Review

# Recent treatment advances in HER2-positive metastatic breast cancer: a clinical approach

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## Practice Points

- Treatment decision in HER2-positive metastatic breast cancer patients must be based on patient factors including evaluation of extent of disease, assessment of performance status, review of cardiac status and consideration of previous treatment including adjuvant taxanes and trastuzumab.
- Generally, taxanes, along with trastuzumab, remain the standard first-line approach. However, recent evidence suggests that patients may be considered for vinorelbine and trastuzumab based on superior toxicity profile and possible improved efficacy.
- Pertuzumab, along with docetaxel and trastuzumab, has demonstrated improved progression-free survival and may be the new standard therapy; however, appropriate cost–effectiveness studies need to be conducted.
- HER2- and hormone receptor-positive metastatic breast cancer patients with low-burden visceral disease and a prolonged disease-free interval may be candidates for treatment with either anastrozole and trastuzumab or lapatinib and letrozole.
- There is a need for prospective studies and predictive biomarkers to determine which patients could be treated with anti-HER2 and endocrine therapy instead of chemotherapy.
- Lapatinib and capecitabine should be considered for those patients who have progressed while on adjuvant trastuzumab and have evidence of brain metastases or for those do not have a significant response or have a shortened progression-free survival with chemotherapy and trastuzumab.
- Dramatic developments have occurred in the management of HER2-positive metastatic breast cancer in the past two decades. New regimens must focus not only on improved efficacy but also on superior toxicity profiles compared with current standard options.

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**SUMMARY** The use of targeted therapy directed against HER2 is currently the standard of care in patients with metastatic HER2-positive breast cancer. The combination of trastuzumab with a taxane as first-line treatment in HER2-positive metastatic breast cancer patients is the most common therapeutic approach in this population. The combination of trastuzumab with other chemotherapeutic agents, including vinorelbine and capecitabine; and hormonal therapy agents, such as aromatase inhibitors, have also demonstrated significant activity, and may be considered as an option for selected patients. Recently, the addition of pertuzumab to trastuzumab and docetaxel in first-line therapy has demonstrated an increased progression-free survival in HER2-positive metastatic breast cancer patients. Novel strategies against HER2 in first-line treatment or after progression include HER tyrosine kinase inhibitors such as lapatinib in combination with either chemotherapy, aromatase inhibitors or trastuzumab. An increasing list of new compounds are currently under investigation, such as trastuzumab–emtansine, afatinib, everolimus and antiangiogenic agents, among others. This review discusses potential therapeutic approaches in the first-line setting and after progression beyond trastuzumab in metastatic breast cancer HER2-positive tumors based on the latest evidence.

HER2 (ErbB2/neu) is a member of a family of transmembrane tyrosine kinase receptors that includes HER1 (the EGF receptor [EGFR]), HER3 (ErbB3) and HER4 (ErbB4). HER2 overexpression induces proliferation by disrupting the function of proteins that regulate cell cycle progression and apoptosis [1].

In the era before HER2-targeted therapy, the HER2-enriched subtype carried a poor prognosis; however, since the commercial availability of trastuzumab in 1998 and its routine incorporation in the management of metastatic breast cancer (MBC) and as adjuvant therapy in 2005, along with the development and integration of other HER2-targeted therapies, the history and evolution of this breast cancer subtype have changed dramatically [2]. Despite the success of targeted therapies in the treatment of metastatic HER2-positive breast cancer, many patients do not respond to trastuzumab therapy or progress after initiating trastuzumab and, eventually, the majority of patients will progress [3].

This review discusses potential therapeutic approaches that, according to recent data, may improve clinical outcomes in HER2-positive MBC, with special emphasis on those patients who have progressed on trastuzumab treatment.

## Role of trastuzumab to date

Trastuzumab (Herceptin®) is a recombinant humanized monoclonal IgG1 antibody that selectively binds to the receptor HER2 to inhibit the growth of tumor cells [4]. Trastuzumab has been shown in preclinical models to have synergistic activity with a variety of chemotherapeutic drugs. The mechanism of trastuzumab action is the subject of debate and several possibilities have been hypothesized [5].

HER2 overexpression leads to activation of the PI3K and the serine/threonine kinase Akt (also known as PKB) signal cascades, turnover of cyclin D1 and, as a result, cell cycle progression [6].

Downstream effects of the PI3K–Akt pathway also include inhibition of transcription of *p27* (a Cdk2 inhibitor). Trastuzumab increases nuclear and cytosolic levels of p27, thereby leading to cell cycle arrest (cytostatic effect) [5,7].

Trastuzumab has not only cytostatic but also cytotoxic properties. At least in part, these two properties may be due to the activation of antibody-dependent cellular cytotoxicity. There are many other possible mechanisms of trastuzumab action described; however, despite years of preclinical and clinical investigation the precise trastuzumab mechanism of action is not fully understood [8].

In the first-line HER2-positive MBC setting, Phase II studies of trastuzumab monotherapy have demonstrated an objective response rate (ORR) of 26% (95% CI: 18.2–34.4%), a clinical benefit rate (CBR) of 50% and a median duration of survival of 22.9 months [9]. In the pivotal Phase III trial conducted by Slamon *et al.*, the addition of trastuzumab to chemotherapy resulted in a significantly improved time to progression (TTP) (median: 7.4 vs 4.6 months; $p < 0.001$), a higher ORR (50 vs 32%; $p < 0.001$), a longer duration of response (median: 9.1 vs

6.1 months; $p < 0.001$) and improved survival (median: 25.1 vs 20.3 months; $p = 0.01$). Among the patients who received trastuzumab and paclitaxel, the overall response was 38% in comparison with 16% in patients treated with paclitaxel alone [10].

The results obtained with paclitaxel and trastuzumab were confirmed in a randomized Phase II study comparing docetaxel versus docetaxel with trastuzumab. This study demonstrated an improvement in the ORR in the trastuzumab arm (61 vs 34%; $p = 0.0002$), progression-free survival (PFS; 11.7 vs 6.1 months; $p = 0.0001$) and overall survival (OS; 31.2 vs 22.7 months; $p = 0.0325$) [11]. This pivotal data helped establish the use of taxanes and trastuzumab as the standard of care in the first-line treatment of HER2-positive MBC patients [11,12].

Platinum-based combinations with trastuzumab have also been evaluated in clinical trials and are associated with an improved ORR and a significant improvement in PFS, with no improvement in OS but an increased grade III–IV hematologic toxicity [13–17].

Vinorelbine in combination with trastuzumab has recently been shown to have a significant benefit and is now a standard first-line chemotherapy option for MBC patients. This combination was explored in the HERNATA trial, a Phase III study comparing trastuzumab plus vinorelbine versus trastuzumab plus docetaxel. This study showed no statistical difference in the response rate (RR), PFS or OS between both arms. However, the vinorelbine plus trastuzumab arm demonstrated a more favorable toxicity profile [18].

This lack of difference in efficacy between taxane and vinorelbine, both in combination with trastuzumab, was found in the TRAVIOTA study. In this study, the RR was 51 and 40% for the vinorelbine plus trastuzumab arm and the taxane plus trastuzumab arm, respectively (Fisher's exact test; $p = 0.37$). The median TTP was 8.5 and 6.0 months for the vinorelbine- and taxane-based arms, respectively (log-rank test; $p = 0.09$) [19]. The HERNATA and TRAVIOTA studies have helped establish the combination of vinorelbine plus trastuzumab as an effective first-line treatment option with a favorable toxicity profile. A list of Phase III clinical trials using HER2-targeted therapy in the first-line HER2-positive MBC setting is summarized in **Table 1**.

Anthracyclines alone are also particularly active in this patient cohort. In the anthracycline plus trastuzumab arm of the pivotal trial conducted by Slamon *et al.* in HER2-positive MBC, patients were treated for a planned duration of six cycles (cumulative anthracycline dose 360 mg/m$^2$), with further cycles administered at investigator discretion. With this, the incidence of cardiac dysfunction and New York Heart Association class III–IV cardiotoxicity was 27 and 16%, respectively. While the toxicity was too prohibitive, the best outcomes were obtained in this combination arm. After the risk of cardiotoxicity was recognized the concurrent administration with anthracyclines was avoided in clinical practice [10,20]. In recent trials of trastuzumab combined with chemotherapy or hormonal therapy, the incidence of cardiac events is in the range of 1–3% [21]. In the HERCULES trial, a prospective Phase I/II study of HER2-positive MBC, patients who received first-line trastuzumab plus cyclophosphamide and epirubicin showed acceptable dose-limiting cardiotoxicity [22]. These findings must be confirmed in further studies. There is a need for more data on the use of combinations of anthracyclines with trastuzumab in the metastatic setting and, in the meantime, this approach should only be utilized in a clinical trial setting.

## Trastuzumab beyond disease progression

The majority of patients with MBC, who initially respond to trastuzumab, develop resistance within 1 year of treatment initiation, and in the adjuvant setting 15% of patients still relapse despite trastuzumab-based therapy [23].

Several mechanisms of trastuzumab resistance have been proposed, such as loss of PTEN function [8]. This is seen in 20–25% of HER2-positive breast cancers and, according to Nagata *et al.*, patients with PTEN-deficient tumors had significantly poorer RRs to trastuzumab-based therapy than those with normal PTEN. Thus, PTEN deficiency could be a predictor for trastuzumab resistance [24]. Data suggest that the accumulation of truncated forms of the HER2 receptor that lack the extracellular trastuzumab-binding domain known as p95 may also lead to resistance to trastuzumab, as trastuzumab is unable to bind to the cancer cell [24]. Recent literature suggests that very high levels of total HER2 protein expression may lead to *de novo* resistance to trastuzumab [25]. Another mechanism suggested

**Table 1. Summary of pivotal Phase III studies in the first-line setting of HER2-positive metastatic breast cancer.**

| Study | Trial design | Patients (n) | PFS (months) | TTP (months) | ORR (%) | OS (months) | Ref. |
|---|---|---|---|---|---|---|---|
| Slamon *et al.* | Trastuzumab + chemotherapy vs chemotherapy alone | 235<br>234 | ND | 7.4<br>4.6<br>(p < 0.001; HR: 0.51) | 50<br>32<br>(p < 0.001) | 25.1<br>20.3<br>(p < 0.046; HR: 0.80) | [10] |
| Andersson *et al.* | Trastuzumab + docetaxel vs trastuzumab + vinorelbine | 143<br>141 | ND | 12.4<br>15.3<br>(p = 0.67; HR: 0.94) | 59.3<br>59.3<br>(p = 1) | 35.7<br>38.8<br>(p = 0.98; HR: 1.01) | [18] |
| Baselga *et al.* | Placebo + trastuzumab + docetaxel vs pertuzumab + trastuzumab + docetaxel | 406<br>402 | 12.4<br>18.5<br>(p < 0.001; HR: 0.62) | ND | 69.3<br>80.2<br>(p = 0.001) | Immature data† | [60,61] |
| Gianni *et al.* | Trastuzumab + docetaxel vs trastuzumab + docetaxel + bevacizumab | 208<br>216 | 13.9‡<br>16.8‡<br>(p = 0.0162; HR: 0.72) | ND | 65.9‡<br>76.5‡<br>(p = 0.0265) | ND | [79] |
| Di Leo *et al.* | Lapatinib + paclitaxel vs paclitaxel + placebo | 49<br>37 | ND | 36.4<br>25.1<br>(p = 0.005; HR: 0.53) | 63.3<br>37.8<br>(p = 0.023) | 104.6§<br>82.4§<br>(p = 0.365; HR: 0.74) | [33] |
| Kaufman *et al.* | Trastuzumab + anastrozole vs anastrozole alone | 103<br>104 | 4.8<br>2.4<br>(p = 0.0016; HR: 0.63) | 4.8<br>2.4<br>(p = 0.007) | 20.3¶<br>6.8¶<br>(p = 0.018) | 28.5<br>23.9<br>(p = 0.325) | [43] |
| Johnston *et al.* | Letrozole + lapatinib vs letrozole + placebo | 111<br>108 | 8.2<br>3.0<br>(p = 0.19; HR: 0.71) | ND | 48#<br>29#<br>(p = 0.003) | ND | [45] |

†Median follow-up 19.3 months; more deaths occurred in the control group than in the pertuzumab group (96 [23.6%] vs 69 [17.2%]; HR: 0.64; p = 0.005). This did not meet the O'Brien–Fleming stopping boundary of the Lan–DeMets alpha spending function for this interim analysis of OS (HR: ≤0.603; p ≤ 0.0012).

‡Independent review committee assessed.

§Weeks not months.

¶Partial response rate.

#Clinical benefit (responsive or stable disease ≥6 months).

HR: Hazard ratio; ND: No data; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival; TTP: Time to progression.

for resistance to trastuzumab is the increased signaling from the IGF-I receptor [26].

Recent advances in molecular biology are improving the understanding of the mechanism of primary or secondary resistance to trastuzumab. While these proposed mechanisms are of great scientific interest, there is no predictive biomarker that is available for clinical use to help predict intrinsic resistance to trastuzumab.

Over the past decade there has been emerging evidence on the benefit of trastuzumab in patients who have previously progressed on trastuzumab-based therapy. Initially, Phase II trials suggested continued benefit of trastuzumab beyond progression. This was validated in a Phase III trial (GBG 26) conducted by von Minckwitz *et al.*, in which HER2-positive MBC patients who had progressed on a trastuzumab and chemotherapy combination were randomly assigned to receive capecitabine alone or capecitabine plus continued trastuzumab. The combination arm was associated with a significantly longer median TTP (8.2 vs 5.6 months) and a nonstatistically significant improvement in OS (25.5 vs 20.4 months) [27]. This study showed that there are some patients that derive benefit from the continuation of trastuzumab beyond progression. Of note, this trial was stopped early due to poor accrual and, as such, may not be adequately powered to truly answer the question on the magnitude of benefit seen with trastuzumab beyond progression [28].

In the Blackwell *et al.* Phase III trial, 296 patients with HER2-positive MBC who progressed on one or more prior trastuzumab-based regimens were randomized to receive trastuzumab plus lapatinib (a dual HER1/HER2 tyrosine kinase inhibitor [TKI], which is discussed later in this review) or lapatinib alone. This study demonstrated a significant improvement in median PFS (12 vs 8 weeks; hazard ratio [HR]: 0.73; 95% CI: 0.57–0.93) and CBR (24.7 vs 12%). There was also a strikingly significant improvement in OS (9.5 vs 14.0 months) [29]. In conjunction, these two randomized Phase III trials support the benefit of continued trastuzumab for patients who have previously progressed on trastuzumab-based combination(s).

## Lapatinib

Lapatinib is a reversible, dual TKI of the receptors HER1 and HER2. Inactivation of HER1/2 leads to the inhibition of downstream signaling, including PI3K–Akt and MAPK pathways. In multiple breast cancer cell lines, lapatinib can produce cell cycle arrest and a subsequent induction of apoptosis [30].

This inhibition was most prominent in tumors with activated ErbB receptors, including HER1 and HER2 [31]. In cells overexpressing HER2, lapatinib produced inhibition of cell proliferation inducing cell cycle arrest and apoptosis [32].

This compound has been evaluated in first-line treatment of HER2-positive MBC in a Phase III trial, which was largely conducted in a HER2-untested or -negative patient population with an inadvertent subset of only 86 HER2-positive patients (15%). The subgroup analysis of the HER2-positive subset revealed that the treatment with paclitaxel plus lapatinib resulted in statistically significant improvements in the TTP (36.4 vs 25.1 weeks), event-free survival (35.1 vs 21.9 weeks), ORR (63.3 vs 37.8%) and CBR (69.4 vs 40.5%) compared with paclitaxel plus placebo. This study failed to show an improvement in OS [33]. At the time of writing this article, lapatinib had not yet been approved by the US FDA in combination with paclitaxel as first-line treatment in HER2-positive MBC.

Lapatinib has mainly been explored after progression to chemotherapy and trastuzumab. In the pivotal Phase III trial, patients who had progressed on trastuzumab in a MBC setting were randomized to receive lapatinib plus capecitabine versus capecitabine alone. The median TTP, reported initially in the *New England Journal of Medicine* in 2006, was 8.4 months in the combination therapy group compared with 4.4 months in the monotherapy group [34]. At a planned interim analysis reported in 2008, the TTP was a median of 6.2 versus 4.3 months, which was significant in favor of the combination arm [35]. The mature and final analysis was reported in 2010 and the median OS times were 75.0 weeks for the combination arm and 64.7 weeks for the monotherapy arm (HR: 0.87; 95% CI: 0.71–1.08; p = 0.210), which was not statistically significant. However, the exclusion of crossover patients from the analysis resulted in a significant improvement in the median OS, with OS times of 75.0 weeks in the combination group and 56.4 weeks in the monotherapy group (HR: 0.78; 95% CI: 0.62–0.97; p = 0.023). Furthermore, the patients in the combination arm had fewer brain metastases in an unplanned exploratory analysis [36].

The other Phase III trial supporting the use of lapatinib beyond progression is with combination of the two HER2-targeted agents, lapatinib and trastuzumab, as discussed above (Blackwell *et al.* [29]). These two Phase III trials using lapatinib, along with the GBG 26 trial [27] evaluating trastuzumab in combination with capecitabine, demonstrate strong evidence that patients with HER2-positive disease derive clear benefit with continuous anti-HER2 therapy even upon progression.

### Lapatinib & brain metastasis

Lapatinib is a small and lipophilic molecule that owing to these properties may cross the blood–brain barrier. Lapatinib has also shown activity in brain metastases (BM) in preclinical studies. Using $^{14}$C-lapatinib in immunocompromised mice, studies have demonstrated an elevated concentration of this compound in BM [37]. This finding has also been recognized in two Phase II clinical trials investigating the benefit of lapatinib as monotherapy in HER2-positive MBC with BM in patients who progressed after cranial radiation and trastuzumab. Lapatinib was associated with a volumetric reduction in tumor size in these studies [38,39]. There is an increasing amount of data suggesting that the combination of lapatinib plus capecitabine is very active in HER2-positive MBC with BM; this therapeutic approach may improve OS when compared with trastuzumab-based therapies in this particular setting [40,41].

## Treatment of hormone receptor-positive & HER2-positive MBC: evidence for combined aromatase inhibitor with anti-HER2 treatment

Several models in breast cancer cells suggest that estrogen receptors can be activated by HER family members in a bidirectional crosstalk. This phenomenon can generate the activation of many intracellular pathways including metalloproteinases, tyrosine kinase cascades, MAPK and PI3K–AKT pathways among others. These downstream activated kinases will phosphorylate and activate estrogen receptors augmenting the activities of estrogen receptor and HER family members as well as other kinase-related pathways [42]. This crosstalk plays a role not only in the endocrine response but also in endocrine therapy resistance. This section discusses the clinical evidence for combined hormonal therapy with anti-HER2 treatment.

The TAnDEM study compared trastuzumab plus anastrozole versus anastrozole alone, and showed an improvement in PFS in the trastuzumab plus anastrozole arm (2.4 vs 4.8 months; HR: 0.63; 95% CI: 0.47–0.84; p = 0.016). In patients with centrally confirmed hormone receptor positivity (n = 150), the median PFS was 5.6 and 3.8 months in the trastuzumab plus anastrozole and anastrozole alone arms, respectively (log-rank; p = 0.006). No difference in OS was seen between the two arms; however, 70% of patients in the anastrozole alone arm received trastuzumab upon progression [43]. Another trial investigated the combination of trastuzumab and letrozole and found similar results [44].

Lapatinib has been studied in combination with letrozole as first-line treatment in HER2-/hormone receptor-positive MBC tumors and this approach was evaluated in the EGF30008 trial. In this Phase III trial, the addition of lapatinib to letrozole significantly reduced the risk of disease progression versus letrozole plus placebo (HR: 0.71; 95% CI: 0.53–0.96; p = 0.019) and the median PFS was 8.2 v 3.0 months, respectively. The CBR was significantly greater for lapatinib plus letrozole versus letrozole plus placebo (48 vs 29%, respectively; odds ratio: 0.4; 95% CI: 0.2–0.8; p = 0.003). The ORR was also significantly higher in lapatinib-treated patients (28 vs 15%; odds ratio: 0.4; 95% CI: 0.2–0.9; p = 0.021) [45,46].

To date there is no head-to-head comparison trial of chemotherapy versus endocrine therapy along with anti-HER2 treatment to suggest the most optimal regimen. On review of the evidence there is a greater benefit seen with chemotherapy and an anti-HER2 approach; however, this comes with increased toxicity. The option of antiestrogen treatment along with anti-HER2 therapy could be considered in patients with low disease volume, such as patients with only bone metastases and those with a long disease-free interval, suggesting a slower rate of disease progression. This approach is based mainly on clinical judgment since there are no prospective data and no evidence for biomarkers to determine which patients will derive real benefit from anti-HER2 in combination with endocrine therapy [47–52].

## Targeting ErbB family receptors: new drugs

Amplification and/or overexpression of the three other HER-related family members may

also influence the clinical course and outcomes of HER2-positive breast cancer. Overexpression of HER1 and HER3 significantly reduces disease-specific survival [53].

It is possible that targeting those receptors at the same time or by a different mechanism could translate into clinical benefit by potentially overcoming mechanisms of resistance and blocking the significant crosstalk among the kinase pathways.

There are data suggesting that targeting HER2 can increase the expression of HER3 and increase the possibility of HER2–HER3 heterodimerization, leading to resistance to trastuzumab and subsequently cancer progression [54,55]. In addition to functioning as a homodimer, HER2 is the preferred partner for the other EGFR family proteins, particularly HER3, and HER2 heterodimers appear to be more active than HER2 homodimers; this event can produce increased tumor proliferation [56].

## Pertuzumab

Pertuzumab is a humanized monoclonal antibody that binds to HER2 near the center of domain II, a domain required for interactions with other EGFR family members, especially HER3, thereby preventing dimerization of HER2 with other HER receptors (HER3, HER1 and HER4) [57,58]. This drug has been studied in a multicenter, open-label, single-arm Phase II study. Sixty six patients with advanced HER2-positive breast cancer in whom disease progression had occurred during prior trastuzumab-based therapy received trastuzumab plus pertuzumab. The ORR was 24.2% and the CBR was 50%. The median PFS was 5.5 months. Overall, the combination of pertuzumab plus trastuzumab was well tolerated, and adverse events were mild to moderate. This study showed that the combination of pertuzumab plus trastuzumab is active in patients with metastatic HER2-positive breast cancer who had experienced progression during prior trastuzumab therapy [59].

Recently, results from a pivotal trial evaluating pertuzumab, CLEOPATRA, were published. This is an international, randomized, double-blind, placebo-controlled Phase III trial, in which patients were randomized (1:1) to receive either docetaxel, trastuzumab and pertuzumab or docetaxel, trastuzumab and placebo. The primary end point of the study was PFS. Results demonstrate that the pertuzumab-containing arm had an improved PFS (18.5 vs 12.4 months in a control group), an absolute improvement of more than 6 months ($p < 0.0001$) compared with the control arm. In terms of OS, with a median follow-up of 19.3 months (immature data), more deaths occurred in the control group than in the pertuzumab group (96 [23.6%] vs 69 [17.2%] deaths; HR: 0.64; $p = 0.005$) [60,61]. This is clearly a significant benefit in PFS and probably in OS, establishing a new standard of care in the first-line setting for selected patients. However, this is a very expensive combination and more information is needed on which patients are more likely to derive benefit from such an approach.

## Trastuzumab–emtansine

Trastuzumab–emtansine (T–DM1) is an antibody–drug conjugate combining trastuzumab with a chemotherapeutic antimicrotubule agent derivative of maytansanine (DM1). The anatomy of this antibody–cytotoxic conjugate is divided in three components: the antibody itself, the cytotoxic agent and, importantly, the linker molecule [62–64]. Activation of cytotoxicity of this conjugate requires internalization into the cell after binding to HER2 [65].

In the TDM4258g Phase II study, in patients with HER2-positive MBC who had tumor progression after prior treatment with HER2-directed therapy and who had received prior chemotherapy, with a follow-up of 12 months among 112 treated patients, T–DM1 demonstrated an ORR of 25.9% (95% CI: 18.4–34.4%). The median PFS was 4.6 months (95% CI: 3.9–8.6 months). T–DM1 was well tolerated with no dose-limiting cardiotoxicity [66].

At the 2011 European Multidisciplinary Cancer Congress, the primary efficacy and updated safety results of the open-label Phase II study (TDM4450g/BO21976) of T–DM1 versus trastuzumab plus docetaxel in previously untreated HER2-positive MBC were presented. With respect to efficacy data, this study showed a significant improvement in PFS in the T–DM1 arm (14.2 vs 9.2 months; HR: 0.59; $p = 0.035$). Overall, T–DM1 was very well tolerated and had a much more favorable toxicity profile compared with docetaxel and trastuzumab [67].

This compound is now being studied in three key trials. EMILIA (NCT00829166) is an open-label Phase III trial evaluating T–DM1 versus

capecitabine plus lapatinib in trastuzumab-pretreated MBC patients [68,101]. Another study, recently closed to patient accrual, MARIANNE (NCT01120184), is a Phase III trial evaluating T–DM1, T–DM1 plus pertuzumab or trastuzumab plus a taxane as first-line therapy for HER2-positive MBC [58,102]. The third Phase III trial with T–DM1, THERESA (NCT01419197), now open, will compare single-agent T–DM1 versus physicians' therapy of choice for patients in the third-line (or greater) setting for HER2-positive MBC who have been previously treated with anthracyclines, capecitabine, taxanes, trastuzumab and lapatinib [69,103].

### Neratinib

Neratinib is an oral, irreversible, inhibitor of HER1, HER2 and HER4 [70]. Burstein *et al.* conducted a Phase II trial with neratinib in HER2-positive MBC. They found that the 16-week PFS rates were 59% for patients with prior trastuzumab treatment and 78% for patients with no prior trastuzumab therapy. The median PFS was 22.3 and 39.6 weeks, respectively. The ORR was 24% among patients with prior trastuzumab treatment and 56% in the trastuzumab-naive cohort. Nausea, diarrhea, vomiting and fatigue were the most common adverse events reported [71]. A Phase II clinical trial was presented at the 2011 San Antonio Breast Cancer Symposium by Martin *et al.*; neratinib was found to be inferior to lapatinib plus capecitabine, with a median PFS of 4.5 versus 6.8 months ($p = 0.23$), and ORRs were substantially higher with lapatinib plus capecitabine versus neratinib (40 vs 29%). The incidence of diarrhea was significantly higher with neratinib versus lapatinib plus capecitabine (85 vs 68%; $p = 0.002$) [72]. A Phase III trial is ongoing using neratinib in MBC: NCT00915018 is investigating paclitaxel with neratinib or combined with trastuzumab [65,104].

### Everolimus

Everolimus (RAD001) is an inhibitor of mTOR, a serine/threonine protein kinase involved in the regulatory mechanisms of cancer cell proliferation. Everolimus is being extensively studied in HER2-positive MBC. In a Phase I study everolimus was combined with weekly paclitaxel plus trastuzumab in trastuzumab-resistant disease; the RR was 44%, disease control for 6 months rate was 74% and median PFS was 34 weeks. This combination showed antitumor activity in patients with trastuzumab-pretreated and resistant metastatic disease [73].

Dalenc *et al.* also evaluated the activity of everolimus in a multicenter Phase II trial using paclitaxel plus trastuzumab with everolimus in patients whose disease was resistant to both trastuzumab and taxanes. The investigators observed five confirmed partial response (20%), 14 stable disease (56%) and six progressive disease (24%). Treatment was well tolerated. In conclusion, this combination showed important activity in patients resistant to lapatinib therapy [74]. Recently published data from a Phase I/IIb trial by Morrow *et al.* evaluated the combination of everolimus and trastuzumab in patients with HER2-overexpressing MBC who progressed on trastuzumab-based therapy. The CBR was 34%, the median PFS was 4.1 months and they concluded that the inhibition of mTOR results in clinical benefit and disease response in patients with trastuzumab-resistant HER2-overexpressing MBC [75].

The clinical adoption of everolimus in HER2-positive MBC patients will depend on the results from two ongoing pivotal Phase III clinical trials. The first study is BOLERO-1 (NCT00876395; currently closed to accrual), a Phase III, randomized, double-blind study of everolimus plus trastuzumab and paclitaxel as upfront therapy in women with HER2-positive locally advanced breast cancer or MBC [105]. Patients are randomized to receive either everolimus or placebo, plus trastuzumab and paclitaxel. The primary end point is PFS, and the secondary main end points are OS, ORR and CBR. The second study is BOLERO-3 (NCT01007942), a Phase III, randomized, double-blind study of everolimus plus trastuzumab and vinorelbine in women with HER2-positive locally advanced breast cancer or MBC previously treated with a taxane and resistant to trastuzumab [62,106].

### Afatinib

Afatinib is an irreversible inhibitor of HER1 and HER2. Afatinib activity in HER2-positive MBC has been evaluated in an open-label Phase II study in which patients received afatinib as monotherapy after failure of treatment to trastuzumab. CBR (complete response plus partial response plus stable disease) was observed in 53% of patients (n = 41) [76]. The LUX-Breast 1 study (NCT01125566) is evaluating the use of afatinib or trastuzumab with vinorelbine in

HER2-positive MBC patients who progressed after trastuzumab [107].

## Antiangiogenic therapy

Many molecules targeting the VEGF or VEGF receptor are under investigation in HER2-positive MBC, since overexpression of HER2 has been shown to be associated with the increased angiogenesis and expression of VEGF in tumor cells. For example, sunitinib in a Phase II trial in patients with MBC previously treated with an anthracycline and a taxane was found to produce notable responses in HER2-positive, trastuzumab-treated patients [77,78].

Bevacizumab was studied in the Phase III trial AVEREL (NCT00391092), a randomized, open-label study designed to compare first-line treatment with bevacizumab plus trastuzumab plus docetaxel versus trastuzumab plus docetaxel alone with a primary end point of investigator-assessed PFS in patients with HER2-positive locally recurrent or MBC [108]. The AVEREL

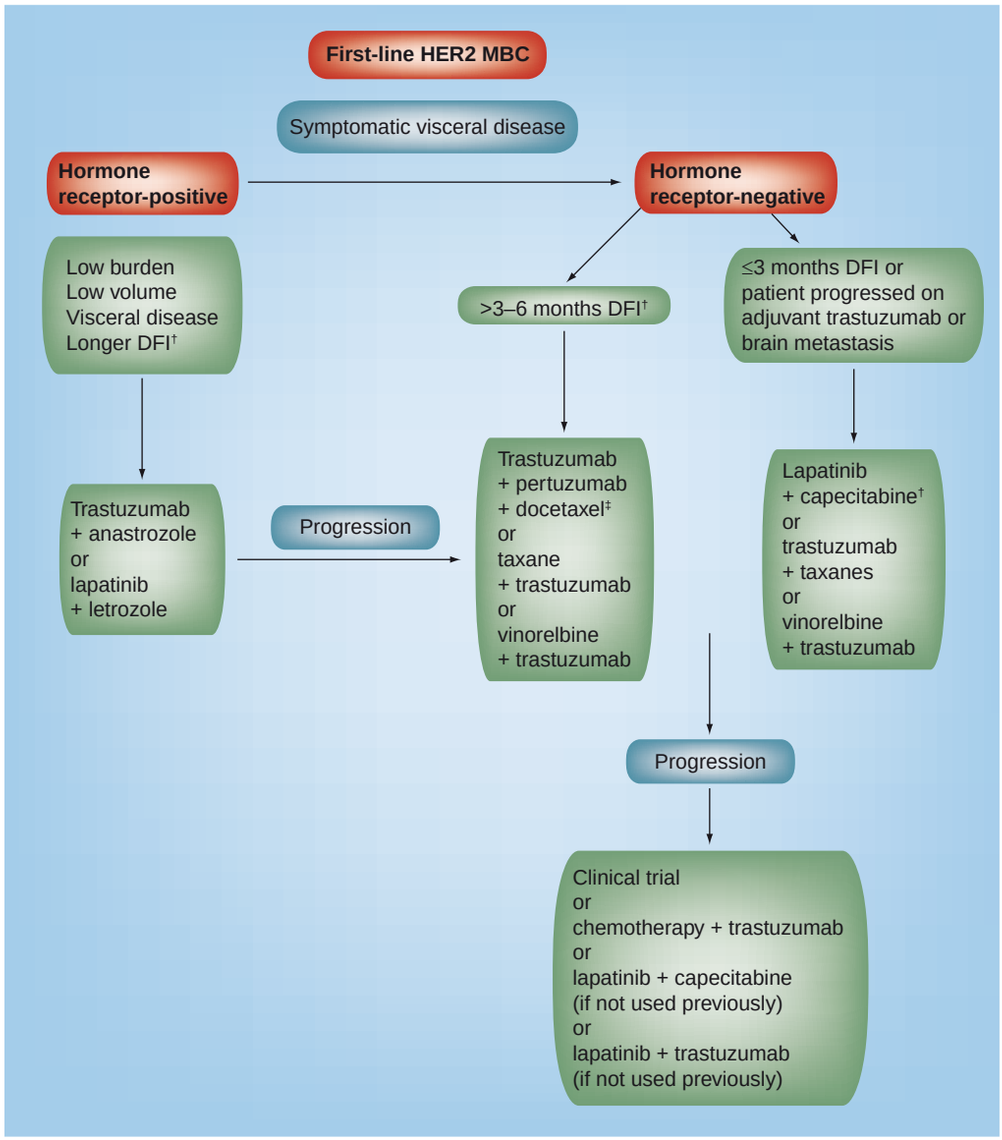


**Figure 1. Treatment algorithm for HER2-positive metastatic breast cancer.**
†This approach based on disease-free interval is primarily based on clinical judgment.
‡This regimen is not currently approved by the US FDA.
DFI: Disease-free interval; MBC: Metastatic breast cancer.

study was presented recently at the 2011 San Antonio Breast Cancer Symposium; it demonstrated a nonstatistically significant improved PFS when bevacizumab was combined with trastuzumab plus docetaxel. The investigator-assessed PFS had a HR of 0.82 (p = 0.0775) and the independent review committee-assessed PFS had a HR of 0.72 (p = 0.0162) [79]. Given the marginal benefit in the overall population, efforts are now underway to determine a specific biomarker to identify the subgroups most likely to benefit.

### Heat shock protein inhibitors

In preclinical models the Hsp90 chaperone complex is important for the stability, maturation and activation of important oncoproteins such as HER2, HER1, Akt and MAPK, among others. These models have demonstrated that Hsp90 inhibition produces proteosomal degradation of HER2, which is enhanced with the addition of trastuzumab. Currently these inhibitors are under clinical evaluation [80].

## Future perspective

There are an increasing number of effective therapeutic options available for HER2-positive MBC. There are many therapies in development but, at this point, it is clear that we need continued suppression of HER2 activity either by a monoclonal antibody, TKI or combination of the two. A clinical uncertainty still remains as to which is the more superior HER2-targeted therapy and the need for chemotherapy with combined HER2-targeted therapy.

There is a clear interest in utilizing a combined targeted approach (either with a TKI plus trastuzumab or trastuzumab plus pertuzumab); however, this is quite costly and we need more information on which patients are more likely to respond to such an approach.

In addition, further biomarker research is needed to better understand mechanisms of resistance to help us personalize a treatment approach upon disease progression.

The authors propose an algorithm of treatment based mainly on Phase III trials according to the data available, which also integrates an approach from our clinical practice **(Figure 1)**. The clinician in the context of multidisciplinary team needs to choose the right drug/combination based on understanding of disease biology and appropriate risk–benefit analysis.

### Financial & competing interests disclosure

*S Verma is a researcher for Sanofi-Aventis and Roche. S Verma is also on advisory boards for GSK, Roche and Sanofi-Aventis. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.*

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