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REVIEW ARTICLE

# Targeted therapy in HER2-positive metastatic breast cancer: a review of the literature

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## ABSTRACT

Breast tumours positive for HER2 (human epidermal growth factor receptor 2) represent approximately 20% of all breast cancer cases and are associated with an aggressive natural history. The advent of targeted anti-HER2 therapies has dramatically improved disease control and survival in patients with metastatic HER2-positive breast cancer. Targeted agents are now considered the standard of care in the first-line setting and beyond.

The present review summarizes the currently available data on targeted anti-HER2 therapies from completed randomized phase III clinical trials and briefly discusses emerging advances that will address unmet needs in metastatic HER2-positive breast cancer.



## KEY WORDS

HER2, metastatic breast cancer, targeted therapy, phase III trials


## 1. INTRODUCTION

Breast cancer is the most common cancer affecting women in Canada[1]. Although most patients with breast cancer are diagnosed at an early stage and are cured, some patients present with metastases either at diagnosis or at later relapse and ultimately succumb to their disease. Breast cancer mortality is second only to lung cancer in Canada, with an estimated 5000 women having died from the disease in 2013[1]. The treatment of patients with metastatic breast cancer (MBCa) represents an urgent public health challenge. A greater focus on the specific needs of those patients is required to improve outcomes.

Approximately 15%–20% of breast cancers show amplification of the *ERBB2* gene [which codes for HER2 (human epidermal growth factor receptor 2)] on chromosome 17. Patients with this subtype of breast cancer historically had worse outcomes than did their peers with other subtypes of the disease. Approval in 1998 of the first anti-HER2 agent (trastuzumab) ushered in a new era of molecularly targeted therapies for HER2-positive breast cancer and significantly improved outcomes in those patients.

The anti-HER2 agents now in clinical use span a number of drug classes, including the monoclonal antibodies trastuzumab and pertuzumab, which bind to the extracellular portion of the HER2 protein; the small-molecule intracellular tyrosine kinase inhibitors lapatinib and neratinib, which block downstream receptor signalling; and the antibody–drug conjugate (ADC) ado-trastuzumab emtansine (T-DM1), which combines HER2 signalling disruption with direct cytotoxicity. These drugs have been shown to be efficacious in the treatment of HER2-positive MBCa in the first-line setting and beyond.

In this article, we describe the natural history of HER2-positive breast cancers, summarize the evidence for the currently available targeted agents from phase III randomized clinical trials, and discuss the role of targeted agents in the current management of HER2-positive MBCa.

The literature in PubMed from January 1990 to October 2014 was searched for published phase III clinical trials relating to HER2-positive MBCa. Abstracts from major conferences, including the annual meetings of the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology, and the San Antonio Breast Cancer Symposium, were also examined. Key words included "HER-2 positive," "metastatic breast cancer," "phase 3," and "clinical trial." Only English-language publications were reviewed.

## 2. NATURAL HISTORY

As a transmembrane tyrosine kinase receptor protein, HER2 belongs to the human epidermal receptor family of proteins. It is expressed in normal tissue including the gastrointestinal, respiratory, and urinary tracts, and skin, breast, and placenta[2]. Although HER2 has



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no known physiologic ligand, it can dimerize with its partners, activating downstream effectors molecules, and it is intimately involved in cell signal transduction and ultimately affects cell motility, proliferation, and survival[3,4].

The importance of HER2 in breast cancer has been appreciated for several decades[5]. Since the late 1980s, multiple studies have identified HER2-positive breast cancers as having a more aggressive biology and being associated with poorer outcomes, including shorter time to recurrence and shorter overall survival (OS)[6,7]. Those characteristics were seen in the metastatic setting as well, where survival in patients with HER2-positive MBCa was reduced compared with that in their counterparts with luminal HER2-negative disease[8]. The advent of anti-HER2 therapy has at least partly abrogated the risk, and patients with HER2-positive breast cancers treated with HER2 inhibition now experience outcomes comparable to those in their HER2-negative counterparts[9].

## 3. FIRST-LINE THERAPY

A number of phase III trials have examined the use of anti-HER2 therapies in the first line for metastatic disease (Table I). Agents for which improvements in survival have been documented include trastuzumab, lapatinib, and the combination of trastuzumab plus pertuzumab.

### 3.1 Trastuzumab

In a pivotal clinical trial published in 2001, Slamon *et al.*[10] provided the first definitive evidence of the efficacy of anti-HER2 agents.

Patients with HER2-positive metastatic breast cancer who had not previously received systemic therapy for metastatic disease ($n$ = 234) were randomized to chemotherapy with or without trastuzumab. A central assessment of HER2 status was performed by immunohistochemistry, with HER2 positivity being defined as 2+ or 3+ staining involving at least 10% of tumour cells. The chemotherapy backbone in the trial varied depending on prior exposure to anthracyclines. Patients who had not received anthracyclines in the adjuvant setting were prescribed either doxorubicin or epirubicin plus cyclophosphamide, and patients with prior anthracycline exposure received paclitaxel. Chemotherapy was given for a minimum of 6 cycles, after which it could be continued at the investigator's discretion, and trastuzumab was given until evidence of progressive disease.

At a median follow-up of 30 months, chemotherapy plus trastuzumab was shown to improve time to progression (TTP) to 7.4 months from 4.6 months. Overall survival improved to 25.1 months from 20.3 months with the addition of trastuzumab, and 1-year survival was 33% with trastuzumab compared with 22% with chemotherapy alone.

Higher rates of cardiac dysfunction were seen with trastuzumab, especially in the combination arm of anthracycline and trastuzumab (27% of patients compared with 8% in the anthracycline-only arm). One patient in each of the anthracycline-containing arms died of cardiac dysfunction. Similarly, cardiac dysfunction rates were higher with paclitaxel–trastuzumab than with paclitaxel alone (8% vs. 1%). The addition of trastuzumab was not associated with increases in other chemotherapy-associated toxicities.

Two phase III trials explored the value of combination chemotherapy in association with trastuzumab.

Robert *et al.*[11] randomized 196 patients to trastuzumab and paclitaxel with or without carboplatin. Response rate, the primary endpoint, was higher in the triplet therapy arm (52% vs. 36%). The addition of carboplatin was also associated with improved progression-free survival (PFS): 10.7 months compared with 7.1 months [hazard ratio (HR): 0.66]. However, no significant difference in OS was observed (35.7 months vs. 32.2 months, $p$ = 0.76). The addition of carboplatin was associated with significantly more hematologic toxicity, including grade 3 thrombocytopenia (9% vs. 1%) and grade 4 neutropenia (36% vs. 12%).

Pursuing a similar concept, the Breast Cancer International Research Group 007 study investigated the addition of carboplatin to docetaxel and trastuzumab[14]. The primary endpoint was TTP, which was found to be 10.4 months with and 11.1 months without carboplatin. The associated OS durations were 37.1 months and 37.4 months. Neither TTP nor OS was significantly different between the study arms. The response rates, unlike those in the Robert *et al.*[11] study, were identical in both arms (72%).

The HERNATA study[13] compared taxane- and non-taxane-based chemotherapy backbones in association with trastuzumab. In that study, 284 patients were randomized to trastuzumab plus either docetaxel or vinorelbine. Only 1 patient had previously received adjuvant trastuzumab. No significant difference was observed in TTP, the primary endpoint, which was 12.4 months for docetaxel and 15.3 months for vinorelbine. Overall survival was also similar, at 35.7 months for docetaxel and 38.8 months for vinorelbine. The response rate was identical in both arms (59%). Despite the similar efficacy, vinorelbine was much better tolerated, and significantly more patients in the docetaxel arm experienced grade 3–4 toxicities and discontinued therapy. Those findings were confirmed in a smaller study that compared trastuzumab with either vinorelbine or a weekly taxane (paclitaxel or docetaxel)[12]. The primary endpoint was response rate; TTP was a secondary endpoint. The trial closed early because of poor accrual, and no outcome was statistically different (response rate: 51% with vinorelbine, 40% with taxane; TTP: 8.5 months with vinorelbine, 6.0 months with taxane). Vinorelbine was associated with more hematologic


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TABLE I First-line phase III trials incorporating anti-HER2 therapy and chemotherapy for HER2-positive metastatic breast cancer

| *Reference (study name)* | *Pts (n)* | *Treatment arms* | *Median* | | *Response rate (%)* |
|---|---|---|---|---|---|
| | | | *TTP or PFS (months)* | *OS (months)* | |
| Slamon *et al.,* 2001[10] | 469 | Chemotherapy (various) with trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly) | 7.4 ($p$<0.001) | 50 ($p$<0.001) | 25.1 ($p$=0.046) |
| | | Chemotherapy (various) | 4.6 | 20.3 | 32 |
| Robert *et al.,* 2006[11] | 196 | Trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly), with paclitaxel 175 mg/m$^2$ and carboplatin AUC 6 every 3 weeks | 10.7 ($p$=0.03) | 35.7 ($p$=0.76) | 52 ($p$=0.04) |
| | | Trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly), with paclitaxel 175 mg/m$^2$ every 3 weeks | 7.1 | 32.2 | 36 |
| Burstein *et al.,* 2007[12] | 81 | Trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly), with paclitaxel 80 mg/m$^2$ weekly OR docetaxel 35 mg/m$^2$ weekly for 7 weeks every 8 weeks | 6.0 ($p$=0.09) | NR | 58 |
| | | Trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly), with vinorelbine 25 mg/m$^2$ weekly | 8.5 | NR | 66 |
| Andersson *et al.,* 2011[13] (HERNATA) | 284 | Trastuzumab (8 mg/kg loading dose, then 6 mg/kg every 3 weeks), with docetaxel 100 mg/m$^2$ every 3 weeks | 12.4 ($p$=0.67) | 35.7 ($p$=0.98) | 59 ($p$=1.00) |
| | | Trastuzumab (8 mg/kg loading dose, then 6 mg/kg every 3 weeks), with vinorelbine 30–35 mg/m$^2$ days 1 and 8 every 3 weeks | 15.3 | 38.8 | 59 |
| Valero *et al.,* 2011[14] (BCIRG 007) | 263 | Trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly), with docetaxel 75 mg/m$^2$ and carboplatin AUC 6 every 3 weeks | 10.4 ($p$=0.57) | 37.4 ($p$=0.99) | 72 ($p$=0.97) |
| | | Trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly), with docetaxel 100 mg/m$^2$ every 3 weeks | 10.4 | 37.1 | 72 |
| Gelmon *et al.,* 2012[15] (NCIC MA.31) | 652 | Paclitaxel 80 mg/m$^2$ weekly OR docetaxel 75 mg/m$^2$ every 3 weeks, with lapatinib 1500 mg daily | 8.8 ($p$=0.01) | NR | NR |
| | | Paclitaxel 80 mg/m$^2$ weekly OR docetaxel 75 mg/m$^2$ every 3 weeks, with trastuzumab 2 mg/kg weekly OR trastuzumab 6 mg/kg every 3 weeks with chemotherapy, then 6 mg/kg every 3 weeks | 11.4 | NR | NR |
| Guan *et al.,* 2013[16] | 444 | Paclitaxel 80 mg/m$^2$ weekly for 3 weeks every 4 weeks, with lapatinib 1500 mg daily | 9.7 ($p$<0.001) | 27.8 ($p$=0.012) | 69 ($p$<0.001) |
| | | Paclitaxel 80 mg/m$^2$ weekly for 3 weeks every 4 weeks, with placebo daily | 6.5 | 20.5 | 50 |
| Baselga *et al.,* 2012[5] and Swain *et al.,* 2014[17] (CLEOPATRA) | 808 | Docetaxel 75–100 mg/m$^2$ every 3 weeks, with trastuzumab (8 mg/kg loading dose, then 6 mg/kg every 3 weeks), and pertuzumab 840 mg loading dose, then 420 mg every 3 weeks | 18.5 ($p$<0.001) | 56.5 ($p$<0.001) | 80 ($p$=0.001) |
| | | Docetaxel 75–100 mg/m$^2$ every 3 weeks, with trastuzumab (8 mg/kg loading dose, then 6 mg/kg every 3 weeks), and placebo every 3 weeks | 12.4 | 40.8 | 69 |

HER2 = human epidermal growth factor receptor 2; Pts = patients; TTP = time to progression; PFS = progression-free survival; OS = overall survival; BCIRG = Breast Cancer International Research Group; NR = not reported; NCIC = National Cancer Institute of Canada.



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toxicity; taxanes were associated with more skin toxicity, myalgias, and fluid retention.

The foregoing studies all affirmed the efficacy and feasibility of trastuzumab-containing chemotherapy regimens in the first-line setting for HER2-positive breast cancer. The similar efficacy seen with taxane and vinorelbine regimens offered clinicians therapeutic flexibility in individualizing treatment for patients, especially given that many patients could previously have received taxanes in the adjuvant setting. Doublet chemotherapy backbones of carboplatin and a taxane can also be combined with trastuzumab, but have yet to demonstrate a meaningful advantage in OS over single-agent chemotherapy plus trastuzumab. In view of the increased toxicity with doublets, the clinical role for that strategy is currently very limited.

### 3.2 Lapatinib

Two phase III trials have explored the use of lapatinib in the first-line setting, one of which compared lapatinib against placebo.

Guan *et al.*[16] randomized 444 patients who had not been treated with chemotherapy for metastatic disease to weekly paclitaxel (80 mg/m$^2$ weekly for 3 weeks every 4 weeks) plus either lapatinib (1500 mg daily) or placebo. The trial was conducted in parts of the world in which trastuzumab, already established as an integral part of therapy against HER2-positive breast cancer, was not readily available. The primary endpoint, OS, was extended to 27.8 months from 20.5 months with the addition of lapatinib (HR: 0.74). Secondary endpoints, including both PFS (9.7 months vs. 6.5 months) and response rate (69% vs. 50%), were also improved. Lapatinib was associated with high rates of grades 3 and 4 diarrhea (20% vs. <1%) and neutropenia (51% vs. 20%).

A second trial, the Canadian-led MA.31 study[15] by the NCIC Clinical Trials Group, compared lapatinib with trastuzumab, both combined with a taxane chemotherapy backbone. Reported in abstract form at the ASCO 2012 annual meeting, MA.31 randomized 652 patients to a taxane (paclitaxel 80 mg/m$^2$ weekly or docetaxel 75 mg/m$^2$ every 3 weeks) plus either lapatinib or trastuzumab. At the interim analysis (median follow-up of 13.6 months), PFS was found to be inferior with lapatinib (8.8 months vs. 11.4 months with trastuzumab; HR: 1.33). Similar results were seen when the analysis was restricted solely to patients with centrally confirmed HER2 status. The OS data are immature, but no difference between the two arms has been observed to date. As in the Guan *et al.* study[16], lapatinib was associated with significantly higher rates of grades 3 and 4 diarrhea.

Taken together, the evidence suggests that, although lapatinib has activity against HER2-positive breast cancer and offers additional benefit over chemotherapy alone, trastuzumab-based regimens should still be considered the standard of care in this setting.

### 3.3 Trastuzumab Plus Pertuzumab

Dual HER2 blockade with multiple anti-HER2 antibodies has recently been shown to be more efficacious than chemotherapy plus trastuzumab alone. The CLEOPATRA trial[5] investigated the addition of pertuzumab to the standard therapy of taxane plus trastuzumab. In that study, 808 patients were randomized to docetaxel (75–100 mg/m$^2$) and trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks), plus either pertuzumab (840 mg loading dose, followed by 420 mg every 3 weeks) or placebo. At least 6 cycles of docetaxel were recommended. The primary endpoint was PFS (by independent assessment). Key secondary endpoints included OS and response rate. One line of endocrine therapy for metastatic disease and prior adjuvant or neoadjuvant chemotherapy were allowed, provided that the chemotherapy had ended at least 12 months earlier. The median PFS with dual HER2 blockade was 18.5 months; it was 12.4 months with trastuzumab alone. Higher response rates were also seen with dual HER2 blockade: 80.2% of patients in the experimental group compared with 69.3% of patients in the control group achieved a response.

The final analysis, with updated OS results, was reported at the 2014 annual meeting of the European Society for Medical Oncology. At a median follow-up of 50 months, a statistically significant improvement in OS in favour of pertuzumab was seen, with a median OS of 56.5 months compared with 40.8 months with placebo (HR: 0.68)[17]. In that study, dual HER2 blockade did not lead to an increased risk of cardiac toxicity. Febrile neutropenia was more commonly seen with pertuzumab (13.8% vs. 7.6%), driven mostly by a high incidence in Asian patients (26% vs. 10%) for reasons not clearly understood at the present time. An increase in the rate of grades 3 and 4 diarrhea (7.9% vs. 5.0%) was also observed in the pertuzumab arm.

### 3.4 Hormone Receptor–Positive Tumours

For patients with bone-only disease and indolent disease progression, the combination of anti-HER2 therapy and endocrine therapy represents a valid therapeutic option. Three trials have examined the addition of HER2-targeted agents to aromatase inhibitors in postmenopausal women (Table II).

In the TANDEM study, 207 patients were randomized to anastrozole (1 mg daily) plus trastuzumab (4 mg/kg loading dose, followed by 2 mg/kg weekly) or to anastrozole alone[19]. The combination arm was associated with an improvement in PFS (4.8 months vs. 2.4 months; HR: 0.63) and a nonsignificant increase in OS (28.5 months vs. 23.9 months). The response rate was also improved (20% vs. 7%). The most common toxicities seen in the combination arm were fatigue (21%), vomiting (21%), and diarrhea (20%); however, the vast majority of events were grades 1 and 2.


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TABLE II First-line phase III trials incorporating anti-HER2 therapy and endocrine therapy for metastatic hormone receptor–positive, HER2-positive breast cancer

| *Reference (study name)* | *Pts (n)* | *Treatment arms* | *Median* | | *Response rate (%)* |
|---|---|---|---|---|---|
| | | | *TTP or PFS* (months) | *OS* (months) | |
| Johnston *et al.,* 2009[18] (EGF30008) | 263 | Letrozole 2.5 mg with lapatinib 1500 mg daily | 8.2 ($p$=0.019) | 33.3 ($p$=0.113) | 28 ($p$=0.021) |
| | | Letrozole 2.5 mg with placebo daily | 3.0 | 32.3 | 15 |
| Kaufman *et al.,* 2009[19] (TANDEM) | 207 | Anastrozole 1 mg daily, with trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly) | 4.8 ($p$=0.002) | 28.5 ($p$=0.325) | 21 ($p$=0.018) |
| | | Anastrozole 1 mg daily | 2.4 | 23.9 | 7 |
| Huober *et al.,* 2012[20] (ELECTRA) | 92 | Letrozole 2.5 mg daily, with trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly) | 14.1 ($p$=0.23) | NR | 27 ($p$=0.002) |
| | | Letrozole 2.5 mg daily | 3.3 | NR | 13 |

HER2 = human epidermal growth factor receptor 2; Pts = patients; TTP = time to progression; PFS = progression-free survival; OS = overall survival; NR = not reported.

The combination of letrozole plus trastuzumab was compared with letrozole alone in the ELECTRA study[20], which randomized 57 postmenopausal patients to letrozole (2.5 mg daily) with or without trastuzumab (4 mg/kg loading dose, followed by 2 mg/kg weekly). In addition, HER2-negative patients were enrolled as a third cohort and were treated with letrozole alone. The trial experienced slow accrual and closed early, before the planned 370 patients could be enrolled. Nevertheless, the addition of trastuzumab to letrozole was associated with a significant improvement in TTP (14.1 months vs. 3.3 months; HR: 0.67), the duration of which was similar to the duration achieved in the HER2-negative group (15.2 months). The rates of response (27% vs. 13%) and clinical benefit (65% vs. 39%) were both higher in the trastuzumab-containing arm.

A third study, EGF30008, compared the all-oral combination of letrozole (2.5 mg daily) and lapatinib (1500 mg daily) with letrozole alone in postmenopausal patients with hormone receptor–positive MBCa[18]. Of the almost 1300 patients enrolled, 219 had hormone receptor–positive HER2-positive disease. In that subgroup, the addition of lapatinib to letrozole was associated with a significant improvement in PFS (8.2 months vs. 3.0 months: HR: 0.71) and response rate (28% vs. 15%). Overall survival was not significantly different (33.3 months vs. 32.3 months). As previously seen with lapatinib, diarrhea was significantly more common in the combination arm (grades 3 and 4 diarrhea: 10% vs. 1%).

Although improvements in TTP or PFS are seen with the addition of anti-HER2 therapy to endocrine therapy for this subset of patients with hormone receptor–positive HER2-positive disease, the gains are modest, and no study has demonstrated an improvement in OS. Hence, the use of such an approach has to be weighed against the significant benefit in PFS and OS seen when anti-HER2 therapy is combined with chemotherapy as outlined earlier.

## 4. SECOND-LINE THERAPY

Multiple phase III clinical trials have shown that, in patients whose disease has recurred or progressed on first-line trastuzumab-based therapy, continuation of anti-HER2 therapy in the second-line setting has been associated with outcome improvements, including improvements in survival (Table III). Current therapeutic options include continuing trastuzumab with a different chemotherapy partner, adding the MTOR (mammalian target of rapamycin) pathway inhibitor everolimus, switching to a regimen of capecitabine plus lapatinib, or switching to the novel ADC T-DM1.

### 4.1 Continuing Trastuzumab

The strategy of continuing trastuzumab while switching its chemotherapy partner was evaluated in two phase III trials. The German Breast Group 26 study enrolled 156 pre-treated patients, almost all of whom had already received trastuzumab for metastatic disease[22]. Patients were randomized to capecitabine (1250 mg twice daily for 14 days every 3 weeks) plus trastuzumab (6 mg/kg every 3 weeks) or to capecitabine alone. With a median follow-up of 15.6 months, the addition of trastuzumab to capecitabine was associated with improvements in TTP (8.2 months vs. 5.6 months; HR: 0.69) and response rate (48% vs. 27%). Although OS was numerically superior with the combination, the effect was not statistically significant (25.5 months vs. 20.4 months, $p$ = 0.257). With the exception of anemia (64% vs. 42%), the combination arm was not associated with increased toxicity.


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TABLE III Second-line phase III trials incorporating anti-HER2 therapy and chemotherapy for HER2-positive metastatic breast cancer

| *Reference (study name)* | *Pts (n)* | *Treatment arms* | *Median* | | *Response rate (%)* |
|---|---|---|---|---|---|
| | | | *TTP or PFS (months)* | *OS (months)* | |
| Geyer *et al.,* 2006[21] | 324 | Capecitabine 1000 mg/m$^2$ twice daily for 2 weeks every 3 weeks, with lapatinib 1250 mg daily | 8.4 ($p$<0.001) | 17.5 ($p$=0.206) | 22 ($p$=0.09) |
| | | Capecitabine 1000 mg/m$^2$ twice daily for 2 weeks every 3 weeks | 4.4 | 15.1 | 14 |
| von Minckwitz *et al.,* 2009[22] (German Breast Group 26) | 156 | Capecitabine 1250 mg/m$^2$ twice daily for 2 weeks every 3 weeks, with trastuzumab 6 mg/kg every 3 weeks | 8.2 ($p$=0.034) | 25.5 ($p$=0.257) | 48 ($p$=0.012) |
| | | Capecitabine 1250 mg/m$^2$ twice daily for 2 weeks every 3 weeks | 5.6 | 20.4 | 27 |
| Blackwell *et al.,* 2010[23] (EGF104900) | 296 | Lapatinib 1000 mg daily with trastuzumab 4 mg/kg loading dose, then 2 mg/kg weekly | 2.8 ($p$=0.008) | 14.0 ($p$=0.026) | 10 ($p$=0.46) |
| | | Lapatinib 1500 mg daily | 1.9 | 9.5 | 7 |
| Verma *et al.,* 2012[24] (EMILIA) | 991 | T-DM1 3.6 mg/kg every 3 weeks, with capecitabine 1000 mg/m$^2$ twice daily for 2 weeks every 3 weeks, and lapatinib 1250 mg daily | 9.6 ($p$<0.001) | 30.9 ($p$<0.001) | 44 ($p$<0.001) |
| | | | 6.4 | 25.1 | 31 |
| André *et al.,* 2014[25] (BOLERO-3) | 569 | Vinorelbine 25 mg/m$^2$ weekly, with trastuzumab 2 mg/kg weekly and everolimus 5 mg daily | 7.0 ($p$=0.007) | NR | 41 ($p$=0.211) |
| | | Vinorelbine 25 mg/m$^2$ weekly, with trastuzumab 2 mg/kg weekly and placebo daily | 5.8 | NR | 37 |

HER2 = human epidermal growth factor receptor 2; Pts = patients; TTP = time to progression; PFS = progression-free survival; OS = overall survival; NR = not reported.

Continuation of trastuzumab in conjunction with lapatinib without cytotoxic chemotherapy was investigated in the EGF104900 study[23]. Blackwell *et al.* randomized 296 heavily pretreated patients (median of 6 prior lines of systemic therapy and 3 lines of trastuzumab-containing regimens for MBCa) to lapatinib plus trastuzumab or to lapatinib alone. The combination of two anti-HER2 targeted agents led to an improvement in PFS (2.8 months vs. 1.9 months; HR: 0.73). The improvement in response rate was not significant (10% vs. 7%, $p$ = 0.46), but the rate of clinical benefit increased significantly (25% vs. 12%). In the final updated analysis[26], the PFS benefit was maintained, and improved survival was also seen (14.0 months vs. 9.5 months; HR: 0.74). Combination therapy was associated with increased diarrhea, but rates of grades 3 and 4 diarrhea remained comparable in the two arms (7% in both).

### 4.2 mTOR Inhibitors to Target Resistance

Resistance to HER2 inhibition is thought in part to be a result of activation of the PI3K/Akt/mTOR pathway, which induces proliferation and survival[27]. Simultaneous blockade of HER2 and the mTOR pathway therefore has the potential to reverse resistance to trastuzumab. That hypothesis was investigated in the BOLERO-3 trial[25], which randomized 569 patients who had previously received a taxane and trastuzumab to weekly vinorelbine (25 mg/m$^2$) and trastuzumab (2 mg/kg), plus either the mTOR inhibitor everolimus (5 mg daily) or placebo. The addition of everolimus resulted in a significantly improved PFS (7.0 months vs. 5.8 months; HR: 0.78), with the greatest benefit being seen in patients with hormone receptor–negative tumours. Survival data were immature at time of publication. Increased grades 3 and 4 neutropenia, mucositis, anemia, leucopenia, fatigue, and febrile neutropenia were seen in the everolimus arm. The modest improvement in PFS, together with the significant increase in toxicity, limits the uptake of this therapeutic approach in the clinical setting.

### 4.3 Capecitabine Plus Lapatinib

Geyer *et al.*[21] conducted a phase III study comparing capecitabine (1000 mg/m$^2$ twice daily for 2 weeks


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every 3 weeks) plus lapatinib (1250 mg/m$^2$ daily) with capecitabine alone (1250 mg/m$^2$ twice daily for 2 weeks every 3 weeks) in patients who had progressed on prior trastuzumab-based therapy. The study enrolled a heavily pretreated population of 324 patients, almost 100% of whom had previously received anthracyclines and taxanes, and approximately 50% of whom had also received fluorouracil or vinorelbine or both. At the interim analysis, a significant improvement in PFS was associated with the combination therapy (8.4 months vs. 4.4 months with capecitabine alone; HR: 0.49). The trial was stopped early, which likely reduced its statistical power and the ability to detect a significant OS benefit. Nevertheless, the final update showed a trend toward a superior OS with combination therapy (17.5 months vs. 15.1 months, $p$ = 0.206)[28]. The addition of lapatinib resulted in higher incidences of all-grade diarrhea (60% vs. 39%), rash (27% vs. 15%), and dyspepsia (11% vs. 0%), but the incidences of severe toxicities (grade 4 or higher) were comparable between the arms.

### 4.4 T-DM1

The superiority of the ADC T-DM1 compared with capecitabine plus lapatinib in the second-line setting was established in the EMILIA trial[24], which randomized 991 patients with HER2-positive advanced breast cancer who had been pretreated with trastuzumab and a taxane to T-DM1 (3.6 mg/kg every 3 weeks) or to capecitabine (1000 mg/m$^2$ twice daily for 2 weeks every 3 weeks) plus lapatinib (1250 mg/m$^2$ daily). Primary endpoints included independently-assessed PFS, OS, and safety. At an interim analysis (median follow-up: 13 months), PFS was found to be significantly improved in the T-DM1 arm (9.6 months vs. 6.4 months with capecitabine plus lapatinib; HR: 0.65). An updated analysis (median follow-up: 18 months) also showed a significant improvement in OS with T-DM1 (30.9 months vs. 25.1 months; HR: 0.68). Overall, T-DM1 was better tolerated and associated with less grade 3 and 4 toxicity (41% vs. 57% with capecitabine plus lapatinib). The most common grades 3 and 4 toxicities with T-DM1 were thrombocytopenia (12.9%), elevated aspartate transaminase (4.3%), and elevated alanine transaminase (2.9%); with capecitabine plus lapatinib, they were diarrhea (79.7%), hand–foot syndrome (58%), and nausea (44.7%).

## 5. THIRD-LINE THERAPY AND BEYOND

The only phase III trial to specifically address the efficacy of anti-HER2 therapy in the third-line setting is TH3RESA[29]. The investigators randomized patients pretreated with both trastuzumab and lapatinib for advanced disease in a 2:1 fashion to T-DM1 (3.6 mg/kg every 3 weeks) and physician's choice of therapy. The latter consisted mostly of combination therapy including at least one anti-HER2 agent (68% trastuzumab plus chemotherapy, 10% trastuzumab plus lapatinib). Treatment with T-DM1 was associated with an improvement in PFS (6.2 months vs. 3.3 months; HR: 0.53). At the time of that analysis, a trend for improved OS was also seen with T-DM1, but the result did not cross the prespecified stopping boundary. Less grades 3 and 4 toxicity were reported with T-DM1 (32% vs. 43%), with the most common toxicity being thrombocytopenia (4%).

Several of the previously mentioned trials conducted in the second-line setting enrolled patients with extensive pretreatment. In EGF104900, patients had received a median of 3 prior trastuzumab-based therapies for metastatic disease. In EMILIA, 39% of patients in both arms had received 2 or more prior lines of chemotherapy, and some had received trastuzumab in both the adjuvant and metastatic settings.

Based on existing data, it is reasonable to continue to offer some form of anti-HER2 therapy to patients who are fit enough for additional systemic therapy. That possibility is supported by the recent guideline from ASCO concerning HER2-positive advanced breast cancer, which recommended the use of anti-HER2 therapy—including T-DM1, pertuzumab, and capecitabine plus lapatinib—in the third-line setting[29].

## 6. SPECIAL CONSIDERATIONS: BRAIN METASTASIS

Metastasis to the brain represents a common and serious concern for patients with metastatic breast cancer, and imparts additional risk for significant morbidity and mortality. Positivity for HER2 has been found to be an independent risk factor for the occurrence of brain metastasis[30,31]. Standard local therapies include any one or a combination of surgery, stereotactic radiosurgery, and whole-brain radiotherapy[32]. Treatment selection depends in part on the extent and location of the disease.

Historically, the effect of chemotherapy on brain metastasis has been limited, in part because of the sanctuary provided by the blood–brain barrier. In the new era of anti-HER2 targeted therapy, the combination of capecitabine and lapatinib has been shown to have activity against brain metastases. In the Geyer *et al.*[21] trial, the addition of lapatinib to capecitabine (compared with capecitabine monotherapy) reduced the risk of symptomatic central nervous system (CNS) progression as the first site of failure (2% vs. 6%)[33]. The phase II LANDSCAPE trial specifically addressed the issue of CNS disease[34]. In that study, 45 patients with HER2-positive breast cancer and brain metastases were enrolled and treated with capecitabine and lapatinib at the same dose and schedule used in the Geyer *et al.* trial. Of 44 assessable patients, 66% experienced an objective CNS response. Mean time to CNS progression was 5.5 months. The most


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recent ASCO clinical practice guideline[35] recommends this capecitabine–lapatinib regimen as an option for patients with HER2-positive breast cancer and asymptomatic low-volume brain metastases who have not received radiotherapy.

## 7. FUTURE DIRECTIONS

Effective inhibition of the HER2 pathway has dramatically altered the landscape of systemic therapy for patients with HER2-positive breast cancer. An OS duration of nearly 5 years has now been documented with the addition of pertuzumab to docetaxel and trastuzumab. Trials to examine the utility of newer agents in various settings are under way, including the combination of T-DM1 plus pertuzumab in the first line (MARIANNE study) and trastuzumab plus pertuzumab in the second line (PHEREXA study). The results of those trials are eagerly awaited, but they will raise additional questions about which combination is the optimum therapy, or whether combination therapy is superior to sequential exposure to all available anti-HER2 agents.

Optimal selection of anti-HER2 therapy and personalization of treatment remain active areas of research. To date, no biomarkers that predict response to anti-HER2 therapy other than HER2 overexpression itself have been discovered. Even with dual HER2 inhibition, a proportion of patients do not respond to therapy, as was seen in the CLEOPATRA study. Recently, the companion biomarker analysis of prospectively banked tissue from CLEOPATRA was published[36]. No new predictive factors were identified, but low levels of HER2 protein and messenger RNA, a low level of HER3 messenger RNA, and *PIK3CA* mutations were associated with worse prognosis. Interestingly, the latter finding was partly seen in the biomarker analysis from the EMILIA trial, in which mutated *PIK3CA* was associated with worse prognosis when patients were treated with lapatinib plus capecitabine but not with T-DM1, suggesting that T-DM1 might overcome the negative implications of *PIK3CA* mutations[37]. Continued efforts in the investigation of novel biomarkers could help to refine and optimize therapy for specific subsets of patients in the future.

Antibody–drug conjugates represent an exciting frontier in cancer medicine. The marriage of exquisite target selectivity and potent cytotoxicity could potentially lead to an improved therapeutic index. In addition to T-DM1, several dozen ADCs have either been approved or are undergoing active development in a variety of hematologic and solid tumours[38,39]. Second-generation anti-HER2 ADCs are currently being investigated, including SYD985, a trastuzumab-based ADC linked to the highly toxic alkylator antibiotic duocarmycin[40]. Preliminary evidence suggests that SYD985 could have an efficacy superior to that of T-DM1, especially in tumours that are negative by fluorescence *in situ* hybridization and 1+ to 2+ by immunohistochemistry[41]. These agents might eventually add to the growing armamentarium of therapeutic possibilities for patients with metastatic HER2-positive breast cancer.

## 8. SUMMARY

The landscape of treatment for HER2-positive breast cancer is rapidly evolving. The incorporation of anti-HER2 targeted agents as part of the standard of care for HER2-positive MBCa has led to dramatic improvements in outcome for patients with this aggressive disease. The introduction and availability of novel agents now offer clinicians the ability to provide deep and prolonged inhibition of the HER2 pathway across multiple lines of treatment. As even more potential therapies appear over the horizon, advancements in biomarker discovery will be critical in optimizing treatment selection and providing personalized therapy for patients.

## 9. CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: SV has received honoraria from or participated on the advisory boards for Boehringer Ingelheim, Roche, AstraZeneca, and Pfizer, and has received research funding from Roche and Sanofi. XZ has no conflicts of interest relating to this paper.

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