (CBR) was 36% (Table 1).[18] Single-agent trastuzumab given every 3 weeks was therefore shown to be effective, safe, and convenient.
Trastuzumab with chemotherapy in metastatic disease

Preclinical data have suggested potential additive or synergistic effects with trastuzumab and multiple cytotoxic agents, including anthracyclines, taxanes, vinorelbine, and cyclophosphamide.[19] In a pivotal multinational phase III clinical trial of 469 patients with previously untreated HER2-positive MBC, women treated with anthracyclines in the adjuvant setting were randomized to paclitaxel with or without trastuzumab, whereas anthracycline-naïve patients were randomized to anthracycline-based chemotherapy with or without trastuzumab.[15] Compared with chemotherapy alone, trastuzumab plus any chemotherapy was associated with a longer median TTP (7.4 vs 4.6 months; \( P < .001 \)), higher ORR (50% vs 32%; \( P < .001 \)), and longer median OS (25 vs 20 months; \( P = .046 \) (Table 1). The rate of cardiotoxicity was increased with the addition of trastuzumab to chemotherapy, particularly in patients receiving anthracyclines with trastuzumab (27% cardiotoxicity vs 8% with anthracycline chemotherapy alone) as compared to paclitaxel with trastuzumab (18% cardiotoxicity vs 1% with paclitaxel chemotherapy alone). Because of significant cardiotoxicity, this trial established that the combination of anthracyclines and trastuzumab cannot be recommended for patients with MBC. Compared with paclitaxel alone, trastuzumab plus paclitaxel was associated with a significant improvement in ORR (38% vs 16%; \( P < .001 \)), a longer median TTP (7 vs 3 months; \( P < .001 \)), and a trend toward a longer median OS (22 vs 18 months; \( P = .17 \)). It is notable that 72% of patients who received chemotherapy alone on this trial crossed over to receive trastuzumab. Thus, the survival benefit of trastuzumab-based chemotherapy is probably underestimated in this study.

Multiple phase II trials have evaluated the combination of different chemotherapeutic agents given with trastuzumab for metastatic disease.[20] Of these combinations, docetaxel plus trastuzumab has the highest activity against metastatic disease, with response rates of 50% to 76% and a favorable toxicity profile.[21-25] In a randomized, multicenter, phase II trial, docetaxel plus trastuzumab was significantly more effective than trastuzumab alone with respect to ORR (61% vs 34%; \( P = .0002 \)), median TTP (12 vs 6 months; \( P = .0001 \)), and median OS (31 vs 23 months; \( P = .0325 \)), and was not associated with a substantial increase in toxicity.[24] In vitro data have suggested that trastuzumab may reverse platinum resistance by modulating HER2 activity.[26] Based on this rationale, a phase III trial enrolled 196 patients with HER2-positive MBC, randomly assigning them to 6 cycles of treatment with trastuzumab plus paclitaxel with or without carboplatin.[27] The three-drug combination was significantly more effective than the two-drug combination with respect to ORR (52% vs 36%; \( P = .04 \)) and median progression-free survival (PFS) (10.7 vs 7.1 months; \( P = .03 \)), but not OS (35.7 vs 32.2 months).[27] In contrast to these results, the randomized phase III Breast Cancer International Research Group (BCIRG) 007 trial of 263 patients with previously untreated MBC did not show a benefit with the addition of carboplatin to docetaxel and trastuzumab.[28] Trastuzumab has also been shown to be effective in combination with vinorelbine. In the TRAVIOTA (trastuzumab and vinorelbine or taxane) study, 81 patients with previously untreated HER2-positive MBC were randomly assigned to trastuzumab plus weekly vinorelbine or taxane therapy.[29] The two regimens had comparable efficacy, with safety differences as expected for the different agents. Most recently, the HERNATA (Herceptin Plus Navelbine or Taxotere) trial compared docetaxel plus trastuzumab to vinorelbine plus trastuzumab in 284 chemotherapy-naïve MBC patients.[30] There was no difference in OR (59.3% in both groups); however, more patients in the docetaxel arm discontinued therapy due to toxicity (\( P < .001 \)). The combination of trastuzumab and capecitabine (Xeloda) has also shown efficacy as a first-line trastuzumab-containing regimen in this patient population.[31,32]

Trastuzumab with endocrine therapy in metastatic disease

Several studies have shown that HER2-targeted therapy is beneficial when added to an aromatase inhibitor in patients with hormone receptor (HR)-positive, HER2-positive MBC (Table 2). In the randomized, placebo-controlled, open-label, multicenter phase III TanDEM (Trastuzumab in Dual HER2 ER-positive Metastatic breast cancer) trial, 208 postmenopausal patients with HER2-positive and estrogen receptor (ER)- and/or progesterone receptor (PR)-positive disease were randomly assigned to anastrozole (Arimidex) alone or with weekly trastuzumab until disease progression.[33] Anastrozole plus trastuzumab was significantly more effective than anastrozole alone with regard to both ORR (20% vs 7%, \( P = .018 \)) and median PFS (4.8 vs 2.4 months; \( P = .0016 \)). OS was not significantly different (28.5 months for anastrozole plus trastuzumab vs 23.9 months for anastrozole alone; \( P = .325 \)); however, 70% of patients in the anastrozole-alone arm crossed over to receive trastuzumab after progression on anastrozole.[33] Cardiac dysfunction developed in 14 out of 103
patients (14%) receiving trastuzumab plus anastrozole and in 2 out of 104 patients (2%) treated with anastrozole alone, but grade 3 or 4 events were balanced between the treatment groups. Nearly 15% of patients who received anastrozole plus trastuzumab did not experience disease progression for at least 2 years, suggesting that concurrent hormonal therapy with trastuzumab can delay chemotherapy in some patients. In the eLEcTRA trial (Study of the Efficacy and Safety of Letrozole Combined With Trastuzumab in Patients With Metastatic Breast Cancer), 57 patients were randomized to either letrozole (Femara) or letrozole plus trastuzumab. Median TTP was 3.3 months vs 14.1 months (hazard ratio [HR] = 0.67; \( P = .23 \)), and ORR was 13% vs 27% in the letrozole and letrozole plus trastuzumab arms, respectively.[34]

**Trastuzumab beyond disease progression**

An issue that has emerged since the initial trials of trastuzumab is how to best manage patients whose tumors progress while on trastuzumab-based therapy. Several recent trials have demonstrated benefit with continuing trastuzumab therapy following disease progression on a trastuzumab-containing regimen.[35,36] One phase III study investigated capecitabine with or without trastuzumab in patients who had progressed on trastuzumab. Although the trial was closed prematurely due to poor accrual, data from the available 156 patients showed no significant difference in OS with capecitabine vs capecitabine plus trastuzumab, with OS of 20.6 months and 24.9 months, respectively (HR = 0.94; \( P = .73 \)).[37] Final OS analysis of the German Breast Group GBG-26 study did not demonstrate a significant survival benefit for treatment beyond progression with trastuzumab. However, in a post-hoc analysis, patients receiving anti-HER2 treatment as third-line therapy showed a better post-progression survival than those who did not receive HER2-targeted treatment. A total of 52 patients who continued or restarted anti-HER2 treatment (trastuzumab or lapatinib) after their second progression had a post-progression survival of 18.8 months compared with 13.3 months for 88 patients who did not receive third-line treatment with anti-HER2 agents (HR = 0.63; \( P = .02 \)). Continuation of trastuzumab was not associated with increased toxicity. These data together support use of HER2-targeted therapy beyond progression of disease for patients being treated with trastuzumab.

**Lapatinib**

The second HER2-targeted therapy to receive FDA approval was lapatinib, originally designed as a dual HER2 and epidermal growth factor receptor (EGFR; also known as HER1) tyrosine kinase inhibitor.[38] Clinical studies showed that lapatinib reversibly inhibits the intracellular tyrosine kinase activity of HER2 primarily, blocking tyrosine kinase phosphorylation and thereby signaling pathways downstream of HER2. In vitro studies demonstrated significant activity of lapatinib in trastuzumab-resistant breast cancer cell lines, and early clinical trials suggested that lapatinib is active in both inflammatory breast cancer and trastuzumab-refractory disease.[39-41] Randomized trials evaluated lapatinib as first-line therapy in MBC. In a single-arm phase II study, 138 patients with HER2-positive previously untreated MBC were randomly assigned to one of two lapatinib doses (1500 mg once daily or 500 mg twice daily).[42] Single-agent lapatinib was associated with an ORR of 24% and a CBR of 31%. The median duration of response was 28.4 weeks, and the treatment was well tolerated. The main toxicities associated with lapatinib were diarrhea, acneiform rash, nausea, and pruritus. There was no apparent correlation noted between the development of the rash and the efficacy of lapatinib.[43] Lapatinib was finally approved by the FDA in 2007 based on an improvement in TTP and ORR when added to capecitabine in patients with advanced breast cancer who had been previously treated with anthracyclines and taxanes and had progressed on trastuzumab-based therapy.[44,45] In a randomized phase III trial, 399 women with HER2-positive advanced disease or MBC refractory to trastuzumab received capecitabine with or without lapatinib (Table 3).[45] The combination of capecitabine plus lapatinib was associated with significant improvements in TTP (6.2 vs 4.3 months; \( P < .001 \)) and ORR (24% vs 14%; \( P = .017 \)), and a reduction in the risk for central nervous system (CNS) metastasis (6% vs 2%; \( P = .045 \)) compared with capecitabine alone. Moreover, there was no increase in serious side effects. Like trastuzumab, lapatinib has been evaluated in combination with endocrine therapy. A double-blind, placebo-controlled phase III trial tested letrozole plus lapatinib compared with letrozole alone in 1,286 postmenopausal women with HR-positive MBC (Table 2). Among the subset of 219 patients with HER2-positive disease, the addition of lapatinib to letrozole was associated with a significant improvement in PFS compared with letrozole alone (8.2 vs 3.0 months; \( P = .019 \)), but not OS (33.3 vs 32.3 months; \( P = .113 \)).[46]
The development of brain metastasis is devastating, and occurs in about 35% of HER2-positive MBC patients treated with trastuzumab.[47] Unlike trastuzumab (a large protein), lapatinib (a small molecule) can cross the blood-brain barrier. In a single-arm phase II, open-label, multicenter study, 45 patients with HER2-positive MBC with brain metastases not previously treated with whole brain radiation (WBRT) received lapatinib plus capecitabine as first-line treatment of brain metastases. After a median follow-up of 21 months, 29 patients (66%) had an objective CNS partial response; the median TTP was 6 months, and the median time to WBRT was 8 months. Half of the patients on study had grade 3 or 4 treatment-related adverse events, of which the most common were diarrhea and hand-foot syndrome.[48]

A treatment approach based on the dual targeting of HER2 without the use of chemotherapy is of great interest. One strategy is to use trastuzumab to abrogate signaling through cell-surface interactions, and lapatinib to abrogate signaling at the inner surface of the cell membrane (upstream/downstream signaling inhibition). A recent randomized trial in 296 heavily pretreated patients with MBC and disease progression on trastuzumab tested the clinical activity of lapatinib vs lapatinib plus trastuzumab. Compared with lapatinib alone, lapatinib plus trastuzumab was associated with a significant improvement in PFS (12 vs 8 weeks; HR = 0.73; P = .008) and CBR (24.7% vs 12%; P = .01).[49] The most frequent adverse events were diarrhea, rash, nausea, and fatigue. Diarrhea was significantly higher in the combination arm compared with the lapatinib arm (60% vs 48%; P = .03). The incidence of symptomatic cardiac events was low, with 3.4% in the combination arm and 1.4% in lapatinib arm. Thus, despite disease progression on prior trastuzumab-based therapy, the addition of lapatinib to trastuzumab significantly improved PFS and CBR compared with lapatinib alone, offering a chemotherapy-free option to patients with HER2-positive MBC.

Pertuzumab

Pertuzumab is a humanized monoclonal antibody (IgG1) recently approved by the FDA for the first-line treatment of HER2-positive MBC in combination with trastuzumab and docetaxel. Like trastuzumab, pertuzumab binds to the extracellular domain of HER2, but at a different epitope, blocking the dimerization of HER2 with other HER family receptors and inhibiting downstream signaling.[50] In a study of 29 patients with HER2-positive MBC who progressed on trastuzumab-based therapy, single-agent pertuzumab therapy had modest activity, with an ORR of 3.4% and a CBR of 10.3%. [51] Trastuzumab was added to pertuzumab in 17 patients at disease progression, yielding an ORR of 17.6% and a CBR of 41.2%.[51] Consistent with this clinical observation, dual blockade of HER2 signaling at the cell surface resulted in greater antitumor activity in preclinical studies.[52] On the basis of these preclinical and clinical data, the combination of pertuzumab and trastuzumab was evaluated in a phase II trial of 66 patients with HER2-positive MBC who had progressed while on trastuzumab. The regimen was active, with an ORR of 24.2%, CBR of 50%, and PFS of 5.5 months.[53] Moreover, the toxicity of the combination was acceptable, with only three patients (5%) experiencing an asymptomatic decrease in ejection fraction. The most common side effects were diarrhea, fatigue, nausea, and rash. These findings once again raise interest in dual HER2 blockade without the use of cytotoxic chemotherapy, in this case with both agents acting at the extracellular cell surface.

The phase III CLEOPATRA (Clinical Evaluation Of Pertuzumab And TRAStuzumab) study was a randomized, double-blind, placebo-controlled international clinical trial that tested pertuzumab in combination with trastuzumab and docetaxel for the first-line treatment of patients with HER2-positive MBC.[54] This study randomized 808 previously untreated HER2-positive MBC patients to pertuzumab with trastuzumab and docetaxel or placebo with trastuzumab and docetaxel (Table 3). Less than half of the patients had received adjuvant or neoadjuvant chemotherapy, and only 11% of patients had been treated with trastuzumab in either the adjuvant or neoadjuvant setting. PFS was significantly improved in the pertuzumab group, with a PFS of 18.5 months compared with 12.4 months in the control group (HR = 0.62; P < .001). The interim analysis of OS was performed after 43% of prespecified total numbers were available for the final analysis, and there was a strong trend in favor of the pertuzumab arm. Although the number of patients who had received prior trastuzumab-containing adjuvant or neoadjuvant chemotherapy was small, the PFS benefit of adding pertuzumab to therapy for those patients was similar to the benefit observed in patients who had received prior adjuvant or neoadjuvant chemotherapy without trastuzumab. The safety profile was generally similar, with no increase in left ventricular systolic dysfunction. Grade 3 or higher left ventricular systolic dysfunction was reported in 2.8% of patients in the control group, and in 1.2% of
patients treated with pertuzumab. In the pertuzumab group, there was more grade 3 febrile neutropenia (13.8% vs 7.6% in control group) and diarrhea (7.9% vs 5%). Based on these data, in June 2012, combination therapy with pertuzumab, trastuzumab, and docetaxel was approved by the FDA for first-line treatment of HER2-positive MBC.

Ongoing trials in HER2-positive MBC are currently evaluating pertuzumab in combination with trastuzumab and capcitabine in a phase II study in the second-line setting (PHEREXA [Ccapcitabine With or Without Pertuzumab in Patients With HER2-Positive Metastatic Breast Cancer]; NCT01026142), and in combination with trastuzumab emtansine (T-DM1) compared to trastuzumab and a taxane (docetaxel or paclitaxel) or T-DM1 alone in a phase III study in the first-line setting (MARIANNE [A Study of Trastuzumab-DM1 Plus Pertuzumab Versus Trastuzumab (Herceptin) Plus a Taxane in Patients With Metastatic Breast Cancer]; NCT01120184).

**Novel HER2-Directed Therapies**

Despite significant progress in developing new treatments that significantly improve clinical outcomes for patients with HER2-positive breast cancer over the last 15 years, the need for additional unique therapies remains. Some patients with early-stage HER2-positive breast cancer either progress on, or relapse very early after, adjuvant or neoadjuvant trastuzumab-based therapy, suggesting primary resistance to trastuzumab treatment. Also, in virtually all patients with HER2-positive MBC, the disease eventually progresses; this highlights the need for new therapies that target HER2 signaling, but with distinct mechanisms of action. Research on HER2-targeted therapy is extremely active, and novel agents continue to be developed at a rapid pace.

**Trastuzumab emtansine (T-DM1)**

Trastuzumab emtansine, or T-DM1, is a HER2-specific antibody-drug conjugate consisting of trastuzumab covalently bound via a linker to DM1, a derivative of the microtubule inhibitor maytansine.[55] T-DM1 is internalized by the cancer cell, and the DM1 moiety is released into the cell, resulting in microtubule damage and cell death. The mechanism of action of DM1 is similar to that of vinca alkaloids, which have demonstrated synergism with trastuzumab.[26] In preclinical studies, T-DM1 showed potent antitumor activity in trastuzumab- and lapatinib-resistant tumors.[55,56] In a phase I study in 24 patients with advanced HER2-positive breast cancer who had progressed on trastuzumab and had received a median of four previous lines of therapy, T-DM1 was associated with a CBR of 73%, including 5 patients with objective responses.[57] T-DM1 was associated with mild, reversible toxicity, including thrombocytopenia, transaminitis, and fatigue. No cardiac toxicity was observed.

A subsequent single-arm phase II study of T-DM1 enrolled 112 patients with HER2-positive MBC previously treated with HER2-targeted therapy. Patients were heavily pretreated, with a median of eight prior lines of therapy; 67% of patients had also previously received lapatinib.[58] T-DM1 showed meaningful activity in this population, with an ORR of 26% and a median PFS of 4.6 months; response rates were higher in the 74 patients with centrally confirmed HER2-positive tumors (ORR 34%; PFS 8.2 months). The most frequent grade 3 or higher adverse events were hypokalemia, thrombocytopenia, and fatigue.[58] A second single-arm phase II study enrolled 110 patients with HER2-positive MBC previously treated with trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine.[59] Here, the ORR was 34.5%, the CBR was 48%, the PFS was 6.9 months, and the median duration of response was 7.2 months. In 80 patients with centrally confirmed HER2-positive tumors, the RR was 41.3%, and the median PFS was 7.3 months.[59] In late 2010, results were reported from an open-label phase II study of T-DM1 compared with trastuzumab plus docetaxel as first-line treatment in 137 patients with HER2-positive MBC.[60] After a median follow-up of 6 months, the ORR was 48% in the T-DM1 arm, and 41% in the trastuzumab-plus-docetaxel arm. A more favorable toxicity profile was observed on the T-DM1 arm, with a lower incidence of grade 3 or 4 adverse events with T-DM1 vs trastuzumab and docetaxel (37% vs 75%). A recent update of these data showed a significant increase in the investigator-reported PFS for T-DM1 compared with trastuzumab plus docetaxel, at 14.2 months vs 9.2 months, respectively.[61] The pivotal EMILIA study was a phase III open-label, international trial of 991 patients with locally advanced unresectable or metastatic HER2-positive breast cancer previously treated with trastuzumab and a taxane who were randomized to T-DM1 or lapatinib plus capecitabine (Table 3).[62] There was significant improvement in both PFS and OS with T-DM1, with a PFS of 9.6 months compared with 6.4 months with lapatinib plus capecitabine (HR = 0.65; P < .001), and an OS of 30.9 months with T-DM1 compared with 25.1 months with lapatinib plus capecitabine (HR = 0.68; P < .001).
The ORR was also higher on the T-DM1 arm compared with the lapatinib plus capecitabine arm (43.6% vs 30.8%; \(P < .001\)). In addition, the toxicity profile favored the T-DM1 arm, with fewer grade 3 and 4 adverse events (41% vs 57%). Thrombocytopenia and transaminitis were the most common grade 3 or higher adverse events associated with T-DM1. The FDA is reviewing these data for accelerated approval, with a decision expected in early 2013.

Preliminary data from a phase Ib/II clinical trial evaluating the combination of T-DM1 plus pertuzumab in 21 previously untreated and 46 relapsed HER2-positive MBC patients demonstrated an ORR of 57% in previously untreated MBC, although the majority of patients had received systemic therapy in the adjuvant setting that included trastuzumab (86%), taxanes (71%), and/or anthracyclines (62%); the ORR was 34.8% in patients with relapsed disease.[63] The combination of T-DM1 and pertuzumab was well tolerated. Based on these data, an ongoing phase III study is evaluating the combination of pertuzumab and T-DM1 vs trastuzumab plus a taxane (docetaxel or paclitaxel) or T-DM1 alone (MARIANNE; NCT01120184).

**Neratinib**

Neratinib is an oral, irreversible smallmolecule pan-HER receptor tyrosine kinase inhibitor with activity in preclinical studies.[64] An open-label, multicenter phase II trial enrolled 136 patients with HER2-positive MBC, 70 of whom had been previously treated with trastuzumab, and 66 of whom were trastuzumab-naive. Single-agent neratinib (orally at 240 mg once daily) was associated with ORRs of 24% and 56% in the trastuzumab-pretreated and trastuzumab-naive groups, respectively.[65] Diarrhea was the most frequent adverse event, but was manageable with antidiarrheal agents and neratinib dose modifications. No significant cardiac toxicity was documented. In a phase I/II clinical trial, the combination of neratinib and capecitabine showed an ORR of 50% in 22 patients previously treated with trastuzumab and a taxane.[66] In a randomized, open-label phase II study, 233 patients previously treated with trastuzumab and a taxane were treated with neratinib or the combination of lapatinib and capecitabine.[67] The PFS was 4.5 months in the neratinib arm and 6.8 months in the combination arm, with an OS of 19.7 months vs 23.6 months, and an ORR of 29% vs 40%, respectively. Diarrhea remained a consistent side effect. Neratinib has also been tested in a phase I/II study with paclitaxel and vinorelbine, with promising results.[68,69] Ongoing studies are evaluating the activity of neratinib in combination with capecitabine (NCT00741260), trastuzumab (NCT00398567), paclitaxel (NCT00445458), and neratinib plus paclitaxel compared with trastuzumab plus paclitaxel (NCT00915018).

**Afatinib**

Afatinib is another oral, irreversible small molecule pan-HER tyrosine kinase inhibitor with demonstrated activity as monotherapy in a phase II study of 41 patients with HER2-positive MBC after disease progression on trastuzumab.[70] Four patients (11%) had a partial response, and 15 patients (37%) had stable disease. The most common side effects were diarrhea and rash. Ongoing trials are evaluating afatinib in combination with trastuzumab (NCT00950742), with letrozole (NCT00708214), and in the first-line setting with trastuzumab or lapatinib (NCT00826267).

**Bevacizumab**

HER2 signaling has been associated with production of proangiogenic factors, including vascular endothelial growth factors (VEGFs) A, C, and D.[71] Bevacizumab (Avastin) is a humanized monoclonal antibody (IgG1) that blocks angiogenesis by binding to circulating VEGF A, preventing its binding to the VEGF receptor. In a chemotherapy-free treatment strategy, a phase II trial tested trastuzumab and bevacizumab in 50 patients with locally recurrent or metastatic HER2-positive breast cancer.[72] The ORR was 48%, the CBR was 60%, the median time to progression was 9.2 months, and the median OS was 43.8 months. Toxicities were acceptable, with hypertension most commonly seen. Another phase II study tested the combination of bevacizumab, trastuzumab, and capecitabine in 88 patients with locally recurrent or metastatic HER2-positive breast cancer.[73] At a median follow-up of 8.8 months, the ORR was 73% and the median PFS was 14.5 months. Grade 3 or greater side effects occurred in 44% of patients, most commonly hand-foot syndrome, diarrhea, and hypertension. Heart failure was seen in two patients (2%). The phase III clinical study AVEREL (AVastin in Combination With HERceptin/DocetaxEL in Patients With HER2-Positive Metastatic Breast Cancer) randomized 424 women to docetaxel plus trastuzumab with or without bevacizumab as first-line treatment for HER2-positive MBC.[74] The addition of bevacizumab to docetaxel plus trastuzumab revealed a trend in improved PFS (16.5 vs 13.7 months), although the difference was
not statistically significant on the first analysis. However, the difference was statistically significant in a separate analysis by an independent review committee (HR = 0.72; \( P = .0162 \)). Although OS did not differ between groups, the data are not yet mature. It remains unclear if these data will support FDA approval. An ongoing phase III study is evaluating addition of bevacizumab to carboplatin and paclitaxel plus trastuzumab for first-line treatment of HER2-positive MBC (Eastern Cooperative Oncology Group [ECOG] 1105; NCT00520975). Small-molecule inhibitors of angiogenesis (sunitinib [Sutent] and pazopanib [Votrient]) are also in early clinical trials in combination with trastuzumab or lapatinib.[75]

**HER2-targeted vaccination strategies**

Therapeutic cancer vaccines designed to induce immune responses specific for HER2 are under active investigation for both early-stage and advanced HER2-positive breast cancer.[76] HER2-directed vaccine platforms that have been evaluated clinically include peptide-based vaccines, protein-based vaccines, plasmid DNA-based vaccines, dendritic cell–based vaccines, and vaccines that deliver HER2 in a viral or bacterial vector. The Tumor Vaccine Group at the University of Washington has tested HER2 peptide- and protein-based vaccines in patients with metastatic HER2-positive breast cancer.[77-83] Patients immunized with vaccines that contain both major histocompatibility complex (MHC) Class I and II epitopes and granulocyte-macrophage colony-stimulating factor (GM-CSF) developed both delayed-type hypersensitivity reactions (an indicator of CD4+ T helper cells) and potent, long-lived CD8+ T cells specific for HER2.[79,83] Additionally, these patients demonstrated epitope spreading both within the HER2 protein itself, and to other antigens not physically delivered by the vaccine.[80,81] In contrast, immunization with a vaccine that delivered only an MHC Class I epitope resulted in only HER2-specific CD8+ T cells that were short-lived.[82] A dendritic cell–based vaccine similar to sipuleucel-T (Provenge) has been tested in 18 patients with metastatic HER2-positive breast cancer.[84] The agent, lapuleucel-T (Neuvenge), was derived from autologous peripheral blood mononuclear cells activated in vitro with a recombinant fusion protein (BA7072). This protein contains sequences derived from both the intracellular and extracellular domains of HER2, and from GM-CSF. Vaccinated patients displayed evidence of new HER2-specific T-cell activity; one patient had a partial response, and three additional patients had stable disease for more than 1 year. Finally, peptide-, protein-, and cell-based GM-CSF– secreting vaccines have been tested in combination with either trastuzumab or lapatinib in patients with metastatic HER2-positive breast cancer, with evidence of enhanced HER2-specific immunity.[85-87]

**Summary**

Understanding both the intricacies and the importance of HER2 signaling in breast cancers that overexpress HER2 has led to the development of several unique HER2-targeted drugs for the management of both early-stage and metastatic HER2-positive breast cancer. Prior to the approval of pertuzumab in combination with trastuzumab and docetaxel, the standard approach to the first-line treatment of HER2-positive metastatic disease was trastuzumab plus a taxane or vinorelbine, or lapatinib and capecitabine (for patients who had relapsed early after trastuzumab-based adjuvant therapy). The approval of pertuzumab in combination with trastuzumab and docetaxel has set a new standard of care for this patient population. Importantly, this combination regimen is well tolerated and without increased cardiac toxicity. Dual-HER2 blockade was effective in both trastuzumab-pretreated and trastuzumab-naive patients, suggesting that trastuzumab-resistant HER2-positive breast cancers likely still depend on the HER2 signaling pathway. Once a good clinical response is achieved, it is reasonable to consider dropping docetaxel chemotherapy and continuing treatment with trastuzumab and pertuzumab. The role of pertuzumab in the second-line setting will be addressed by results of the PHEREXA trial. The continuation of HER2 blockade remains an important component of therapy at disease progression, and therapy with lapatinib or novel agents available through clinical trials should be considered. Data from the EMILIA trial showed that T-DM1 has therapeutic potential for patients who progress on trastuzumab and a taxane, and T-DM1 is under active FDA review for accelerated approval. For patients with HER2-positive brain metastasis, lapatinib is currently the only FDA-approved HER2-targeted agent with documented activity; current data support the use of lapatinib and capecitabine in these patients. Clinical and research efforts must focus on new ways to penetrate the blood-brain barrier and target HER2-positive disease within the CNS. Finally, alternative therapeutic approaches targeting the molecular chaperones that stabilize HER2 (HSP90), elements of signaling pathways...
downstream of HER2 (PI3K/Akt/mTOR pathways), or cell surface receptor cross-talk (insulin growth factor receptor 1 [IGFR1]) are being tested to overcome resistance to HER2-specific agents.[75]

Given the potential cumulative toxicity and cost implications of these various combinations, the identification of biomarkers to guide treatment selection, maximizing efficacy while minimizing toxicity and cost, is imperative. A coordinated strategy driven by the biology of the pathway will allow the full power of HER2-targeted therapy to be realized.

**Financial Disclosure:** Dr. Emens receives research funding from Genentech, and has received honoraria for advisory board participation from Bristol-Myers Squibb. Dr. Jelovac has no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

---

**References:**


HER2-Directed Therapy for Metastatic Breast Cancer
Published on Cancer Network (http://www.cancernetwork.com)


84. Park JW, Melisko ME, Esserman LJ, et al. Treatment with autologous antigen-presenting cells activated with the HER-2-based antigen lapuleucel-T: results of a phase I study of immunologic and


Source URL:
http://www.cancernetwork.com/oncology-journal/her2-directed-therapy-metastatic-breast-cancer

Links:
[1] http://www.cancernetwork.com/review-article
[2] http://www.cancernetwork.com/oncology-journal
[5] http://www.cancernetwork.com/authors/danjela-jelovac-md
[6] http://www.cancernetwork.com/authors/leisha-emens-md-phd