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Therapeutic Considerations in Treating HER2-Positive Metastatic Breast Cancer

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Abstract

Despite advances in detection and treatment, metastatic breast cancer (MBC) remains the second highest cause of cancer-related death for women in the United States. Human epidermal growth factor receptor-2 (HER2) is amplified in 25–30% of breast cancers and is associated with aggressive disease and, historically, with poorer outcomes. The advent of trastuzumab, a monoclonal antibody to HER2, revolutionized the management of HER2-positive breast cancer (BC) in the metastatic and adjuvant settings. However, relapse despite adjuvant trastuzumab and resistance to trastuzumab in the metastatic setting remain substantial clinical problems for many patients with HER2-positive BC. As such, analyzing the mechanisms of trastuzumab resistance and developing new therapy to overcome trastuzumab resistance are research priorities. There has been progress, with the approval of three additional HER2-targeted agents in the last six years: lapatinib, pertuzumab, and ado-trastuzumab emtansine (T-DM1). Other HER2-targeted therapies, including neratinib and afatinib, are in clinical development, and trials of novel agents such as heat shock protein-90 (HSP90) inhibitors, phosphatidylinositol-3-kinase (PI3K) inhibitors, and HER2-targeted vaccines are ongoing. In addition to developing new therapy, research is addressing several unique challenges in the management of HER2-positive MBC. In this article, we discuss advances in the treatment of HER2-positive MBC, with a focus on novel HER2-targeted therapy and HER2-targeted agents recently approved by the United States Food and Drug Administration (FDA). Additionally, we also address the management of brain metastases (BM) and hormone receptor (HR) - positive, HER2-positive MBC.

Keywords

trastuzumab; metastatic breast cancer; lapatinib; pertuzumab; adotrastuzumab emtansine; brain metastases

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Compliance with Ethics Guidelines

Conflict of Interest

Dr. O'Sullivan and Dr. Smith have nothing to disclose.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Although breast cancer outcomes have improved, MBC remains incurable, with 40,000 women expected to die from MBC in the United States in 2014[1]. Approximately 25–30% of BC is HER2-positive, which predicts more aggressive disease and response to HER2-targeted therapy [2]. HER2-positivity is defined by evidence of protein over-expression (measured by immunohistochemistry) and/or by evidence of gene amplification (measured by *HER2* copy number or *HER2*/CEP17 ratio on *in situ* hybridization) [3•]. Whereas HER2-positive BC was historically associated with poor prognosis[2, 4–6], the development of HER2-targeted therapy beginning with trastuzumab, a monoclonal antibody to HER2, has resulted in dramatically improved overall survival (OS) for women with HER2-positive MBC and HER2-positive early-stage BC[7, 8].

Despite the overall success of trastuzumab in treating HER2-positive MBC, approximately 70% of patients become resistant to therapy within one year (secondary resistance)[9] and approximately 35% do not respond to trastuzumab at all (*de novo* resistance)[10, 11]. There are several potential mechanisms of resistance to trastuzumab therapy [9], but there are no established biomarkers predictive of resistance to trastuzumab [12]. Continuation of trastuzumab beyond progression is beneficial for some patients [13], however there is a clear need for other treatment options. Since 2007, three new HER2-targeted therapies (lapatinib, pertuzumab and T-DM1) have been licensed by the FDA for use in HER2-positive MBC. Multiple clinical trials evaluating the efficacy of newer HER2-targeted therapies and novel agents including tyrosine kinase inhibitors (TKIs), PI3K inhibitors, HSP90 inhibitors, and HER2-targeted vaccines are currently ongoing (Table 1). In this review we describe important developments in the treatment of HER2-positive MBC, ongoing research to improve outcomes for this subgroup of BC patients and remaining challenges.

Molecular Biology of HER2

HER2 is a member of the epidermal growth factor receptor (EGFR or ErbB) family of receptor tyrosine kinases (TK), including four structurally related HER proteins - HER1 (EGFR, ErbB1), HER2, HER3 (ErbB3) and HER4 (ErbB4) – which all have a function in controlling cell growth, proliferation and survival. HER2, which is encoded by the *HER2* proto-oncogene on chromosome 17, is a 185 kDa membrane-spanning protein composed of a ligand-binding extracellular domain (ECD), an α -helical transmembrane segment, and an intracellular TK domain [41–43]. Homo- or heterodimerization of the HER receptors results in downstream intracellular signaling via canonical pathways that mediate cell growth and proliferation: -- the PI3K/mammalian target of rapamycin (mTOR) pathway, the Akt pathway and the mitogen-activated protein kinase (MAPK) pathway. Unlike the other HER proteins, HER2 has no known ligand and exists in a constitutively open conformation, making it the preferred partner for heterodimerization with other HER proteins. The formation of HER2 heterodimers (e.g.HER2/HER3) is more effective than the formation of HER2 homodimers in promoting carcinogenesis by activating ligand-initiated intracellular signaling via the MAPK/PI3K/Akt/mTOR pathways [44](Fig. 1).

As described above, although trastuzumab has significantly improved outcomes for patients with HER2-positive MBC, the median duration of response is less than one year [45]. Determining the molecular mechanisms of resistance to trastuzumab has been difficult, but potential mechanisms of resistance include up-regulation of the PI3K pathway, accumulation of p95-HER2 (a truncated form of the HER2 receptor), and increased signaling from HER family receptors and the insulin growth factor 1 receptor (IGF-1R)[46].

FDA -approved therapy for HER2- positive MBC

Trastuzumab

Trastuzumab is a humanized monoclonal antibody that binds to domain IV of the juxta-membrane region of the ECD of HER2. Its mechanisms of action include inhibition of intracellular signaling, inhibition of angiogenesis, inhibition of ECD cleavage, increased intracellular HER2 degradation and activation of antibody dependent cellular cytotoxicity (ADCC)[47].

In a pioneering trial, Slamon et al. compared combined chemotherapy and trastuzumab with chemotherapy alone for first-line treatment of HER2-positive MBC. Findings revealed improved response rate (50% vs. 32%; $p < 0.001$), duration of response (9.1 months vs. 6 months; $p < 0.001$), time to progression (TTP) (7.4 months vs. 5.6 months; $p < 0.001$) and median overall survival (OS) (25.1 months vs. 20.3 months, $p = 0.01$) with the combination [7]. Since this trial, trastuzumab has been safely combined with multiple different chemotherapy agents for the treatment of MBC [13]. Additionally, several large adjuvant trials revealed that addition of trastuzumab to chemotherapy for early-stage HER2-positive BC resulted in an approximately 50 % reduction in relapse and 30 % reduction in fatality [8, 48–53].

Cardiotoxicity, most frequently presenting as a decline in ejection fraction [54], is the most significant toxicity associated with trastuzumab. Pre-clinical models of mice with cardiac-restricted deletion of HER2 revealed dilated cardiomyopathy [55]. Based on concern about cardiac toxicity during the initial clinical trials of trastuzumab, an independent Cardiac Review and Evaluation Committee was convened and their analysis confirmed a risk of heart failure, with the highest rates associated with concurrent administration of trastuzumab and anthracycline (27%) and lower rates with concurrent trastuzumab and taxanes (13%) or trastuzumab alone (3–7%)[56]. More recent data evaluating cardiac toxicity revealed asymptomatic declines in ejection fraction in approximately 25 % of patients and symptomatic declines in ejection fraction in approximately 4–5% of patients [48–53, 57].

Most women receiving trastuzumab for MBC will ultimately develop resistance. Preclinical data suggests that withdrawal of trastuzumab can result in rapid tumor cell re-growth [58, 59], implying that trastuzumab-resistant tumors may still be dependent on HER2 TK-mediated signaling [10]. On this basis, the German Breast Group 26/Breast International Group 03–05 trial was designed to investigate whether trastuzumab should be continued beyond clinical progression [13]. Patients with HER2-positive MBC who had progressed on trastuzumab-based treatment were randomized to capecitabine monotherapy or to capecitabine plus trastuzumab. Although there was no difference in OS between the two

groups, response rates were higher for the capecitabine-plus-trastuzumab group (27 % vs. 48.1 % respectively, odds ratio, 2.50; $p=0.0115$), supporting the practice of continuing trastuzumab beyond progression [13].

Lapatinib

In 2004, Burris et al. reported that lapatinib, a dual EGFR/ErbB-2 TKI, inhibits tumor cell growth *in vitro* and in xenograft models of several human tumors[60]. Lapatinib blocks HER1 and HER2 TKs to the same extent, but its efficacy is limited to HER2-positive tumors [61, 62]. Unlike trastuzumab, lapatinib can cross the blood- brain barrier (BBB) and therefore has a therapeutic effect on intracranial metastases [63, 64]. In a pioneering trial, Geyer et al. randomized women with HER2-positive MBC who had previously received anthracycline, taxane and trastuzumab therapy to capecitabine alone or to capecitabine plus lapatinib. Median TTP was longer for the combination group than the monotherapy group (8.4 vs. 4.4 months, $p<0.001$) and there was a trend towards improved OS with the combination ($p=0.177$). In addition, fewer patients presented with brain metastases (BM) at first progression in the combination group [65, 66]. Burstein et al. conducted a phase II trial of lapatinib monotherapy for heavily pretreated patients with MBC. No patients with HER2-negative disease responded; however in the HER2-positive cohort, three patients had a complete response (CR) and three patients had a partial response (PR), with a median progression-free survival (PFS) of 9.1 weeks and OS of 29.4 months. Of note, all the HER2-positive patients received prior trastuzumab [67].

Pre-clinical studies noted a synergistic interaction between lapatinib and trastuzumab in ErbB2-positive cell lines, suggesting that dual HER2 blockade may be more effective than single agent blockade [61]. Additionally, cross-resistance between lapatinib and trastuzumab is incomplete, suggesting mechanisms of resistance to these drugs may differ[46]. The EGF104900 trial compared lapatinib alone with lapatinib plus trastuzumab in patients with HER2-positive, trastuzumab-refractory MBC. In this heavily pre-treated population, a 4.5 month survival advantage was associated with dual HER2-targeted therapy [68, 69]. This finding laid the groundwork for future studies evaluating dual HER2-targeted therapy and suggested that HER2-targeted therapy alone (i.e. without chemotherapy) can be an option for HER2-positive MBC.

Unlike trastuzumab, lapatinib is rarely associated with cardiac toxicity[70], a finding which may be explained by the fact that trastuzumab has a greater effect on calcium handling, reduction of HER2 protein levels, and increasing of HER2 mRNA levels than does lapatinib [71–73]. Also, most studies of lapatinib were performed on women who had previously received trastuzumab, a group likely to have relatively normal cardiac function. Overall, the main toxicities associated with lapatinib are mild diarrhea and rash [74].

Pertuzumab

Pertuzumab, a humanized monoclonal IgG antibody, binds to domain II of the HER2 ECD and inhibits HER2-dimerization [75–76]. Pre-clinical trials revealed synergy between pertuzumab and trastuzumab [77–81], a finding that was confirmed in a phase II trial evaluating pertuzumab and trastuzumab for patients with HER2-positive MBC who had

progressed on prior trastuzumab-containing regimens [82]. Notably, response rates for pertuzumab monotherapy are low [75].

The pioneering CLEOPATRA trial evaluated first-line docetaxel and trastuzumab with either placebo or pertuzumab for 808 women with HER2-positive MBC. PFS was longer for the pertuzumab group (18.5 months vs. 12.4 months, $p < 0.001$). As of the most recent analysis, median OS was 37.6 months for the placebo group and had not yet been reached for the pertuzumab group ($p = 0.0008$) [83,84]. Trials evaluating pertuzumab in combination with other agents for first-line and later-line treatment of HER2-positive MBC are ongoing [24–85–87]. Pertuzumab is generally well tolerated, with the most common toxicities including rash, diarrhea, mucositis, and febrile neutropenia when combined with chemotherapy and trastuzumab [88]. Importantly, there is no increase in cardiotoxicity when pertuzumab is combined with trastuzumab and docetaxel compared with trastuzumab and docetaxel without pertuzumab [89, 90].

Ado- trastuzumab emtansine (T-DM1)

T-DM1 is a novel antibody-drug conjugate composed of a potent cytotoxic drug, emtansine, connected to trastuzumab via a stable linker, enabling targeted delivery of chemotherapy to HER2-positive cells [91]. The phase III EMILIA trial randomized patients previously treated with chemotherapy and trastuzumab to T-DM1 or to lapatinib plus capecitabine. Median PFS was 9.6 months with T-DM1 compared with 6.4 months with lapatinib plus capecitabine ($p < 0.001$), and median OS at the second interim analysis crossed the stopping boundary for efficacy favoring T-DM1 (30.9 months vs. 25.1 months, $p < 0.001$) [92].

T-DM1 is associated with minimal toxicity, however patients may develop thrombocytopenia and/or elevated liver enzymes [92]. Ongoing studies further evaluating use of T-DM1 for HER2-positive MBC include the MARIANNE trial, assessing T-DM1 in combination with pertuzumab for first-line treatment, and the TH3RESA trial, which recently reported preliminary findings indicating improved PFS and overall response rate (ORR) with T-DM1 for patients who had received 2 prior HER2-targeted therapies [87, 93].

Investigational agents

Multiple new agents are currently under investigation for the treatment of HER2-positive MBC.

Small Molecule HER Family Tyrosine Kinase Inhibitors

Neratinib—Neratinib is an oral, irreversible inhibitor of HER1, HER2, and HER4 TK activity. Based on promising pre-clinical and phase I results [94,95], a single agent phase II study of neratinib for patients with advanced HER2-positive MBC was conducted. For patients who had been previously exposed to trastuzumab, median PFS was 22.3 weeks compared to 39.6 weeks for patients who were trastuzumab naive. The most common grade III and/or IV adverse event was diarrhea, which occurred in 30 % of patients who had prior trastuzumab and 13 % of patients who had not received prior trastuzumab [96]. A small trial evaluating the combination of neratinib and capecitabine revealed an impressive response

rate of 50 % among patients previously treated with taxane and trastuzumab therapy [97]. Important ongoing trials are evaluating neratinib in multiple clinical settings, including in combination with temsirolimus for first line treatment of HER2-positive MBC, in combination with capecitabine for previously treated patients and, since neratinib crosses the BBB, for the treatment of progressive BM in patients with HER2-positive MBC [29, 98, 99]. The most frequent adverse events associated with neratinib to date include diarrhea and rash [96].

Afatinib—Afatinib is an oral, irreversible pan-HER TKI which, like other small molecular anti-HER2 TKIs, crosses the BBB [100]. Phase I studies revealed that the most frequent toxicities associated with afatinib are diarrhea, nausea, vomiting, rash, and fatigue [101]. Early efficacy results for afatinib are promising, with a phase II study involving 41 patients who had progressed on trastuzumab obtaining PR and stable disease (SD) for 11 % and 37 % of patients, respectively [102]. The Lux-Breast trials are currently evaluating afatinib in additional clinical settings. In the phase III Lux-Breast I trial, patients with HER2-positive MBC who have progressed on trastuzumab are randomized to vinorelbine plus trastuzumab or to vinorelbine plus afatinib [103]. The Lux-Breast II trial is evaluating the efficacy of afatinib monotherapy for patients who have progressed on prior trastuzumab and/or lapatinib [104]. And, the Lux-Breast III trial is evaluating afatinib monotherapy or afatinib plus vinorelbine compared with the investigators' choice of treatment for patients with HER2-positive MBC and progressive BM who have progressed on prior trastuzumab or lapatinib based therapy [105]. In addition to the Lux-Breast trials, afatinib is being evaluated by other trials in combination with endocrine therapy [106], and in combination with trastuzumab or lapatinib [107,108].

Investigational antibodies

MM-111—MM-111 is a bio-specific antibody, an artificial protein composed of fragments of two different monoclonal antibodies, which can bind two different kinds of antigen [109]. MM-111 forms a trimeric complex with HER2 and HER3, resulting in inhibition of HER3 signaling. In preclinical models, MM-111 had anti-tumor activity against tumors dependent on HER2 overexpression [110]. It has been proposed that blockade of both HER2 and HER3 may be a more effective method of treating HER2-amplified tumors than HER2 blockade alone [111]. There is an ongoing phase I trial of MM-111 and trastuzumab for patients with trastuzumab-refractory HER2-positive MBC [112]. In addition, NCT01304784 is a phase I and pharmacological study of MM-111 in combination with multiple treatment regimens for patients with advanced HER2-positive solid tumors [34].

PI3K inhibitors and mTOR Inhibitors

Somatic mutations which activate the PI3K- Akt- mTOR pathway are present in >50 % of BC, providing a sound rationale for evaluating inhibitors of this pathway for BC treatment [113]. Because PI3K is downstream from HER2 and mTOR is downstream from PI3K, targeting this pathway may be an important step in overcoming trastuzumab resistance in HER2-positive BC. The PI3K inhibitors under development are classified by mechanism of action, i.e. pure PI3K inhibitors, compounds which block both PI3K and mTOR (dual inhibitors), pure catalytic mTOR inhibitors, and inhibitors which block Akt [114]. XL147

selectively inhibits the class I PI3K family and, on the basis of promising pre-clinical efficacy, has been evaluated in phase I clinical trials, where it has revealed an acceptable safety profile. On the basis of encouraging preclinical data, a phase I and II study of XL147 in combination with trastuzumab or paclitaxel and trastuzumab was conducted on patients with HER2-positive MBC who had progressed on a prior trastuzumab -containing regimen; results are awaited [115]. The pan-class-1 PI3K inhibitor, BKM120, is also under investigation in a phase I trial evaluating its efficacy in combination with trastuzumab for patients with advanced HER2-positive BC who have progressed on a trastuzumab-based regimen[116].

The largest trials evaluating mTOR inhibition in HER2-positive MBC include the BOLERO-1 and BOLERO-3 trials. The phase III BOLERO-1 trial, which has completed accrual, compares paclitaxel and trastuzumab with or without everolimus for first-line treatment of women with HER2-positive MBC [117]. Preliminary results of the BOLERO-3 trial, evaluating vinorelbine and trastuzumab with or without everolimus for treating HER2-positive MBC which has progressed on taxanes and trastuzumab therapy, were presented in 2013[118]. Median PFS for the everolimus group was seven months, compared with 5.78 months for the placebo group (HR 0.78, 95 % CI 0.65, 0.95; $p = 0.0067$). OS data are not yet mature. Although the results of BOLERO-3 are proof of principle for the use of mTOR inhibition to overcome trastuzumab resistance, it is uncertain that these results will be clinically significant given the small increase in PFS and the additional toxicity. Other phase I and II trials are investigating the efficacy of PI3Kis as monotherapy or in combination with endocrine therapy or HER2-targeted therapy [113]. Whether all patients with HER2-positive MBC or solely those with PI3K mutations derive benefit from these agents remains to be confirmed [114].

HSP90 inhibitors

The chaperone protein HSP90 interacts with client proteins in the cell cycle, including HER2, and potentiates the action of antineoplastic agents including trastuzumab [119]. Pre-clinical studies suggest that the combination of HSP90 inhibitors and trastuzumab can overcome resistance to trastuzumab monotherapy. Several HSP90 inhibitors have been evaluated in phase I and II trials; however, the development of some of these compounds, including geldanamycin, has been limited because of toxicity [120]. Tanespimycin/17-AAG is a derivative of geldanamycin, which has similar efficacy but reduced toxicity. A phase II trial conducted on patients with HER2-positive MBC obtained promising results, with an ORR of 22 % and a clinical benefit rate (CBR) of 59 % [121]. The most common toxicities were grade I and included diarrhea, nausea, fatigue, and headaches, but development of tanespimycin/17-AAG was halted in 2008 because of production problems. Alvespimycin is a water-soluble derivative of geldanamycin. A phase I trial of this agent combined with trastuzumab in patients with HER2-positive MBC noted an ORR of 6.25 % and SD of 18.75 %; however, concerns regarding ocular toxicity precluded further clinical development [122]. Retaspimycin in combination with trastuzumab was evaluated in a phase II trial on a similar patient population and had modest clinical activity with an ORR of 5 % and SD of 70 %. The most common toxicities were grade I and II, including fatigue (49 %), nausea (31 %) and diarrhea (23 %)[123]. Another HSP90 inhibitor, ganetespib, is under evaluation in

the first-line setting for patients with HER2-positive MBC in a phase II trial (ENCHANTTM)[124]; results to date noted modest activity in patients with HER2-positive MBC, with an ORR of 6.7% and SD obtained for 33.3 % of patients. Grade III and IV events included hypopituitarism, diarrhea and aphasia [125]. AUY922 is a potent small-molecule synthetic HSP90 inhibitor with promising clinical activity. A phase Ib and II trial is ongoing evaluating the combination of AUY922 and trastuzumab for patients with HER2-positive MBC who have progressed on prior trastuzumab-based therapy[126].

Anti-angiogenic agents

Bevacizumab—Bevacizumab, a recombinant recombinant humanized monoclonal antibody targets vascular endothelial growth factor (VEGF) and inhibits angiogenesis, which is necessary for tumor growth and survival. HER2 overexpression is associated with increased VEGF expression and pre-clinical evidence suggests that the HER2 and VEGF signaling pathways are linked in human BC [127], thus providing the rationale for evaluating anti-angiogenic therapy for HER2-positive BC. Based on promising phase I and II data combining bevacizumab with chemotherapy and HER2-targeted therapy [128,129], the AVEREL study compared bevacizumab, docetaxel and trastuzumab with trastuzumab and docetaxel alone for first-line treatment of HER2-positive MBC [130]. Disappointingly, no difference in PFS or OS was observed with the addition of bevacizumab. Further evidence of the lack of benefit of adding anti-angiogenic therapy to chemotherapy plus trastuzumab comes from the recently presented findings of the adjuvant BETH trial in which bevacizumab did not confer additional benefit when added to chemotherapy and trastuzumab for patients with HER2-positive early BC[131].

Vaccine therapy

On the basis of the observation that patients can spontaneously develop anti-HER2 specific immunity with high levels of humoral and cellular immunity, HER2 is one of the most suitable targets for immunotherapy in BC [132]. Types of vaccine therapy presently under evaluation include peptide-based, protein-based, DNA based, whole tumor cell-based and dendritic cell-based compounds. A phase I and II study evaluated the combination of trastuzumab and a HER2 peptide-based vaccine for 22 pre-treated patients with HER2-positive MBC[133]. Treatment was well tolerated, with a median PFS of 17.7 months, which compared favorably with results achieved with standard therapy for this population. E75 is an immunogenic peptide from the HER2/neu protein, which is strongly expressed in BC [134]. Benavides et al. studied the combination of trastuzumab and the E75 vaccine, which was safe and immunologically beneficial [135]. A Phase I trial assessed the combination of an allogeneic HER2-positive granulocyte-macrophage colony stimulating factor (GM-CSF) secreting breast tumor vaccine with trastuzumab and cyclophosphamide. Twenty-two patients with HER2-positive MBC were enrolled and no dose limiting toxicities (DLTs) were noted; the clinical benefit rate at six and 12 months was 50 % and 35 %, respectively [136]. Another trial evaluated the combination of a DNA vaccine, low-dose IL-2, and GM-CSF in combination with trastuzumab for eight patients with HER2-positive MBC; low levels of toxicity and a strong therapeutic antibody response were noted, and two patients are long-term survivors [137]. Although available immunotherapy is safe and tolerable, there have been no direct comparisons with standard therapy for HER2-positive

BC. Therefore, it remains to be seen whether meaningful clinical responses, as defined by an improvement in OS compared with that obtained by standard therapy for HER2-overexpressing BC will be observed [132].

Predictive biomarkers for HER2 targeted therapy

Biomarker analysis of patients with HER2-positive MBC has failed to identify any marker that enables better refinement of therapy than HER2 itself. However, data suggests that the prognosis of patients with HER2-positive MBC treated with trastuzumab is significantly worse for patients with PI3KCA mutations [138]. Therefore PI3KCA mutational status may confer poor prognosis for patients with HER2-positive MBC, and patients may be suitable candidates for clinical trials of HER2-targeted agents in combination with PI3K inhibitors or mTOR inhibitors [139]. A prospective analysis of 737 patients enrolled in the GeparSixto and GeparQuinto trials noted that patients with PI3KCA mutant, HER2-positive, HR-positive BC are resistant to chemotherapy and dual HER2-targeted therapy, which implies that PI3KCA mutational status is also predictive of response to treatment [140]. Biomarker analysis from EMILIA revealed that patients with PI3KCA mutations treated with lapatinib and capecitabine had an inferior median PFS and OS; however, the presence of PI3KCA mutations did not significantly affect outcome for patients treated with T-DM1[141].

Special Clinical Considerations in the Management of HER2-positive MBC

Brain Metastases

Unfortunately, BM occur in approximately 30 – 55% of patients with HER2-positive MBC [142], with data suggesting that BM may be particularly common in patients previously treated with adjuvant trastuzumab for early stage HER2-positive BC[143]. Small molecule TKIs which cross the BBB are a potentially promising new addition to standard therapy for BM in HER2-positive MBC patients. For example, the single-group, multicenter phase II LANDSCAPE trial evaluating the combination of capecitabine and lapatinib for patients with HER2-positive MBC and untreated BM revealed a 65.9 % objective CNS response rate[144]. An ongoing clinical trial is evaluating the efficacy of neratinib for patients with HER2-positive BM (NCT01494662)[29].

Management of Hormone Receptor-positive, HER2-positive MBC

The role of endocrine therapy for treating HR-positive, HER2-positive MBC is not well defined, because the decision is often made to use chemotherapy plus HER2-targeted therapy because of an aggressive clinical course. However, preclinical data suggests that HER2-targeted therapy can overcome endocrine resistance in HR-positive, HER2-positive BC [145]. The TAnDEM study evaluated anastrozole and trastuzumab versus anastrozole alone for treating postmenopausal women with HR and HER2-positive MBC [146]. Median PFS was improved with the combination (5.6 versus 3.8 months (log-rank $p=0.006$), however, no benefit to OS was noted, possibly because 70 % of patients in the anastrozole-alone group crossed over to trastuzumab after progression. Lapatinib has also been evaluated in combination with endocrine therapy on the basis that cross-talk between the EGFR and estrogen-receptor pathways can cause endocrine resistance. In a phase-II trial on postmenopausal, HR-positive women with HER2-positive MBC, the addition of lapatinib to

letrozole significantly reduced the risk of disease progression compared with letrozole alone (median PFS 8.2 vs.3.0 months)[147].

Conclusion

Overall, there has been rapid progress in the treatment of HER2-positive MBC, and it is likely that further practice-changing developments will occur. Dual HER2-targeted therapy has been a powerful addition to the treatment options, but the appropriate combination and sequencing of the newer agents with more established HER2-targeted therapy is still not fully defined. However, the American Society of Clinical Oncology recently released clinical guidelines based on currently available data which provide recommendations for the treatment of HER2-positive MBC in first- and later lines of care using the array of currently available HER2-targeted therapy [148•]. As we move forward, identification of predictive biomarkers will be crucial in further refining treatment options and more knowledge of mechanisms of resistance to trastuzumab will help identify new targets. Unique challenges of managing HER2-positive MBC include the treatment of HER2-positive BM, and management options for patients who have HR-positive and HER2-positive MBC. Several compounds are in different stages of clinical development, and it remains to be seen which of these agents will affect the swiftly changing therapeutic options for HER2-positive MBC.

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Figure 1. Targeted therapies and the HER2 pathway

The human epidermal growth factor receptor (HER) family consists of four members: the epidermal growth factor receptor (EGFR) or HER1, as well as HER2, HER3, and HER4, which are transmembrane receptor tyrosine kinases that control cell growth survival, differentiation, and migration as well as other cellular responses. Of note, HER2 has no known ligand that triggers its activity, and HER3 predominantly functions as a ligand-activated dimer partner for other members of the HER2 family. Activation of these receptors promotes tumor growth by triggering signaling through commonly used growth factor pathways such as RAS/RAF/MEK/ERK and PI3K/AKT/mTOR. The use of targeted therapies to block these pathways is being explored with a view to improving HER2 targeted therapies and overcoming resistance to trastuzumab.

Legend: TRAS- trastuzumab; PER; pertuzumab; LAP- lapatinib; AFA- afatinib; NER- neratinib; PI3K- phosphatidylinositol-3-kinase; EVE-everolimus; mTOR-mammalian target of rapamycin; TEM-temsirolimus; P-phosphate; HSP-heat shock protein; T-DM1-ado trastuzumab emtansine

Table 1

Key agents currently approved or under investigation for the treatment of HER2-positive MBC

Agent	Mechanism of action	FDA approved indications	Examples of key ongoing studies evaluating the agent in HER2-positive MBC
Trastuzumab	mAB to HER2	Adjuvant Breast Cancer <ul style="list-style-type: none"> - For HER2-overexpressing node-positive BC, or HER2-overexpressing node-negative BC that is ER/PR negative or has one high-risk feature - In combination with multi-agent chemotherapy consisting of doxorubicin, cyclophosphamide, paclitaxel or docetaxel, or with docetaxel and carboplatin - As monotherapy after multi-agent anthracycline-based chemotherapy Metastatic Breast Cancer <ul style="list-style-type: none"> - In the first line setting in combination with docetaxel or paclitaxel and pertuzumab for patients with HER2-overexpressing MBC - As monotherapy for the treatment of HER2-overexpressing breast cancer in patients who have been treated with 1 lines of chemotherapy in the metastatic setting [14] 	<ul style="list-style-type: none"> - In combination with eribulin as 1st line therapy for patients with advanced HER2+ BC [NCT01269346][15] (Phase II) - In combination with carboplatin and vinorelbine in advanced HER2+ BC [NCT00431704][16] (Phase II) - In combination with paclitaxel versus trastuzumab, lapatinib and paclitaxel for patients with advanced HER2+ BC [NCT01526369][17] (Phase III)
Lapatinib	Dual TKI of EGFR and HER2	Metastatic Breast Cancer <ul style="list-style-type: none"> - Combined with capecitabine for patients who have advanced or MBC whose tumors overexpress HER2, and have previously been treated with an anthracycline, a 	<ul style="list-style-type: none"> - In combination with everolimus in patients with advanced HER2+ BC [NCT01283789][19] (Phase II) - In combination with cabazitaxel in patients with HER2+ MBC and BM [NCT01934894][20] (Phase II) - In combination with Myocet after progression on trastuzumab

Agent	Mechanism of action	FDA approved indications	Examples of key ongoing studies evaluating the agent in HER2-positive MBC
		taxane and trastuzumab - Combined with letrozole for the treatment of postmenopausal women with ER+ BC that also overexpresses HER2 and for which endocrine therapy is required[18]	and taxanes [NCT01495884][21] (Phase I/II)
Pertuzumab	Inhibits HER2/HER3 hetero-dimerization	Metastatic Breast Cancer - In combination with trastuzumab and docetaxel for the treatment of patients with HER2-overexpressing MBC who have not received prior chemotherapy or HER2-targeted therapy in the metastatic setting. Neoadjuvant Treatment of Early Stage Breast Cancer - In combination with docetaxel and trastuzumab for patients with HER2-overexpressing, locally advanced, inflammatory or early stage BC ($\geq$ 2cm in diameter or node-positive) as part of a complete treatment regimen for early BC [22].	- In combination with trastuzumab and AI in patients with ER/PR+ HER2+ advanced BC (1st line setting)[NCT01491737][23] (Phase II) - In combination with trastuzumab and either paclitaxel, docetaxel, or nab paclitaxel in patients with HER2+ advanced BC [NCT01572038][24] (Phase III) - In combination with trastuzumab and eribulin in patients with advanced HER2+ MBC [NCT01912963][25] (Phase II)
T-DM1	Targeted intracellular delivery of cytotoxic DM1	Metastatic Breast Cancer - As monotherapy in the treatment of patients with HER2-overexpressing MBC who previously received either trastuzumab or a taxane, either separately or in combination. - Patients should either have a)received prior therapy for metastatic disease or b) relapsed within 6 months of	- In combination with abraxane and lapatinib in patients with HER2+ MBC [NCT02073916] [27] (Phase I) - HER2 imaging study to identify patients with HER2+ MBC unlikely to benefit from T-DM1. [NCT01565200] [28] (Phase II)

Agent	Mechanism of action	FDA approved indications	Examples of key ongoing studies evaluating the agent in HER2-positive MBC
		completing adjuvant therapy[26].	
Neratinib	TKI,HER2 and HER4 inhibitor	- Not FDA approved	<ul style="list-style-type: none"> - For patients with HER2+BM [NCT01494662] [29](Phase II) - In combination with capecitabine or lapatinib in patients with HER2+ MBC who have progressed on 2 lines of chemotherapy in the metastatic setting [NCT01808573][30] (Phase III)
Afatinib	Irreversible dual HER1/HER2 inhibitor	- Not FDA approved	<ul style="list-style-type: none"> - Monotherapy/combined with vinorelbine in patients with HER2+ BM [NCT01441596] [31](Phase II) - Patients with MBC who have progressed on one line of trastuzumab based treatment [NCT01125566][32](Phase III)
MM-111	Biospecific antibody which forms a trimer with HER2 and HER3, preventing HER3 signaling	- Not FDA approved	<ul style="list-style-type: none"> - In combination with trastuzumab in patients with advanced HER2+ BC[NCT01097460][33] (Phase I) - In combination with various chemotherapy agents and HER2-targeted therapy for patients with HER2+MBC[NCT01304784][34] (Phase I)
AUY922	Hsp90i	- Not FDA approved	<ul style="list-style-type: none"> - In combination with trastuzumab for patients with advanced HER2+ BC progressing on prior trastuzumab[NCT01271920][35] (Phase II)
XL147	PI3K inhibitor	- Not FDA approved	<ul style="list-style-type: none"> - No open studies for patients with HER2+ MBC listed in clinicaltrials.gov presently
Everolimus	mTOR inhibitor	- Not FDA approved for HER2+ MBC	<ul style="list-style-type: none"> - Combined with vinorelbine and trastuzumab for HER2+ BM[NCT01305941][36](Phase II) - Combined with paclitaxel and trastuzumab for HER2+ MBC[NCT00876395][37] (Phase III)
Bevacizumab	mAB to VEGF	- Not FDA approved for HER2+ MBC	<ul style="list-style-type: none"> - Combined with capecitabine and trastuzumab in patients with advanced HER2+ BC[NCT00811135][38](Phase II)
Vaccines against HER2-overexpressing BC	Generate immunogenicity against HER2+ cell	Not FDA approved	<ul style="list-style-type: none"> - Combined with trastuzumab in HER2+ MBC[NCT01570036] [39](Phase II)

Agent	Mechanism of action	FDA approved indications	Examples of key ongoing studies evaluating the agent in HER2-positive MBC
			- Combined with cyclophosphamide and trastuzumab in patients with HER2+ high risk/ MBC[NCT00847171][40] (Phase II)

Abbreviations Used in Table 1:

mAB- monoclonal antibody; HER2- human epidermal growth factor receptor 2; ET-endocrine therapy; ER- estrogen receptor; PR-progesterone receptor; HR-hormone receptor; AI-aromatase inhibitor, BM-brain metastases; MBC-metastatic breast cancer ; EGFR- epithelial growth factor receptor; TKI-tyrosine kinase inhibitor;HER3; human epidermal growth factor receptor 3; HER2+ HER2-positive; TKI- tyrosine kinase inhibitor; HER1-human epidermal growth factor receptor 1; Hsp90i- Hsp90 inhibitor; VEGF- vascular endothelial growth factor; PI3K-phosphatidy1-3-kinase inhibitor; mTOR-mammalian target of rapamycin; BC-breast cancer