

Current and Emerging Treatment Regimens for HER2-Positive Breast Cancer

Maribeth Maher

INTRODUCTION

Human epidermal growth factor receptor 2 (HER2) is one of four transmembrane tyrosine kinase receptors (TKRs) within the family of epidermal growth factor receptors (EGFRs). HER2 plays an important role in normal cell growth, development, and differentiation.¹ The overexpression of HER2 has been associated with vascular endothelial growth factor (VEGF) expression and increased angiogenesis.²

Also known as the neu oncogene, HER2 was discovered about 30 years ago by a group of researchers at Massachusetts Institute of Technology.³ The following year, King and colleagues discovered that this “new member of the tyrosine kinase proto-oncogene family” was amplified in a human breast cancer cell line.⁴ A short time later, Slamon and colleagues found that HER2 was amplified in 30% of the 189 primary human breast cancers that they were studying and that it significantly predicted both shorter disease-free survival and shorter overall survival, suggesting that it played a role in the pathogenesis of such cancers.⁵

Subsequently, amplification of the HER2 oncogene and overexpression of the HER2 protein have been recognized as important factors in cancer cell survival, proliferation pathway activation, and metastasis.⁶ Testing for HER2 overexpression in invasive breast cancer is now routine, and a number of agents that target HER2-positive tumors have been developed for use in combination with traditional chemotherapies, in conjunction with other targeted therapies, or as monotherapy.

This article reviews the current and emerging regimens that have been developed to target HER2-positive metastatic breast cancers, including those that employ trastuzumab (Herceptin, Genentech); lapatinib (Tykerb, GlaxoSmithKline); pertuzumab (Perjeta, Genentech); and ado-trastuzumab emtansine, also known as T-DM1 (Kadcyla, Genentech). Their mechanisms of action, the context and the regimens within which each is currently used, and highlights of important clinical trials are discussed.

TREATMENT

Trastuzumab (Herceptin)

Administered by intravenous (IV) infusion, trastuzumab is a humanized monoclonal antibody that targets the extracellular domain of the HER2 protein. It binds to subdomain IV, which is located near the transmembrane domain and is thought to play a role in stabilizing and locking the receptor in an open conformation.⁷⁻¹⁰ Trastuzumab opposes HER2 by promoting antibody-dependent cytotoxicity, blocking activation of intracellular tyrosine kinase, inhibiting proliferative signaling, hindering angiogenesis, and reducing shedding of the extracellular domain.^{7,8,11}

As an adjuvant treatment for HER2-positive breast cancer, trastuzumab is indicated for concurrent administration with either paclitaxel (Taxol, Bristol-Myers Squibb) or docetaxel

(Taxotere, Sanofi) following regimens that include doxorubicin (Doxil, Janssen), and cyclophosphamide (Cytoxan, Bristol-Myers Squibb); in conjunction with docetaxel and carboplatin (Paraplatin, Bristol-Myers Squibb); and as a single agent following multimodality anthracycline therapy.⁷ As an adjuvant treatment, trastuzumab therapy is continued for 52 weeks. The FDA approved trastuzumab in combination with paclitaxel as a first-line therapy and as a single agent in patients with metastatic HER2-positive breast cancer who have received one or more chemotherapy regimens. Therapy is continued until disease progression.⁷

Trastuzumab Plus Chemotherapy

Slamon *et al.*¹²

In a phase 3 trial, 469 patients were randomly assigned to receive either chemotherapy alone ($n = 234$) or chemotherapy with trastuzumab ($n = 235$). For anthracycline-naïve patients, chemotherapy consisted of doxorubicin 60 mg/m² or epirubicin (Ellence, Pfizer) 75 mg/m² plus cyclophosphamide 600 mg/m². For patients who had previously received adjuvant anthracycline, chemotherapy consisted of paclitaxel 175 mg/m². Patients in the group receiving trastuzumab were given a 4-mg/kg loading dose, followed by 2 mg/kg weekly until disease progression. In both groups, chemotherapy was administered once every three weeks for six cycles. Additional cycles could be administered at the investigators' discretion.

Upon disease progression, patients receiving chemotherapy alone were allowed to enter a nonrandomized, open-label study in which they would be given trastuzumab at the same dosage alone or in combination with other therapies. Two-thirds of the patients initially receiving chemotherapy alone opted to enter the open-label trastuzumab study after disease progression.

The primary efficacy endpoint (median time to disease progression) was 7.4 months in the chemotherapy/trastuzumab group and 4.6 months in the chemotherapy-alone group ($P < 0.001$). Secondary efficacy endpoints were rate and duration of response, time to treatment failure, and overall survival.

The overall response rate (ORR) was significantly higher in chemotherapy/trastuzumab patients (50% vs. 32%, respectively; $P < 0.001$), as was the median duration of response (9.1 vs. 6.1 months, respectively; $P < 0.001$) and the median time to treatment failure (6.9 vs. 4.5 months, respectively; $P < 0.001$).

The median survival rate among patients initially assigned to receive the trastuzumab regimen was significantly higher than among those initially receiving chemotherapy alone—including those who crossed over to a trastuzumab regimen after disease progression (25.1 vs. 20.3 months, respectively; $P = 0.046$). Typically, such a crossover would be expected to substantially reduce any observed survival advantage.

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Ms. Maher is a freelance medical writer living in New Jersey.

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Cardiac dysfunction, as defined by New York Heart Association criteria, was identified in 27% of patients who received an anthracycline, cyclophosphamide, and trastuzumab; in 8% of those who received an anthracycline and cyclophosphamide; in 13% who received paclitaxel and trastuzumab; and in 1% who received paclitaxel alone. As a result of the cardiac dysfunction associated with combined anthracycline/trastuzumab therapy, the study authors suggest exercising caution when considering trastuzumab for patients who have received or are receiving anthracyclines.

*Marty et al.*¹³

In a phase 2 trial (M77001), 188 patients with HER2-positive metastatic breast cancer were randomly assigned to receive either docetaxel plus trastuzumab or docetaxel alone. After two patients withdrew from the study before starting treatment, 92 patients received combination therapy and 94 received docetaxel alone. Docetaxel (six cycles at 100 mg/m² every three weeks) plus trastuzumab (a 4-mg/kg loading dose, followed by 2 mg/kg weekly until disease progression) demonstrated better efficacy compared with docetaxel alone in terms of ORR (61% vs. 34%, respectively; $P < 0.0002$), median overall survival (31.2 vs. 22.7 months, respectively; $P = 0.0325$), median time to disease progression (11.7 vs. 6.1 months, respectively; $P = 0.0001$), median time to treatment failure (9.8 vs. 5.3 months, respectively; $P = 0.0001$), and median duration of response (11.7 vs. 5.7 months, respectively; $P = 0.009$).

The incidence and severity of adverse events (AEs) between the two treatment groups were similar. Combination treatment, however, was associated with more grade 3 to 4 neutropenia (32% vs. 22%, respectively) and febrile neutropenia (23% vs. 17%, respectively). In addition, two patients in the combination group, both of whom had received previous doxorubicin therapy, developed symptomatic heart failure. The first patient exhibited heart failure during the study, discontinued trastuzumab therapy, and died four weeks later; death was attributed to progressive metastatic disease. The second patient developed heart failure five months after completing combination therapy while undergoing treatment with an investigational anthracycline that had been started one month after trastuzumab. Findings suggested that trastuzumab, combined with docetaxel, was a more effective treatment for HER2-positive metastatic breast cancer than docetaxel alone, although it was associated with additional toxicity.

*Gasparini et al.*¹⁴

Similarly, Gasparini et al. found that combining paclitaxel (80 mg/m² per week) with trastuzumab (a 4-mg/kg loading dose, followed by 2 mg/kg weekly) produced significantly better responses in patients with advanced HER2-positive breast cancer than did paclitaxel alone. In this phase 2 randomized trial, 124 patients received paclitaxel alone ($n = 61$) or paclitaxel plus trastuzumab ($n = 63$). Of these patients, investigators could evaluate 123 for toxicity and 118 for ORR. Both treatments were well tolerated, and none of the patients experienced either cardiac toxicity or grade 4 hematological toxicity.

The ORR was significantly higher with the combination than with paclitaxel only (75% vs. 56.9%, respectively; $P = 0.0378$), and the median time to progression was higher, although not

statistically significant (301 vs. 204 days, respectively; $P = 0.076$). The median duration of response was also longer in patients receiving the combination (362 vs. 280 days, respectively).

Trastuzumab Monotherapy

*Vogel et al.*¹⁵

A phase 2 trial of trastuzumab monotherapy as first-line palliative treatment for HER2-positive metastatic breast cancer was conducted to evaluate 111 women who had chosen not to undergo cytotoxic chemotherapy. Patients received either trastuzumab 4 mg/kg as an initial dose, followed by 2 mg/kg per week ($n = 58$), or 8 mg/kg as an initial dose, followed by 4 mg/kg per week ($n = 53$), until disease progression.¹⁵ These patients had an immunohistochemistry (IHC) score of 2+ or 3+.

The trial's primary endpoints were ORR and safety. The ORR was 26% (24% in the standard-dose group and 28% in the high-dose group). All responses, both complete and partial, occurred within the IHC 3+ subgroup (35%).

Of the 62 patients for whom fluorescence *in situ* hybridization (FISH) results were available, 41 were FISH-positive for HER2 overexpression; 17 of these patients (41%) responded to treatment. Although patients with only superficial metastases demonstrated a higher response rate, those with liver or lung metastases responded as well.

Secondary endpoints included time to progression and duration of survival. Median time to progression was 18.8 months among responding patients and 1.8 months among patients who derived no clinical benefit. Median duration of survival was 24.4 months (range, 1.2–45.8 months or more).

Treatment was generally well tolerated. The incidence of AEs was similar in the two treatment groups, although infusion-related events (fever, chills, rash, and dyspnea) were more common with the high dose. Events commonly associated with cytotoxic agents—alopecia, leukopenia, anemia, stomatitis, and thrombocytopenia—were rare. Three patients (2.6%) experienced cardiac dysfunction, but in one patient this problem was determined to be unrelated to trastuzumab therapy. Because efficacy and safety were similar between the two cohorts, the investigators concluded that the standard (lower) dosing schedule was preferable.

Trastuzumab Plus Endocrine Therapy

*Kaufman et al.*¹⁶

The Trastuzumab and Anastrozole Directed Against ER-Positive HER2-Positive Mammary Carcinoma (TAnDEM) study was the first phase 3 trial to evaluate the use of an endocrine therapy combined with trastuzumab in patients with HER2-positive metastatic breast cancer who were not receiving chemotherapy.

The study authors randomly assigned 207 postmenopausal women whose metastatic breast cancer demonstrated both HER2 and hormone receptor positivity to receive either anastrozole (Arimidex, AstraZeneca), 1 mg/day by mouth ($n = 104$), or anastrozole at the same dosage with trastuzumab, 4 mg/kg by infusion on day 1, followed by 2 mg/kg weekly ($n = 103$). Patients in the anastrozole-only group were allowed to switch to a trastuzumab regimen upon disease progression.

A total of 20 patients completed 24 months of treatment, four in the anastrozole-only group and 16 in the combination therapy group. The most common reason for withdrawal

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in both treatment groups was progressive disease. Of the 104 patients initially assigned to anastrozole alone, 73 (70%) received trastuzumab following progression.

The primary endpoint, progression-free survival (PFS), was significantly greater with combination therapy than with anastrozole alone, 4.8 versus 2.4 months, respectively (hazard ratio [HR] = 0.063; $P = .0016$). The difference in overall survival (28.5 vs. 23.9 months, respectively, for the combination vs. anastrozole alone) was not statistically significant, although the measurable benefit of combination therapy on this secondary endpoint may have been reduced by the crossover study design.

More AEs occurred in the combination therapy group, including grades 3 and 4 events (23% and 5%, respectively, in the combination group vs. 15% and 1%, respectively, in the anastrozole-only group). The combination group experienced more cardiac events (14) compared with the anastrozole-only group (two). Grade 3 and grade 4 events were limited to two patients in each group.

*Huober et al.*¹⁷

Between 2003 and 2007, the randomized phase 3 Study of the Efficacy and Safety of Letrozole Combined With Trastuzumab in Patients With Metastatic Breast Cancer (the eLEcTRA trial) enrolled 57 patients with HER2/hormone receptor-co-positive metastatic breast cancer. Patients received letrozole (Femara, Novartis) 2.5 mg/day, either with ($n = 31$) or without ($n = 26$) trastuzumab, a 4-mg/kg loading dose followed by 2 mg/kg per week until disease progression. Because the planned enrollment of 370 patients had not been achieved by 2007, the trial was stopped prematurely. At the trial's close, the primary endpoint (time to disease progression) and the secondary endpoints (objective response rate and clinical benefit rate) were higher with the combination therapy, although statistical significance was not achieved.

Continued Treatment With Trastuzumab After Disease Progression

German Breast Group 26 and Breast International Group 3-05^{18,19}

The German Breast Group 26 (GBG 26) and Breast International Group 3-05 (BIG 3-05) conducted a randomized phase 3 study to investigate the effects of continuing trastuzumab therapy with the co-administration of capecitabine (Xeloda, Roche) in patients whose HER2-positive advanced breast cancer had progressed during first-line trastuzumab-based treatment.

Investigators assigned 156 patients whose cancer had progressed during trastuzumab treatment to receive capecitabine (2,500 mg/m² daily on days 1 through 14 of a 21-day cycle) either with ($n = 78$) or without ($n = 78$) trastuzumab 6 mg/kg as a 30-minute infusion every three weeks until disease progression. The group continuing to receive trastuzumab/capecitabine had a higher complete or partial response rate (48% vs. 27%, respectively, with an odds ratio [OR] of 2.50 [$P = 0.0115$]) and a longer median time to progression (8.2 vs. 5.6 months, respectively; HR = 0.69; $P = 0.0338$). Median overall survival at 15.6 months of follow-up was greater in the trastuzumab patients (25.5 vs. 20.4 months), but the benefit was not statistically significant ($P = 0.257$).¹⁸

Grade 3 and 4 toxicities affected 49 patients undergoing 81 cycles in the capecitabine-only group, and 49 patients

undergoing 95 cycles in the capecitabine/trastuzumab group ($P = 0.865$). Anemia, grades 1 through 4, was significantly more frequent in the combination therapy group ($P = .021$). Four patients in the combination therapy group experienced cardiac events, but no deaths were attributed to therapy.¹⁸ At 20.7 months of follow-up, patients receiving trastuzumab continued to demonstrate a better, although still statistically nonsignificant, median overall survival (24.9 vs. 20.6 months, respectively; HR = 0.94; $P = 0.73$).¹⁹

*O'Regan et al.*²⁰

The Breast cancer trials of Oral Everolimus-3 (BOLERO-3) phase 3 study evaluated the effect of adding the mammalian target of rapamycin (mTOR) inhibitor everolimus (Afinitor, Novartis) to trastuzumab plus vinorelbine (Navelbine, GlaxoSmithKline) regimen in patients with HER2-positive advanced breast cancer who had received prior taxane therapy and whose disease had progressed while receiving trastuzumab.²⁰ The mTOR pathway is recognized as playing a key role in angiogenesis, apoptosis, and cell metabolism, growth, and proliferation.²¹

Because the mTOR pathway is up-regulated in many chemoresistant cancers, mTOR inhibitors would be expected to resensitize tumor cells to chemotherapy or delay resistance. In HER2-positive breast cancer, combining an mTOR inhibitor and vinorelbine has been shown to increase apoptosis *in vitro* and antitumor efficacy *in vivo*.²¹ In addition, mTOR inhibitors have been shown to delay, or prevent in some cases, acquired resistance to such HER2-targeted agents as trastuzumab.²¹

The BOLERO-3 study authors randomly assigned 569 participants, in a 1:1 ratio, to receive either everolimus 5 mg/day or placebo plus vinorelbine 25 mg/m² weekly and a loading dose of trastuzumab 4 mg/kg, followed by trastuzumab 2 mg/kg weekly.²⁰ The primary endpoint was PFS. Patients treated with everolimus in addition to trastuzumab and vinorelbine exhibited a significantly longer PFS (7.0 months) than those receiving placebo, trastuzumab, and vinorelbine (5.8 months) (HR = 0.78; $P = 0.0067$).²⁰

Clinical benefit, defined as objective response or stable disease at 24 weeks or more, did not differ significantly between the two groups—59.2% with supplementary everolimus and 53.3% for placebo in its place ($P = 0.0945$). Response rates were also similar between both groups—41% and 37.2%, respectively, for the everolimus and placebo groups. Overall survival data are not available, but a preliminary analysis suggests a lower mortality rate in the everolimus patients (36.3% vs. 41.1%, respectively). The proportion of deaths that occurred during treatment (2.5%) or that were attributed to AEs (0.7%) was similar in both groups.²⁰

Hematological AEs occurred more often in the everolimus patients than in the placebo group. These included neutropenia (81% vs. 70%), anemia (49% vs. 29%), febrile neutropenia (17% vs. 4%), and thrombocytopenia (14% vs. 2%). Stomatitis was the most common nonhematological AE, occurring in 63% of patients in the everolimus group and in 28% of patients in the placebo group.²⁰

Findings of the BOLERO-3 study were presented at the 2013 meeting of the American Society of Clinical Oncology (ASCO). The combination used in the study has not yet received FDA approval, nor has it been incorporated into

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National Comprehensive Cancer Network (NCCN) guidelines or routine clinical practice.

Lapatinib (Tykerb)

An oral tyrosine kinase inhibitor of both human epidermal growth factor receptor 1 (HER1) and HER2,²² lapatinib works at the cytoplasmic ATP-binding site to impede receptor phosphorylation and activation, which in turn blocks downstream signals that trigger tumor cell growth.²³ It is used in combination with capecitabine to treat advanced or metastatic HER2-positive breast cancer in patients who have received prior therapy with an anthracycline, a taxane, and trastuzumab. It is also combined with letrozole to treat postmenopausal women with hormone receptor- and HER2-co-positive metastatic breast cancer.²²

Lapatinib Plus Capecitabine

*Geyer et al.*²⁴

In a randomized phase 3, open-label trial (NCT00078572), women who had HER2-positive metastatic breast cancer that had progressed after treatment with a regimen containing an anthracycline, a taxane, and trastuzumab received capecitabine on days 1 through 14 of a 21-day cycle, either as monotherapy at 2,500 mg/m² per day or at 2,000 mg/m² per day in combination with lapatinib 1,250 mg/day.²⁴

Central nervous system (CNS) metastases develop in approximately one-third of women treated with trastuzumab. Such women were eligible for enrollment if they had remained clinically stable for at least three months after stopping corticosteroid and anticonvulsant therapy.

In the event of grade 2 hematological toxicity or any toxicity of grade 3 or 4, lapatinib was withheld for up to two weeks and was permanently discontinued if improvement to grade 0 or 1 toxicity did not occur within that period. After recovery from grade 2 hematological toxicity or any grade 3 toxicity, lapatinib was resumed at a dose of 1,250 mg/day or, after grade 3 toxicity, at a dose of 1,000 mg/day at the discretion of investigators.

After grade 4 toxicity, resumption of therapy was optional and a dose reduction to 1,000 mg/day was required. If grade 3 or 4 interstitial pneumonitis or cardiac dysfunction occurred, lapatinib was permanently discontinued.

In the initial analysis, which included data on 324 women enrolled over the course of 20 months (163 in the combination treatment group and 161 in the capecitabine monotherapy group), the combination regimen containing lapatinib significantly improved both median time to progression (8.4 vs. 4.4 months, respectively; HR = 0.49; $P < 0.001$) and median PFS (8.4 vs. 4.1 months, respectively; HR = 0.47; $P < 0.001$) compared with capecitabine monotherapy.

Lapatinib/capecitabine was not associated with any greater incidence of toxicity or treatment discontinuation compared with capecitabine alone. CNS metastases occurred in 15 women during the study, 11 in the monotherapy group and four in the combination-therapy group. This difference was not statistically significant ($P = 0.10$).

After a review of the data, the independent data monitoring committee recommended reporting the results and offering combination therapy to the women who had been assigned to monotherapy; subsequently, enrollment was stopped two years after it began.^{24,25} The final analysis, based on 399 patients, was

insufficiently powered to detect overall survival differences because of early termination of enrollment and the crossover of patients from monotherapy to combination therapy. However, data continued to support improved survival with combination therapy, and a Cox regression model, using crossover as a time-dependent covariate, suggested a 20% lower risk of death with the combination (HR = 0.80; $P = 0.043$).²⁵

Lapatinib Plus Trastuzumab

*Blackwell et al.*²⁶

The efficacy and safety of lapatinib/trastuzumab was compared with that of lapatinib alone in a randomized phase 3, multicenter, open-label trial (EGF104900). The trial enrolled patients with HER2-positive metastatic breast cancer whose disease had progressed with a trastuzumab-based regimen.

At 88 centers in North America and Europe, 296 patients received either monotherapy with lapatinib 1,500 mg daily ($n = 148$) or combination therapy with lapatinib 1,000 mg daily plus trastuzumab 2 mg/kg weekly, following a 4-mg/kg loading dose of trastuzumab ($n = 148$). The primary endpoint was PFS.

Median PFS was 12 weeks for the combination and 8.1 weeks for monotherapy (HR = 0.73; $P = 0.008$). Twice as many patients in the combination therapy group (28%) as in the monotherapy group (13%) were progression-free at six months ($P = 0.003$).

Secondary endpoints included ORR, clinical benefit rate, and overall survival. The clinical benefit rate was significantly greater (OR = 2.2; $P = 0.01$) in the combination therapy group (24.7%) than in the monotherapy group (12.4%). No other secondary endpoints differed significantly, although overall survival data showed a trend toward improvement with combination therapy.

Median overall survival was 51.6 weeks for the combination patients and 39 weeks for the monotherapy group. Six- and 12-month overall survival rates were 80% and 45% for combination therapy compared with 70% and 36% for monotherapy.

AEs were similar between the two treatment groups. The most frequently occurring AEs were diarrhea, rash, nausea, and grades 1 or 2 fatigue that resolved without dose modifications. The incidence of grade 1 and 2 diarrhea was significantly higher in the combination therapy group ($P = 0.03$), but the incidence of grade 3 or higher diarrhea was similar in both groups. Although both symptomatic and asymptomatic cardiac events were uncommon, they were more frequent in the combination therapy group (2% and 3.4% vs. 0.7% and 1.4%, respectively).

Lapatinib Plus Letrozole

*Schwartzberg et al.*²⁷

To evaluate the benefit of adding lapatinib to letrozole as a first-line therapy for hormone receptor-positive, HER2-positive metastatic breast cancer, researchers studied 219 women, who were enrolled in a larger (1,286-subject) phase 3 trial that investigated the efficacy of therapy for hormone receptor-positive breast cancer and whose tumors were HER2-positive.²⁷ The women were randomly assigned to receive either letrozole 2.5 mg plus lapatinib 1,500 mg ($n = 111$) or letrozole 2.5 mg plus placebo ($n = 108$).

Unacceptable toxicity or grade 3 or 4 interstitial pneumonitis, hepatotoxicity, or cardiac dysfunction necessitated permanent withdrawal from the study. Toxicity was assessed every four weeks, and cardiac function was assessed every eight

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weeks until week 108, at which point both AEs were assessed every 12 weeks.

Efficacy was assessed every 12 weeks and at study withdrawal, after which follow-up for survival continued. The addition of lapatinib significantly increased PFS, the primary endpoint, from a median of three months to a median of 8.2 months, with 0.71 HR for risk progression favoring lapatinib ($P = 0.019$).

The PFS benefit for the lapatinib group remained significant after adjustments for baseline prognostic factors (HR = 0.65; $P = 0.008$). Lapatinib-treated patients also demonstrated a significantly higher ORR (28% vs. 15%; OR = 0.4; $P = 0.021$) and clinical benefit (48% vs. 29%; OR = 0.4; $P = 0.003$). Toxicities associated with the combination therapy primarily consisted of grades 1 and 2.

Pertuzumab (Perjeta)

As a humanized monoclonal antibody that targets the extracellular domain of the HER2 protein, binding to subdomain II,^{8,28} pertuzumab works on several levels. It blocks the heterodimerization of HER2 with other HER family members; inhibits two major intracellular signaling systems, the mitogen-activated protein kinase and phosphoinositide 3-kinase transduction pathways; and, like trastuzumab, promotes antibody-dependent cytotoxicity.^{8,28} Used in combination with trastuzumab and docetaxel, pertuzumab is indicated for the treatment of HER2-positive metastatic breast cancer in patients who have not previously received targeted HER2 therapy or chemotherapy for metastatic breast cancer.²⁸

Pertuzumab in a Nonchemotherapy Regimen

*Baselga et al.*²⁹

The efficacy and safety of pertuzumab plus trastuzumab was evaluated in a multicenter, open-label, single-arm, phase 2 trial that enrolled 66 women with HER2-positive breast cancer. These patients had previously received up to three regimens of chemotherapy (cumulative doses of up to 360 mg/m² of doxorubicin), and their disease had progressed during trastuzumab-based therapy.

Patients received trastuzumab at the same dosage and schedule as before their entry into the study—either a 4-mg/kg loading dose, followed by 2 mg/kg on days 1, 8, and 15 of each three-week cycle, or an 8-mg/kg loading dose, followed by 6 mg/kg on day 1 of each cycle—plus pertuzumab (in the first cycle, an 840-mg loading dose and, in subsequent cycles, 420 mg on day 1). The planned treatment continued until disease progression or undue toxicity for up to eight cycles (24 weeks), although patients could continue treatment if their disease had not progressed.

The primary endpoints were objective response and complete response rates, which were 24.2% and 7.6%, respectively, corresponding to five complete and 11 partial responses. The clinical benefit rate was 50%. Median PFS was 5.5 months, and 17 patients achieved stable disease of at least six months. The median duration of response was 5.8 months.

Observed AEs were mild to moderate; the most frequent AEs were skin and gastrointestinal toxicities. Only two patients withdrew from the study because of AEs (somnolence and diplopia), which were not related to treatment. The investigators suggested that the pertuzumab/trastuzumab combination was well tolerated and active against HER2-positive tumors even

after disease progression during trastuzumab-based therapy.

Pertuzumab Plus Trastuzumab and Docetaxel

*Baselga et al.*⁸

The phase 3 Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) trial studied the efficacy and safety of pertuzumab combined with trastuzumab and docetaxel as a first-line treatment for HER2-positive metastatic breast cancer.⁸ Investigators randomly assigned 808 patients to receive either placebo (n = 406) or pertuzumab (n = 402) with trastuzumab and docetaxel.

Patients were given 8 mg/kg of trastuzumab as a loading dose, followed by a 6-mg/kg maintenance dose every three weeks. Docetaxel was given every three weeks at an initial dose of 75 mg/m², which could be raised to 100 mg/m² or lowered to 55 mg/m², depending on patient tolerance. Patients received placebo or pertuzumab at a loading dose of 840 mg, followed by 420 mg every three weeks. Treatment continued until disease progression or unmanageable toxicity.

The primary endpoint (median PFS), as determined by an independent review facility, was significantly longer (18.5 months) with pertuzumab than with placebo (12.4 months) (HR = 0.62; $P < 0.001$). The objective response rate was also significantly higher with pertuzumab (80.2% vs. 69.3%, respectively; $P = 0.001$).

An interim analysis of overall survival showed a strong but nonsignificant trend favoring the pertuzumab group with a death rate of 17.2% (69 deaths) versus 23.6% (96 deaths) in the control group. The safety profile (the incidence of AEs and associated deaths) was similar in both groups: 10 deaths resulted from AEs in the control group and eight in the pertuzumab group. Infection was the most common cause of death due to an AE. Combining pertuzumab with trastuzumab and docetaxel as a first-line treatment for HER2-positive metastatic breast cancer was found to significantly prolong PFS without increasing cardiac toxicity.

T-DM1, Ado-Trastuzumab Emtansine (Kadcyla)

An antibody–drug conjugate consisting of trastuzumab and the chemotherapeutic agent emtansine, T-DM1 combines trastuzumab's HER2-targeted antitumor action with the cytotoxic effects of emtansine, which kills cancer cells by inhibiting microtubule assembly and, thereby, mitosis.³⁰ As a single agent, T-DM1 is indicated for the treatment of HER2-positive breast cancer in patients who previously received trastuzumab and a taxane, separately or in combination, and whose disease is metastatic or recurred within six months of completing adjuvant therapy.³¹

T-DM1 After Disease Progression Following HER2-Directed Therapy

*Burris et al.*³²

A single-arm phase 2 study, TDM4258g, investigated the efficacy and safety of T-DM1 in patients with HER2-positive metastatic breast cancer whose disease had progressed during prior HER2-directed therapy. Investigators enrolled 112 patients, who had received a median of eight prior anticancer agents; medications included taxanes (84%), an anthracycline (71%), capecitabine (66%), and carboplatin (Paraplatin, Bristol-Myers Squibb) (42%). All patients had previously received trastuzumab for a median exposure of 17.6 months. Patients were to receive

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3.6 mg/kg of IV T-DM1 every three weeks for up to one year. They received a median of seven (range, one to 17) doses over a median duration of 4.2 months, with 21 completing a year of treatment and 19 continuing treatment in an extension study. Follow-up continued for at least 12 months.

Primary endpoints were the objective response rate by independent assessment, safety, and tolerability. The independent radiological facility assessing response determined that 29 patients (25.9%) had an objective tumor response (all partial responses). No single serious AEs occurred in more than three patients. None of the patients experienced grade 4 AEs related to T-DM1, and no patients stopped treatment because of cardiac toxicity.

The most common AEs of any grade were fatigue, nausea, and headache. The most common grade 3 or 4 AEs were hypokalemia (8.9%), thrombocytopenia (8.0%), and fatigue (4.5%). T-DM1 was well tolerated, with a median dose intensity (dose delivered/expected dose) of 99.7%. No dose modifications were a result of cardiac events. A *post hoc* exploratory analysis revealed that the overall objective response rate did not differ significantly between patients who were and who were not previously treated with both lapatinib and trastuzumab.

*Krop et al.*³³

Unlike the phase 2 TDM4258g study, which evaluated the efficacy and safety of T-DM1 in patients whose metastatic breast cancer had progressed while they were receiving at least one chemotherapeutic agent and one HER2-directed agent, the single-arm, phase 2 TDM4374g study sought to evaluate the efficacy of T-DM1 in patients who had received prior treatment with trastuzumab, lapatinib, a taxane, an anthracycline, and capecitabine. The 110 patients enrolled had been previously treated with all such agents, except for one patient who had been previously treated with ixabepilone (Ixempra, Bristol-Myers Squibb) instead of a taxane. In addition, all patients enrolled in this study had to have undergone at least two HER2-directed regimens in the context of metastatic or locally advanced breast cancer and to have experienced disease progression with the most recent of these regimens.

As in the earlier TDM4258g trial, patients were scheduled to receive 3.6 mg/kg of IV T-DM1 every three weeks. Median follow-up was 17.4 months. At the point of data cutoff, patients had received a median of seven doses of T-DM1 (range, 1–30) or 19.3 weeks of treatment (range, 0.1–88 weeks); 18 (16.4%) of the patients were still enrolled and receiving treatment.

The primary endpoint (ORR, as assessed by independent review) was 34.5%. T-DM1 was generally well tolerated. Most AEs were grades 1 or 2. Withdrawal attributed to the study drug was uncommon. One AE of grade 3 or higher was experienced by more than 5% of the patients: thrombocytopenia, which was associated with significant hemorrhage in one case. Elevated serum transaminase levels seemed to be temporally associated with the T-DM1 dose, but hepatic toxicities tended to be mild. There were no reports of dose-limiting cardiotoxicities.

T-DM1 Versus Lapatinib Plus Capecitabine

*Verma et al.*³⁰

A phase 3 trial, Trastuzumab Emtansine (T-DM1) versus Capecitabine + Lapatinib in Patients With HER2-positive Locally

Advanced or Metastatic Breast Cancer (EMILIA), compared the efficacy and safety of T-DM1 with that of lapatinib plus capecitabine in patients with HER2-positive advanced breast cancer who had received prior treatment with trastuzumab and a taxane.³⁰ Investigators randomly assigned 991 patients to receive either IV T-DM1 (n = 495) at a dose of 3.6 mg/kg every 21 days or to self-administer oral lapatinib (n = 496) at a dose of 1,250 mg/day plus oral capecitabine at a dose of 1,000 mg/m² every 12 hours, not to exceed 2,000 mg/m²/day, on days 1 through 14 of each 21-day cycle.

Primary endpoints were independently assessed PFS, overall survival, and safety. In the T-DM1 group, median PFS, assessed by independent review, was significantly higher than in the lapatinib/capecitabine group (9.6 vs. 6.4 months, respectively; HR = 0.65; *P* < 0.001). Longer median PFS was associated with T-DM1 across all subgroups, although patients who were 75 years of age and older derived less benefit in this regard.

Overall survival did not cross the predefined stopping boundary at the first interim analysis, but at the second analysis, T-DM1 had significantly increased median overall survival compared with the lapatinib/capecitabine group of patients (30.9 vs. 25.1 months, respectively; HR = 0.68; *P* < 0.001). Compared with lapatinib/capecitabine patients, fewer T-DM1 patients experienced serious AEs (15.5% vs. 18%, respectively). Similarly, the incidence of grade 3 and 4 AEs was lower in the T-DM1 group (40.8% vs. 57%, respectively). Thrombocytopenia and elevated aminotransferase (ALT and AST) levels were the grade 3 and 4 AEs that were most commonly associated with T-DM1. All secondary endpoints (PFS, as determined by investigators; objective response rate; and time to symptom progression) also favored T-DM1. The objective response rate was significantly higher in the T-DM1 patients (43.6% vs. 30.8%, respectively; *P* < 0.001).

T-DM1 Versus Trastuzumab Plus Docetaxel

*Hurvitz*³⁴

A phase 2 clinical trial, TDM4450g, was conducted to compare the safety and efficacy of T-DM1 with a trastuzumab-docetaxel regimen as a first-line treatment for HER2-positive metastatic or recurrent locally advanced breast cancer. The multicenter, open-label study enrolled 137 patients who were randomly assigned to receive either 3.6 mg/kg of IV T-DM1 every three weeks (n = 67) or a regimen consisting of IV trastuzumab 8 mg/kg as a loading dose, followed by 6 mg/kg every three weeks plus IV docetaxel 75 or 100 mg/m² (at the discretion of the investigator) every three weeks (n = 70). Treatment was continued until disease progression in both arms.

The primary endpoints were PFS and safety. PFS was found to be significantly greater among the T-DM1 patients than in the trastuzumab/docetaxel group (14.2 vs. 9.2 months, respectively; HR = 0.59; *P* = 0.035). Similarly, T-DM1 was associated with a favorable safety profile.

AEs of grade 3 or higher occurred in 46.4% of the T-DM1 patients and in 90.9% of the trastuzumab/docetaxel patients. Grade 4 AEs occurred in 5.8% of patients treated with T-DM1 and in 57.6% of patients in the trastuzumab/docetaxel group. Both serious AEs and AEs leading to treatment discontinuation were less frequent with T-DM1 (20.3% vs. 25.8% and 7.2% vs. 34.8%, respectively).

Treatment Regimens for HER2-Positive Breast Cancer

The secondary endpoint, quality of life, as measured by the Trial Outcome Index–Physical/Functional/Breast (TOI–PFB) questionnaire, significantly favored the T-DM1 patients, for whom the time to a reduction of five or more points was delayed from 3.5 months in the trastuzumab/docetaxel group to 7.5 months (HR = 0.58; $P = 0.022$). There were no statistically significant differences between the two groups with regard to the secondary endpoints of overall survival, objective response rate, or clinical benefit rate.

FUTURE INITIATIVES

In the 30 years that have passed since HER2 was discovered and recognized as a prognostic factor in breast cancer, several therapies have demonstrated significant efficacy against this oncogene, particularly in the context of metastatic disease. Over the next several years, clinicians are likely to see the introduction of new HER2-targeted therapies and the refinement of combination regimens as researchers continue in their efforts to treat this aggressive form of breast cancer and reduce therapy-related toxicity.

REFERENCES

1. Sundaresan S, Penuel E, Sliwkowski MX. The biology of human epidermal growth factor receptor 2. *Curr Oncol Rep* 1999;1(1):16–22.
2. Kumar R, Yarmand-Bagheri R. The role of HER2 in angiogenesis. *Semin Oncol* 2001;28(5 Suppl 16):27–32.
3. Schechter AL, Stem DF, Vaidyanathan L, et al. The neu oncogene: An erb-B-related gene encoding a 185,000-Mr tumour antigen. *Nature* 1984;312(5994):513–516.
4. King CR, Kraus MH, Aaronson SA. Amplification of a novel v-erbB-related gene in a human mammary carcinoma. *Science* 1985;229(4717):974–976.
5. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: Correlation of relapse and survival with amplification of HER-2/neu oncogene. *Science* 1987;235(4785):177–182.
6. Ménard S, Pupa SM, Campiglio M, Tagliabue E. Biologic and therapeutic role of HER2 in cancer. *Oncogene* 2003;22(42):6570–6578.
7. Herceptin (trastuzumab), prescribing information. South San Francisco, Calif.: Genentech/Roche; October 2010.
8. Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2012;366(2):109–119.
9. Tai W, Mahato R, Cheng K. The role of HER2 in cancer therapy and targeted drug delivery. *J Control Release* 2010;146(3):264–275.
10. The structure of HER2: Domains and dimerization. Genentech. Available at: www.bioncology.com/research-education/hdis/her2-domains-dimer#. Accessed February 13, 2014.
11. Hudis CA. Trastuzumab—mechanism of action and use in clinical practice. *N Engl J Med* 2007;357(1):39–51.
12. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;344(11):783–792.
13. Marty M, Cogne F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: The M77001 study group. *J Clin Oncol* 2005;23(19):4265–4274.
14. Gasparini G, Gion M, Mariani L, et al. Randomized phase II trial of weekly paclitaxel alone versus trastuzumab plus weekly paclitaxel as first-line therapy of patients with Her-2 positive advanced breast cancer. *Breast Cancer Res Treat* 2007;101:355–365.
15. Vogel CL, Cobleigh MA, Tripathy D, et al. First-line Herceptin monotherapy in metastatic breast cancer. *Oncology* 2001;61(Suppl 2):37–42.
16. Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: Results from the randomized phase III TAnDEM study. *J Clin Oncol* 2009;27(33):5529–5537.
17. Huober J, Fasching PA, Barsous M, et al. Higher efficacy of letrozole in combination with trastuzumab compared to letrozole monotherapy as first-line treatment in patients with HER2-positive, hormone-receptor-positive metastatic breast cancer: Results of the eLECTRA trial. *Breast* 2012;21(1):27–33.
18. Von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: A German Breast Group 26/Breast International Group 03–05 Study. *J Clin Oncol* 2009;27(12):1999–2006.
19. Von Minckwitz G, Schwedler K, Schmidt M, et al. Trastuzumab beyond progression: Overall survival analysis of the GBG 26/BIG 3–05 phase III study in HER2-positive breast cancer. *Eur J Cancer* 2011;2273–2281.
20. O'Regan R, Ozguroglu M, Andre F, et al. Phase III, randomized, double-blind, placebo-controlled multicenter trial of daily everolimus plus weekly trastuzumab and vinorelbine in trastuzumab-resistant, advanced breast cancer (BOLERO-3). American Society of Clinical Oncology meeting, Abstract 505. *J Clin Oncol* 2013;31(Suppl).
21. Yardley DA. Combining mTOR inhibitors with chemotherapy and other targeted therapies in advanced breast cancer: rationale, clinical experience, and future directions. *Breast Cancer (Auckl)* 2013;7:7–22.
22. Tykerb (lapatinib), prescribing information. Research Triangle Park, N.C.: GlaxoSmithKline; March 2012.
23. Untch M, Lück H-J. Lapatinib: Member of a new generation of ErbB-targeting drugs. *Breast Care* 2010;5(Suppl 1):8–12.
24. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006;355(26):2733–2743.
25. Cameron D, Casey M, Olivia C, Newstat B, et al. Lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer: Final survival analysis of a phase III randomized trial. *Oncologist* 2010;15(9):924–934.
26. Blackwell KL, Burstein HJ, Storniolo AM, et al. Randomized study of lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. *J Clin Oncol* 2010;28(7):1124–1130.
27. Schwartzberg LS, Franco SX, Florance A, et al. Lapatinib plus letrozole as first-line therapy for HER-2+ hormone receptor-positive metastatic breast cancer. *Oncologist* 2010;15(2):122–129. Erratum, *Oncologist* 2010;15(3):327.
28. Perjeta (pertuzumab), prescribing information. South San Francisco, Calif.: Genentech/Roche; April 2013.
29. Baselga J, Gelmon KA, Verma S, et al. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. *J Clin Oncol* 2010;28(7):1138–1144.
30. Verma S, Miles D, Gianni L, et al., for the EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012;367(19):1783–1791.
31. Kadcyla (ado-trastuzumab emtansine [T-DM1]), prescribing information. South San Francisco, Calif.: Genentech/Roche; May 2013.
32. Burris HA III, Rugo HS, Vukelja SJ, et al. Phase II study of the antibody drug conjugate trastuzumab-DM1 for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer after prior HER2-directed therapy. *J Clin Oncol* 2011;29(4):398–405.
33. Krop IE, LoRusso P, Miller KD, et al. A phase II study of trastuzumab emtansine in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer who were previously treated with trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine. *J Clin Oncol* 2012;30(26):3234–3241.
34. Hurvitz SA. 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(9):1157–1163. Erratum, *J Clin Oncol* 2013;31(23):2977. ■