Emerging approaches for treating HER2-positive metastatic breast cancer beyond trastuzumab

W. J. Gradishar*
Northwestern University Feinberg School of Medicine, Robert H. Lurie Comprehensive Cancer Center, Chicago, USA

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Because metastatic breast cancer (MBC) is incurable in most cases, the goals of treatment are improvement in quality of life, management of symptoms, and prolonged survival. The human epidermal growth factor receptor 2 (HER2) is overexpressed in up to 30% of breast tumors, and before the development of HER-targeted therapy, HER2 positivity was predictive of poorer clinical outcomes. Trastuzumab and pertuzumab (anti-HER2 monoclonal antibodies), lapatinib (a small molecule inhibitor of HER2 and the epidermal growth factor receptor [EGFR]) are approved for treating HER2-positive MBC in the United States. Although trastuzumab plus chemotherapy is currently regarded as the first-line standard of care for HER2-positive MBC, it is not without shortcomings; these include its association with certain adverse events (e.g., cardiotoxic effect) and development of resistance. A number of investigational agents that target HER2 and other members of that receptor family are in clinical development for patients with HER2-positive MBC whose disease has progressed on trastuzumab. In addition, in an effort to overcome treatment resistance, clinical trials are evaluating combination therapy (investigational HER-targeted agents with trastuzumab or lapatinib). This review discusses recently completed and ongoing phase II and III clinical trials of investigational HER-targeted agents in the setting of trastuzumab–progressive, HER2-positive MBC.

Key words: HER inhibitors, HER2-positive, metastatic breast cancer, monoclonal antibodies, neoadjuvant therapy, trastuzumab

introduction

In 2013, it is estimated that there will be 39 620 breast cancer–related deaths among women in the United States [1] and 88 886 in Europe [2]. Systemic treatment modalities for breast cancer management include cytotoxic chemotherapy, endocrine therapy, biologic therapy, or combinations of these modalities, with selection based on a number of factors (including patient and tumor characteristics, stage of disease, and patient preference) [3]. In most cases, metastatic breast cancer (MBC) is incurable, and the goals of treatment are to optimize quality of life, manage symptoms, and prolong survival.

Approximately 25%–30% of breast tumors overexpress human epidermal growth factor receptor 2 (HER2, a transmembrane tyrosine kinase [TK] receptor within the HER family), a tumor characteristic that tends to occur in younger patients and, before the advent of HER2-directed therapy, predicted a poor clinical outcome [4, 5]. This review focuses on the current status of investigational anti-HER2 agents actively being evaluated in phase II or III clinical trials, specifically in the setting of trastuzumab–pretreated/progressive MBC, and includes an overview of accumulating neoadjuvant data for earlier use of anti-HER2 combinations. Relevant clinical trials were selected for inclusion based on searches of PubMed, key oncology congresses, and the ClinicalTrials.gov registry.

*Correspondence to: Dr William J. Gradishar, Northwestern University Feinberg School of Medicine, Department of Medicine, Division of Hematology Oncology, Robert H. Lurie Comprehensive Cancer Center, 676 North St. Clair St, Suite 850, Chicago, IL 60611, USA. Tel: +1-312-695-4541; Fax: +1-312-695-6189; E-mail: w-gradishar@northwestern.edu

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approved anti-HER2 agents: trastuzumab, lapatinib, pertuzumab, and ado-trastuzumab emtansine

Trastuzumab (Herceptin®, Genentech; South San Francisco, CA), lapatinib (Tykerb®, GlaxoSmithKline; London, UK), and pertuzumab (PERJETA™ Genentech; South San Francisco, CA) are approved in the United States for treating HER2-positive MBC [6]; trastuzumab plus chemotherapy is regarded as standard first-line treatment of HER2-positive MBC [3, 4]. Lapatinib, a reversible inhibitor of epidermal growth factor receptor (EGFR) and HER2, is approved for use with capecitabine for treating HER2-positive MBC after chemotherapy and trastuzumab failure [7]. In a randomized phase III trial of women with HER2 positive, locally advanced or MBC progressing after an anthracycline, a taxane, and trastuzumab, lapatinib significantly prolonged median time to progression (TTP) relative to capecitabine alone [8.4 versus 4.4 months; hazard ratio (HR) 0.49; 95% confidence interval (CI) 0.34–0.71; P < 0.001] [8]. Mean overall survival (OS) in the intent-to-treat population was 75.0 weeks with lapatinib/capecitabine compared with 64.7 weeks with capecitabine alone (HR 0.87; 95% CI 0.70–1.08; P = 0.206) [9]. Diarrhea was the most common adverse event (AE) in both treatment groups (all grade incidence, 39% with lapatinib alone and 60% with lapatinib/capecitabine; P < 0.001) [8]. Combining lapatinib with trastuzumab has also demonstrated activity in trastuzumab-refractory MBC, with a significant improvement in median progression-free survival (PFS) versus single-agent lapatinib (12.0 versus 8.1 weeks; HR 0.73; 95% CI 0.57–0.93; P = 0.008) observed in an open-label phase III trial (N = 296) [10]. With both lapatinib alone and combination lapatinib/trastuzumab, the most common all-grade AEs were diarrhea (48% and 60%, respectively), rash (29% and 22%, respectively), and nausea (28% each).

Overall, although trastuzumab has revolutionized the treatment of HER2-positive breast cancer, high rates of primary and treatment-emergent resistance are among the barriers to improving long-term outcomes [11, 12]; additional shortcomings include the potential association with cardiotoxic effect and increased incidence of brain metastases when used in the adjuvant setting [13]. While the correlation between trastuzumab and brain metastases has not been confirmed, it has been suggested that systemic disease control with trastuzumab along with its inability to penetrate the blood–brain barrier may result in a higher incidence of brain metastases [13]. Despite these shortcomings, a potential role for anti-HER2 therapy in trastuzumab-progressive MBC is also supported by results of the German Breast Group 26/Breast International Group 03-05 study (N = 156), which demonstrated a significantly prolonged TTP when continuing trastuzumab beyond progression [14]. Median TTP was 5.6 months with capecitabine alone and 8.2 months with the combination of capecitabine and trastuzumab (HR 0.69; 95% CI 0.48–0.97; P = 0.034), with median OS of 20.4 and 25.5 months, respectively (P = 0.257) and a response rate (RR) of 27.0% and 48.1%, respectively (odds ratio, 2.50; P = 0.0115). With both capecitabine alone and the capecitabine and trastuzumab combination, the most common grade 3/4 AEs were skin changes (24% and 32%, respectively) and diarrhea (19% and 16%, respectively); the only significant difference in AEs between arms was for grade 1–4 anemia (44% and 64%, respectively; P = 0.021). Final OS results were recently published and failed to show a significant improvement in OS with trastuzumab/capecitabine versus capecitabine alone (HR 0.94; 95% CI 0.65–1.3; P = 0.734) [15]. In addition, a systematic review focused on elucidating the benefits of trastuzumab beyond progression was confounded by the lack of other randomized clinical trials designed with this question in mind [16]. However, results from the pharmacoepidemiologic, observational Hermine study showed that patients who received trastuzumab treatment beyond progression had significantly longer OS compared with patients whose treatment was discontinued at disease progression (P < 0.001; based on the initiation of trastuzumab therapy) [17]. Subgroup analyses identified trastuzumab treatment beyond progression as an independent predictive factor for longer OS.

Lapatinib has also demonstrated benefit when used as a component of first-line treatment regimens for HER2-positive MBC. Lapatinib significantly prolonged median TTP when combined with paclitaxel (36.4 versus 25.1 weeks for paclitaxel...
trastuzumab in nonmetastatic, invasive breast cancer (the phase III ALTTO trial of adjuvant lapatinib and/or placebo). Incidence of all-grade rash (43% versus 20%; P < 0.0001), diarrhea (58% versus 26%; P < 0.0001), and vomiting (25% versus 17%; P = 0.01) was significantly higher with lapatinib/paclitaxel than with placebo/paclitaxel, while incidence of all-grade alopecia was significantly higher with paclitaxel/placebo versus lapatinib/paclitaxel (52% versus 64%; P = 0.004) [18]. Lapatinib significantly prolonged median PFS when combined with letrozole in 219 patients with hormone receptor- and HER2-positive MBC (8.2 versus 3.0 months with letrozole/placebo; HR 0.71; 95% CI 0.53–0.96; P = 0.019) [19]. Back pain (grade 3, 2%; grade 4, <1%) and dyspnea (grade 3, 1%; grade 4, <1%) were the most common grade 3/4 AEs reported with letrozole/placebo and diarrhea (grade 3, 9%; grade 4, <1%) and back pain (grade 3, 2%; grade 4, 0%) were the most common with lapatinib/letrozole. In addition, the benefits of lapatinib in improving outcomes (including OS) in HER2-positive MBC have been described by systematic review and meta-analysis [20, 21].

Lapatinib has also demonstrated activity in HER2-positive MBC patients with previously untreated brain metastases. A recent phase II study (LANDSCAPE) evaluated the activity of lapatinib plus capecitabine on central nervous system (CNS) metastases in patients with HER2-positive MBC who had not received previous whole-brain radiation therapy (N = 45) [22]. By Response Evaluation Criteria In Solid Tumors (RECIST) criteria, 24 patients (57%) achieved an objective CNS response, 22 patients (52%) had a partial response (PR), and 2 (5%) had a complete response (CR). Median TTP was 5.5 months and median OS was 17.0 months.

Of note, however, several studies in breast cancer (not limited to MBC) have shown limited activity with lapatinib. In a phase III trial of first-line taxane-based chemotherapy plus lapatinib or trastuzumab in patients with HER2-positive MBC (N = 652), interim results showed median PFS was 8.8 months with lapatinib compared with 11.4 months with trastuzumab (HR 1.33; 95% CI 1.06–1.67; P = 0.01), but there was no significant difference in OS (P = 0.62) [23]. In the TEACH trial of adjuvant lapatinib or placebo in HER2-positive early-stage breast cancer (N = 3161), lapatinib did not show a significant benefit in disease-free survival (DFS) compared with placebo (P = 0.053); however, DFS was better for hormone receptor-negative patients in the lapatinib arm compared with those in the placebo arm (P = 0.006) [24]. In addition, interim analysis of the phase III ALTTO trial of adjuvant lapatinib and/or trastuzumab in nonmetastatic, invasive breast cancer (N = 8381; NCT0490139) prompted discontinuation of the lapatinib monotherapy arm because it was deemed unlikely to meet prespecified noninferiority criteria.

Pertuzumab is a humanized monoclonal antibody that targets the HER2 receptor; because of its binding site, unlike trastuzumab, pertuzumab prevents HER2 from coupling with other HER members (including HER1/EGFR/ErbB1, HER3/ErbB3, and HER4/ErbB4) [25, 26]. Pertuzumab is approved in combination with trastuzumab and docetaxel in patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease [27]. Preclinical evidence of synergy between pertuzumab and trastuzumab has been observed [28, 29]. Overall, clinical development of pertuzumab has focused on its combination use with other HER2-targeted agents, on the basis of limited single-agent clinical activity in phase I trials in various advanced cancers [30, 31]. A phase II trial evaluated pertuzumab plus trastuzumab in patients with trastuzumab-progressive HER2-positive MBC (N = 66) [32]. The RR was 24.2% (including 5 CRs and 11 PRs) and 17 additional patients (25.8%) had stable disease (SD) for >6 months; median PFS was 5.5 months. Grade 3/4 toxic effect was infrequent, the most common being diarrhea (3%) followed by asthenia, rash, and pruritus (2% each). Results have since been published for a third cohort, including patients with disease progression on trastuzumab-based therapy who were given pertuzumab monotherapy. Of note, pertuzumab monotherapy may have been followed by reintroduction of trastuzumab at the time of progression on pertuzumab (to be added to pertuzumab [provided it had been tolerated], per investigator discretion) [33]. The RRs and clinical benefit rates (CBR [objective responses plus SD ≥6 months]) for the 29 patients receiving pertuzumab monotherapy were 3.4% and 10.3%, respectively; among 17 patients who subsequently received pertuzumab plus trastuzumab, these were 17.6% and 41.2%, respectively. Median PFS and TTP after the reintroduction of trastuzumab (17.4 and 17.4 weeks, respectively) were longer than for the period of pertuzumab monotherapy (both median PFS and TTP were 7.1 weeks), although these differences were not subject to statistical analysis.

Phase III trials of pertuzumab for HER2-positive MBC are completed or ongoing in the first-line setting (CLEOPATRA/NCT00567190 [34]; MARIANNE/NCT01120184 [35]). Based on the results of CLEOPATRA [34], in which a significant improvement in the primary end point of PFS was seen with pertuzumab/trastuzumab/docetaxel versus placebo/trastuzumab/docetaxel (18.5 versus 12.4 months; HR 0.62; 95% CI 0.51–0.75; P < 0.001) without increased cardiotoxic effect, pertuzumab was granted priority review in the United States for previously untreated HER2-positive MBC [36]. Interim OS results reported more deaths in the control arm (96 [23.6%]) than in the pertuzumab arm (69 [17.2%]), and the objective RR was significantly higher with pertuzumab versus placebo (80.2% versus 69.3%; P = 0.001) [34]. Regarding its evaluation in trastuzumab-progressive disease, a randomized phase II trial of trastuzumab/capecitabine alone or with pertuzumab for HER2-positive MBC progressing during or after trastuzumab-based, first-line MBC therapy is ongoing (PHEREXA/NCT01262142) [37]. Additionally, in an ongoing nonrandomized phase II trial, patients treated with up to one prior regimen for MBC (allowing prior trastuzumab for MBC or in the adjuvant setting) are receiving pertuzumab in combination with trastuzumab and paclitaxel (NCT01276041).

Ado-trastuzumab emtansine (T-DM1; Kadcyla™; Genentech; South San Francisco, CA) is an immunoconjugate combining trastuzumab with maytansine (DM1), an antimitotubule cytotoxic agent, which was recently approved as monotherapy for HER2-positive MBC previously treated with trastuzumab and a taxane [38, 39]. A phase II study
evaluated T-DM1 in HER2-positive MBC progressing after prior anti-HER2 therapy and chemotherapy (N = 112) [40]. The RR by independent review was 25.9% (29/112), with a median PFS of 4.6 months. The most common grade 3/4 toxic effects were hypokalemia (8.9%), thrombocytopenia (8.0%), and fatigue (4.5%). EMILIA is an ongoing open-label, phase III trial comparing T-DM1 versus capcitabine/ lapatinib in trastuzumab-pretreated HER2-positive advanced/MBC, with PFS and OS as its co-primary end points (NCT00829166) [41]. Results for EMILIA report a significant improvement in median PFS with T-DM1 versus capcitabine/ lapatinib (9.6 versus 6.4 months; HR 0.650; 95% CI 0.549–0.771; P < 0.0001). Median OS was not reached in the T-DM1 arm; OS was 23.3 months in the capcitabine/ lapatinib arm (HR 0.621; 95% CI 0.475–0.813; P = 0.0005). The 1-year OS rate was 84.7% with T-DM1 and 77.0% with capcitabine/ lapatinib; 2-year OS rates were 65.4% and 47.5% for the T-DM1 and capcitabine/ lapatinib arms, respectively. Thrombocytopenia (12.9%) was the most common grade ≥3 AE with T-DM1; with capcitabine/ lapatinib, the most common was diarrhea (20.7%) [42]. In another open-label, phase III trial, T-DM1 is being compared with the physician’s choice of treatment in a HER2-positive population pretreated with at least two prior anti-HER2 regimens specifically for unresectable locally advanced or MBC (NCT01419197). T-DM1 has also been evaluated in combination with other anti-HER2 antibodies, including pertuzumab. In a phase Ib/II study of T-DM1 plus pertuzumab in HER2-positive, trastuzumab-pretreated advanced breast cancer (N = 60; n = 37 enrolled at preliminary analysis) [43], preliminary results included 2 confirmed and 7 unconfirmed PRs among the first 23 efficacy-assessable patients. Individual grade 4 and 5 toxic effects were thrombocytopenia and pneumonia, respectively; fatigue was the most common grade 3 toxic effect (n = 4).

**investigational anti-HER2 agents for trastuzumab-pretreated HER2-positive MBC**

Investigational anti-HER2 agents are being studied for their therapeutic potential in the first-line management of HER2-positive MBC as well as in trastuzumab-pretreated/progressive disease (Table 1), with completed and ongoing clinical trials in the latter setting discussed below. The sites of action of the investigational anti-HER2 agents being studied beyond trastuzumab progression are illustrated in Figure 1. Details of phase II and phase III clinical trials of investigational HER family-targeted agents being investigated in HER2-positive MBC are presented in Table 2.

**investigational antibodies**

MM-111 (Merrimack Pharmaceuticals; Cambridge, MA) is a bispecific antibody that targets the HER2/HER3 heterodimer [44]. A first-in-human, phase I/II study is evaluating MM-111 monotherapy in HER2-positive, heregulin-positive, advanced, refractory solid tumors (part 1; NCT00911898), and in HER2-positive advanced breast cancer patients who have received prior trastuzumab or lapatinib therapy (part 2) [45]. A second phase I study is evaluating MM-111 in combination with

| **Table 1.** Investigational HER2-targeting agents under evaluation for the treatment of trastuzumab-pretreated/progressive MBC |
|---|---|---|
| **Agent** | **Description** | **Phase of development** |
| Afatinib | Small molecule, irreversible inhibitor of EGFR/HER1, HER2, and HER4 | III |
| Neratinib | Small molecule, irreversible inhibitor of EGFR/HER1, HER2, and HER4 | II |
| MM-111 | Bispecific antibody against HER2/HER3 heterodimer | I/II |

*Specifically for trastuzumab-pretreated/progressive disease, based on clinical trials indexed on ClinicalTrials.gov as of February 2013.

HER, human epidermal growth factor receptor; MBC, metastatic breast cancer; EGFR, epidermal growth factor receptor.

trastuzumab in HER2-positive, heregulin-positive, advanced, refractory breast cancer (NCT01097460) [44].

**investigational small molecules: HER family inhibitors**

Afatinib (BIBW 2992; Boehringer Ingelheim; Ingelheim, Germany) is an oral, irreversible inhibitor targeting EGFR/HER1, HER2, and HER4 [46, 47]. Results from a phase II study of afatinib for HER2-positive MBC progressing post-trastuzumab (N = 41) showed 4 PRs among 35 assessable patients [48]. The most common all-grade treatment-related AEs included diarrhea (90.2%) and rash (65.9%). LUX-Breast 1 is an ongoing phase III study of vinorelbine plus either afatinib or trastuzumab for HER2-positive MBC in patients who failed one trastuzumab-containing regimen as first-line treatment of MBC or as adjuvant therapy (NCT01125566) [49]. In addition, an ongoing nonrandomized, phase II trial is evaluating afatinib alone followed by combinations with paclitaxel or vinorelbine (in patients who failed afatinib monotherapy during this trial) in patients with HER2-positive MBC who failed HER2-targeted therapy in the neoadjuvant and/or adjuvant settings (LUX-Breast 2/NCT01271725) [50]. A nonrandomized phase II trial (NCT01325428) is evaluating afatinib and subsequent afatinib/ vinorelbine in patients progressing on afatinib in inflammatory locally advanced or metastatic HER2-positive breast cancer; both patients who have and have not failed prior trastuzumab therapy will be included. Finally, a randomized phase II trial (LUX-Breast 3/NCT01441596) is evaluating afatinib as monotherapy and in combination with vinorelbine versus investigator’s choice of treatment in patients with HER2-positive breast cancer and brain metastases after treatment with trastuzumab or lapatinib [51].

Neratinib (PB-272; Puma Biotechnology, Inc., Los Angeles, CA [licensed in October 2011 from Pfizer; New London, CT, USA; [52]) is an oral, irreversible inhibitor of EGFR/HER1, HER2, and HER4 [53, 54]. A phase II study evaluated neratinib in a HER2-positive breast cancer population (N = 136), including 2 cohorts based on trastuzumab exposure: trastuzumab pretreated (n = 66) and trastuzumab naive (n = 70) [55]. In the trastuzumab-pretreated and trastuzumab-naive cohorts, 16-week PFS rates were 59% and 78%, median PFS was
<table>
<thead>
<tr>
<th>Trial</th>
<th>Study population</th>
<th>Regimen</th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
<th>Most common grade ≥3 AEs</th>
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<tbody>
<tr>
<td>Afatinib</td>
<td></td>
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<tr>
<td>Lin 2012; phase II; completed [48]</td>
<td>HER2-positive MBC progressing after trastuzumab-containing therapy</td>
<td>Afatinib</td>
<td>11% (of 35 assessable patients)</td>
<td>15.1 wk</td>
<td>61.0 wk</td>
<td>Diarrhea (24.4%), rash (9.8%), vomiting (7.3%), and stomatitis (7.3%)</td>
</tr>
<tr>
<td>LUX-Breast 1 (NCT01125566); phase III; recruiting [49]</td>
<td>HER2-positive MBC progressing after trastuzumab therapy</td>
<td>A: trastuzumab + vinorelbine</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>LUX-Breast 2 (NCT01271725); phase II; recruiting [50]</td>
<td>HER2-positive MBC with prior HER2-targeted therapy (neoadjuvant and/or adjuvant)</td>
<td>A: afatinib until progression followed by afatinib + paclitaxel</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
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<tr>
<td>LUX-Breast 3 (NCT01441596); phase II; recruiting [51]</td>
<td>HER2-positive MBC with progressive brain metastases with prior trastuzumab- and/or lapatinib-based therapy</td>
<td>A: afatinib</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
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<tr>
<td>NCT01325428; phase II; recruiting</td>
<td>HER2-positive locally advanced or metastatic inflammatory breast cancer</td>
<td>Afatinib monotherapy until progression followed by afatinib + vinorelbine</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Neratinib</td>
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<td>Burstein 2010; phase II; completed [55]</td>
<td>HER2-positive locally advanced or MBC</td>
<td>A: neratinib (prior trastuzumab therapy)</td>
<td>A: 24%</td>
<td>A: 22.3 wk</td>
<td>NR</td>
<td>Diarrhea (21%)</td>
</tr>
<tr>
<td>NCT00777101; phase II; ongoing [60]</td>
<td>HER2-positive locally advanced or MBC with prior trastuzumab and taxane therapy</td>
<td>B: neratinib (no prior trastuzumab therapy)</td>
<td>B: 56%</td>
<td>B: 39.6 wk</td>
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</tr>
<tr>
<td>NCT00706030; phase II; ongoing [68]</td>
<td>HER2-positive MBC with prior trastuzumab therapy</td>
<td>A: neratinib + vinorelbine (prior lapatinib therapy)</td>
<td>A: 29%</td>
<td>A: 4.5 mo</td>
<td>A: 19.4 mo</td>
<td>A: diarrhea (28%) B: PPE (14%) and diarrhea (10%)</td>
</tr>
<tr>
<td>NEFERTT (NCT00915018); phase II; ongoing</td>
<td>HER2-positive locally recurrent or MBC</td>
<td>B: neratinib + vinorelbine (no prior lapatinib therapy)</td>
<td>A: 41%</td>
<td>B: 6.8 mo</td>
<td>B: 19.0 mo</td>
<td></td>
</tr>
<tr>
<td>NCT01494662; phase II; recruiting</td>
<td>HER2-positive MBC with brain metastases</td>
<td>A: neratinib + paclitaxel</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: trastuzumab + paclitaxel</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: neratinib + cranial resection</td>
<td>NR</td>
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</table>

*Per ClinicalTrials.gov as of February 2013.

HER, human epidermal growth factor; MBC, metastatic breast cancer; RR, response rate; PFS, progression-free survival; OS, overall survival; AE, adverse event; NR, not reported; PPE, palmar plantar erythrodysesthesia.
HER2-positive, MBC-associated brain metastases trial (NCT00445458) and as monotherapy in patients with pretreated, HER2-positive breast cancer (as part 2 of a phase I/II trial [NCT00878709]) but not in MBC; however, results have been presented from a randomized phase II trial in which trastuzumab-taxane-pretreated patients with advanced/MBC were treated, PRs were seen in four patients and grade 3 diarrhea was the dose-limiting toxic effect. In the phase II CHER-LOB trial of neoadjuvant trastuzumab/docetaxel, pertuzumab/trastuzumab/docetaxel, pertuzumab/trastuzumab, and docetaxel/pertuzumab in HER2-positive stage II or III breast cancer (N = 417) [63]. The pCR (defined as the absence of invasive tumor cells in the breast at surgery) rate was 29.5% with trastuzumab alone, 24.7% with lapatinib alone, and 51.3% with lapatinib/trastuzumab (odds ratio relative to trastuzumab alone 2.6; 97.5% CI 1.50–4.58; P = 0.0001). Lapatinib recipients experienced more grade 3/4 toxic effect, primarily grade 3 diarrhea (23.4% and 21.1% with lapatinib and lapatinib/trastuzumab versus 2.0% with trastuzumab), grade 3 liver enzyme elevations (17.5% and 9.9%, respectively, versus 7.4%), and grade 3 neutropenia (14.3% and 7.2%, respectively, versus 1.3%).

Phase III evaluation of neratinib is ongoing in adjuvant trastuzumab-pretreated early-stage breast cancer (ExteNET/NCT00878709) but not in MBC; however, results have been presented from a randomized phase II trial in which trastuzumab/taxane-pretreated patients with advanced/MBC received neratinib or lapatinib plus capecitabine, with 16-week PFS as its primary end point (NCT00777101) [60]. With neratinib, the RR was 29% (versus 41% with lapatinib/capecitabine; P = 0.067), CBR was 44% (versus 64%; P = 0.003), median PFS was 4.5 months (versus 6.8 months; HR 1.3; 95% CI 1.0–1.8; P = 0.091), and median OS was 19.4 months (versus 19.0 months; P = 0.180). Diarrhea was the most common drug-related toxic effect in the neratinib arm, including all-grade (84%) and grade ≥3 events (28%), but was described as manageable with antidiarrheal agents. Nonrandomized phase II trials are evaluating neratinib in other clinical scenarios, including its combination use with paclitaxel for trastuzumab-pretreated, HER2-positive breast cancer (as part 2 of a phase I/II trial [NCT00445458]) and as monotherapy in patients with HER2-positive, MBC-associated brain metastases (NCT01494662). The latter trial includes two cohorts: those with progressive brain metastases and those considered candidates for craniotomy, for whom surgery is to be carried out 7–21 days after starting neratinib.

**additional combinations with trastuzumab and/or lapatinib**

Research efforts are intensifying regarding the early use of anti-HER2 combination regimens, which have the potential to reduce resistance as well as the need for chemotherapy [61]. Emerging data from neoadjuvant trials has suggested activity of various anti-HER2 combination regimens when given alone or with chemotherapy. The phase III NeoALTTO trial evaluated neoadjuvant lapatinib/trastuzumab/paclitaxel, trastuzumab/paclitaxel, and lapatinib/paclitaxel in patients with HER2-positive breast cancer (N = 455) [62]. The pathologic CR (pCR) (defined as the absence of invasive tumor cells in the breast at surgery) was 29.5% with trastuzumab alone, 24.7% with lapatinib alone, and 51.3% with lapatinib/trastuzumab (odds ratio relative to trastuzumab alone 2.6; 97.5% CI 1.50–4.58; P = 0.0001). Lapatinib recipients experienced more grade 3/4 toxic effect, primarily grade 3 diarrhea (23.4% and 21.1% with lapatinib and lapatinib/trastuzumab versus 2.0% with trastuzumab), grade 3 liver enzyme elevations (17.5% and 9.9%, respectively, versus 7.4%), and grade 3 neutropenia (14.3% and 7.2%, respectively, versus 1.3%).

The phase II NeoSphere trial evaluated neoadjuvant trastuzumab/docetaxel, pertuzumab/trastuzumab/docetaxel, pertuzumab/trastuzumab, and docetaxel/pertuzumab in HER2-positive stage II or III breast cancer (N = 417) [63]. The pCR (defined as the absence of invasive tumor cells in the breast at surgery) rate was 45.8% with pertuzumab/trastuzumab/docetaxel, significantly higher than the 29.0% rate with trastuzumab/docetaxel alone (P = 0.0141); conversely, the 16.8% pCR rate with pertuzumab/trastuzumab was significantly lower than that with trastuzumab/docetaxel (P = 0.0198). Pertuzumab/trastuzumab/docetaxel was associated with a grade ≥3 toxic effect profile primarily consisting of neutropenia, febrile neutropenia, leukopenia, and diarrhea (in 45%, 8%, 5%, and 6% of patients, respectively); with trastuzumab/docetaxel alone these were observed in 57%, 7%, 12%, and 4%, respectively. Grade ≥3 toxic effect with pertuzumab/trastuzumab was limited to neutropenia and drug hypersensitivity (1% and 2%, respectively).

In the phase II CHER-LOB trial of neoadjuvant anthracycline/taxane chemotherapy plus lapatinib, trastuzumab, or both in HER2-positive breast cancer (N = 121), the pCR (defined as the absence of invasive tumor cells in the breast and axillary nodes at surgery) rate was 48% with the lapatinib/trastuzumab combination versus 28% with trastuzumab alone and 32% with lapatinib alone [64]. The mean left ventricular ejection fraction remained stable during the study (62%, 61%, and 61% at baseline, after 12–13 weeks, and at treatment end, respectively), with no symptomatic cardiac events. In the phase II TBCRC 006 trial that evaluated neoadjuvant lapatinib plus trastuzumab for large HER2-positive breast tumors (N = 66), the pCR rate was 28% among 64 response-assessable patients [65]. Most toxic effects were of grade 1/2 severity; however,
there were reports of grade 3 metabolic, gastrointestinal, and liver toxic effect (n = 12) and grade 4 liver toxic effect (n = 1).

The phase III NSABP B-41 trial evaluated the efficacy and safety of neoadjuvant combination chemotherapy (doxorubicin/cyclophosphamide) followed by paclitaxel plus lapatinib or trastuzumab or both in HER2-positive, operable breast cancer (N = 529) [66]. The pCR (in the breast) rate was 52.5%, 53.2%, and 62% for the trastuzumab, lapatinib, and trastuzumab/lapatinib arms, respectively. Grade ≥3 toxic effects included diarrhea (2%, 20%, and 27% with lapatinib, trastuzumab, and lapatinib/trastuzumab, respectively) and symptomatic left ventricular systolic dysfunction (4%, 4%, and 2%, respectively).

The phase II TRYPHAENA study of neoadjuvant pertuzumab and trastuzumab concurrent or sequential with an anthracycline-containing chemotherapy or concurrent with an anthracycline-free chemotherapy regimen in locally advanced or inflammatory HER2-positive breast cancer (N = 225) is ongoing (NCT00976989) [67]. The primary end point is tolerability; secondary end points include pCR (defined as the absence of invasive tumor cells in the breast at surgery), safety, time to response, clinical response rate, DFS, PFS, and OS.

conclusions
Investigational anti-HER2-directed antibodies and small molecule inhibitors may have activity in patients with trastuzumab-progressive HER2-positive MBC, and phase III clinical trials are underway in this patient population. Translating a greater understanding of the biology of the HER2 family and how these therapeutic agents interact with them has resulted in the design of several rationally clinical trials that frequently include a ‘dual-targeting’ approach to inhibiting the HER2 pathway. The results from several of these trials suggest that optimally exploiting the biology of the pathway results in the best clinical outcome for patients with HER2-positive disease. The use of these strategies in the neoadjuvant, preoperative setting may improve the pCR rate while minimizing side-effects. Ultimately, these strategies may be applied in the adjuvant setting with an expectation of incrementally improving the already excellent results expected with adjuvant anti-HER2 therapy. Data on neoadjuvant therapy with anti-HER2 combinations also suggest potential benefit as a supplement or alternative to chemotherapy earlier in the course of treating HER2-positive breast cancer. Further studies with prolonged follow-up are needed to determine the extent to which this approach may attenuate the development of acquired resistance to anti-HER2-directed therapy.

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