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CLINICAL TRIALS (MN DICKLER, SECTION EDITOR)

Novel Therapies for Metastatic HER2 Positive Breast Cancer

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Abstract The clinical course of HER2 positive (HER2+) breast cancer has changed since the introduction of trastuzumab, the first approved HER2 targeted agent. However, a significant number of patients relapse because of either de novo or acquired resistance to trastuzumab, imposing a need for other targeted agents. Lapatinib, the first targeted agent to demonstrate efficacy after trastuzumab progression, is licensed in combination with chemotherapy or with trastuzumab and has shown efficacy post-trastuzumab progression. Newer, recently approved agents include pertuzumab, an antibody preventing dimerization of HER2 and HER3, and T-DM1, an antibody-drug conjugate capable of delivering a highly cytotoxic agent into the cancer cells. Both agents have modest systemic toxicity. The dual combination of pertuzumab and trastuzumab given in combination with docetaxel is the current standard first-line treatment for HER2+ MBC. T-DM1 is now approved for second-line treatment. Specific clinical scenarios, including brain metastases, still lack good therapeutic options. Newer targeted agents are being tested with an exciting future for the treatment of HER2+ MBC although there are challenges to develop them in today's environment. Clinicians now have a number of options for treatment of metastatic HER2 advanced breast cancer although access to some drugs may be limited globally, often because of economic realities.

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Introduction

Since the initial description of HER-2/*neu* gene overexpression and amplification in the 1980s [1, 2], the management of breast cancer has radically changed. The HER2 gene encodes a transmembrane receptor that initiates a cascade of intracellular signaling events upon activation of its tyrosine-kinase domain, culminating in tumor growth [3–5].

HER2 positive breast cancers historically were associated with a poor prognosis [6, 7]. However, trastuzumab, the first HER2-targeted agent, has improved survival in both metastatic and early HER2 positive breast cancer. Despite this success, a significant percentage of HER positive tumors relapse due to either de novo or acquired resistance to trastuzumab, imposing new challenges in treatment and the need for new therapeutic options [8].

Trastuzumab: an "Old" New Era

Trastuzumab (Herceptin; Genentech, San Francisco, CA) is a humanized monoclonal antibody that exerts a variety of antitumor effects selectively on HER2-overexpressing tumor cells. The mechanism of action is summarized in Table 1. A landmark study by Slamon et al. [8] reported improved time to progression (TTP) from 4.6 to 7.4 months, objective response rates (ORR) from 32 % to 50 %, and duration of response from 6.1 to 9.1 months with the addition of trastuzumab to standard therapy. Median overall survival (OS) increased from 20.3 to 25.1 months. This led to the licensing of trastuzumab for the treatment of advanced HER2 positive breast cancer and

Table 1 Proposed mechanisms of action of targeted agents against HER2 positive breast cancer

Trastuzumab	- binds to extracellular domain IV of HER2 - downregulates HER2 expression - blocks cleavage of the extracellular portion of the HER receptor - blocks ligand-independent HER2–HER3 heterodimerization - downregulation of cyclin D1 - triggers ADCC - antiangiogenic effects
Lapatinib	- reversible ATP-competitive inhibitor of autophosphorylation sites on the HER2 and EGF receptors - downregulates AKT signaling - blocks tumor cell proliferation
Pertuzumab	- binds to extracellular domain II of HER2 - blocks ligand-induced HER2-HER3 dimerization
T-DM1	- binds to HER2 and the HER2/T-DM1 complex is internalized - intracellular releases of DM1 - prevention of microtubule polymerization - suppression of microtubule dynamic instability - induction of apoptosis after G_2/M cell cycle arrest - disruption of the HER3/PIK/AKT signaling pathway - prevention of shedding of the extracellular domain of HER2 - activation of antibody ADCC
Bevacizumab	- inhibits VEGF and its angiogenic effects

paved the way for the development of other HER2 targeted agents (Table 2).

Subsequent studies of trastuzumab defined the schedule, dose, combinations with cytotoxics, treatment past progression, and toxicities [9•]. The adverse events (AE) associated with trastuzumab were mostly mild to moderate, and included chills, asthenia, fever, pain, and nausea [8, 10] as well as the unexpected finding of cardiac toxicity. The initial 27 % rate of cardiac dysfunction in patients receiving trastuzumab concomitant to anthracycline and cyclophosphamide, has not been maintained in contemporary studies [8], and now is reported at a 3 %–4 % incidence of cardiac events in the adjuvant setting, and a less than 1 % incidence of congestive heart failure (CHF) [11, 12•, 13••].

Resistance to Trastuzumab

Resistance to trastuzumab therapy may occur through modifications in both upstream and downstream signaling pathways [4]. Three main mechanisms of trastuzumab resistance are suggested. Steric effects account for structural change in the HER2 protein, including cleavage of the extracellular portion of HER2, generating the p95-HER2 isoform with constitutive kinase activity, and the masking of the trastuzumab-binding site due to elevated expression of Mucin-4. Another mechanism is the overexpression of tyrosine kinase receptors that overcome trastuzumab-mediated inhibition of HER2 signaling, such as overexpression of HER3, IGF-1R, and c-Met. The third mechanism involves the intracellular pathway, and includes activating mutations of the PIK3 pathway or PTEN deficiency [4, 14]. Understanding these resistance mechanisms has guided the development of new targeted agents. As well, xenograft models of HER2 breast cancers demonstrate that trastuzumab exerts a suppressive effect against rapid tumor growth as long as it is present and withdrawal of the drug results in acceleration of tumor growth. These results suggest that some of the anti-tumor mechanisms of trastuzumab may persist even after resistance develops [4] and supports the use of trastuzumab beyond progression.

Lapatinib

Lapatinib is an orally active small molecule tyrosine kinase inhibitor (TKI) that acts as a reversible ATP-competitive inhibitor of autophosphorylation sites on the HER2 and EGF receptors [15].

Lapatinib after Trastuzumab Failure

In preclinical studies, lapatinib was active in trastuzumab resistant HER2-positive tumors due to its different mechanism of action (Table 1). Lapatinib was shown to downregulate AKT signaling and potently block tumor cell proliferation, maintaining activity in PTEN null HER2-overexpressing cell lines, and in p95-HER2 expressing tumors [4].

A randomized open-label phase III trial compared capecitabine with capecitabine plus lapatinib in advanced HER-2 positive breast cancer patients who had progressed after prior treatment with an anthracycline, taxane, and trastuzumab. The study was terminated at the first interim analysis after crossing the superiority boundary for TTP with a median TTP of 8.4 months in the combination arm vs 4.4 months for the monotherapy arm (HR 0.51, 95%CI 0.35–0.74; $P<0.001$). The ORR was 22 % vs 14 % in favor of the lapatinib combination. The most common AEs associated with lapatinib were diarrhea, hand-foot syndrome, nausea, vomiting, fatigue, and rash, almost all grades 1 to 3. Eleven patients experienced cardiac events, with 4 patients in each arm meeting the protocol pre specified toxicity definitions; however, they were all asymptomatic [16, 17•].

Lapatinib Plus Trastuzumab in Second-Line Treatment

The combination of lapatinib and trastuzumab markedly enhanced the rate of apoptosis in HER2-amplified cell lines and xenograft models [18], suggesting that dual blockade is more effective than a single agent. This was confirmed in the

Table 2 Landmark phase III trials of targeted agents for HER2 positive metastatic breast cancer

Trial	Treatment arms	Treatment line	Results
Slamon, 2001 [8]	- Chemotherapy alone (anthracycline plus cychlophosphamide or paclitaxel) - Chemotherapy plus Trastuzumab	First-line	TTP: 4.6 vs 7.4 mo. ORR: 32 % vs 50 % OS: 20.3 vs 25.1 mo.
Geyer, 2006 [16]; David Cameron, 2010 [17•]	- Capecitabine - Capecitabine plus Lapatinib	Second-line	TTP: 4.4 vs 8.4 mo. ORR: 14 % vs 22 % OS: 64.7 vs 75 mo. (trend)
EGF104900 [19•, 20•]	- Lapatinib - Lapatinib plus Trastuzumab	Second-line	PFS: 8.1 vs 11.1 wk. OS: 9.5 vs 14 mo.
MA.31[A] [21•]	- Lapatinib plus taxane - Trastuzumab plus taxane	First-line	PFS: 8.8 vs 11.4 mo. OS: no difference
CLEOPATRA [27••, 28•]	- Placebo plus Trastuzumab plus Docetaxel - Pertuzumab plus Trastuzumab plus Docetaxel	First-line	PFS: 12.4 vs 18.5 mo. OS: 37.6 mo. (placebo arm) vs not reached (pertuzumab arm)
EMILIA [34••]	- Lapatinib plus Capecitabine - T-DM1	Second-line	ORR: 30.8 % vs 43.6 % PFS: 6.4 vs 9.6 mo. OS: 25.1 vs 30.9 mo.
AVEREL [41•]	- Docetaxel plus trastuzumab - Docetaxel plus Trastuzumab plus Bevacizumab	First-line	PFS: 13.7 vs 16.5 mo. (p not significant) ORR: 70 % vs 74 % (p not significant)
CEREBEL[a] [83]	- Lapatinib plus capecitabine - Trastuzumab plus capecitabine	Any line	PFS: 6.6 vs 8.0 mo. OS: 22.7 vs 27.3 mo. No difference in CNS disease incidence

[a] Data presented, but not yet published

EGF104900 phase III trial of lapatinib and trastuzumab vs lapatinib alone in HER2-positive metastatic breast cancer patients with previous disease progression on trastuzumab therapy [19•]. There was improvement in PFS from 8.1 to 11.1 weeks (HR 0.74; 95 % CI 0.58–0.94; *P* .011) and in median OS from 9.5 to 14 months (HR, 0.74; 95 % CI 0.57–0.97; stratified log-rank *P* .026) [20•]. These results provide an alternative to chemotherapy for patients with trastuzumab-refractory disease.

Lapatinib vs Trastuzumab in First-Line Treatment

The MA.31 trial, a randomized, open label, phase III study, compared a taxane-based regimen with lapatinib (LTax/L) or trastuzumab (TTax/T) in the first-line treatment for HER2 positive metastatic breast cancer. At the interim analysis at a median follow-up of 13.6 months, the TTax/T showed a longer PFS compared with the LTax/L of 11.4 vs 8.8 months, (HR 1.33; 95 % CI 1.06–1.67; $P=0.01$). As expected, more grade 3–4 diarrhea and rash was observed in the LTax/L arm [21•].

Pertuzumab

Pertuzumab is a monoclonal antibody that binds to the HER2 receptor near the center of domain II, sterically blocking a binding pocket necessary for receptor dimerization and signaling, resulting in blockade of ligand-induced HER2-HER3 dimerization [22, 23].

Pertuzumab Combined with Trastuzumab

Xenograft models of HER2-amplified breast cancer demonstrated enhanced tumor regression for the combination therapy of both targeted HER2 antibodies including anti-tumor activity in models of trastuzumab resistance, suggesting that trastuzumab and pertuzumab have complementary mechanisms of action [24].

Efficacy and safety of the combination was demonstrated in a phase II trial with patients who experienced disease progression on trastuzumab-based therapy. The clinical benefit rate (CBR) was 50 % and the most frequent AEs were mild to moderate, and included diarrhea (64 %), fatigue (33 %), and nausea (27 %). Although 3 patients developed a decrease in LVEF≥10 % and less than 50 % absolute value, none had clinical cardiac symptoms [25]. However, pertuzumab monotherapy after trastuzumab progression failed to show a benefit, with an ORR for pertuzumab monotherapy of 3.4 % and a CBR of 10.3 %. In this cohort, 17 patients with disease progression continued to receive pertuzumab with the addition of trastuzumab, and had an ORR of 17.6 % and a CBR of 41.2 % [26].

This led to the CLEOPATRA study [27••] in the first-line setting, comparing the combination of pertuzumab plus trastuzumab plus docetaxel with standard trastuzumab plus

docetaxel. The pertuzumab combination yielded a PFS of 18.5 months, compared with 12.4 months for trastuzumab plus docetaxel (HR 0.62, 95 % CI 0.51–0.75, $P<0.001$). Among the 288 patients previously exposed to trastuzumab as adjuvant or neoadjuvant treatment, PFS was 12.6 months in the control group compared with 21.6 months in the pertuzumab group (HR 0.6, 95 % CI 0.43–0.83). A significant survival benefit was seen for the pertuzumab group at a median follow-up of 30 months, with a median OS of 37.6 months for the placebo group; median OS had not been reached for the pertuzumab group [28•].

Serious AEs were reported in 115 (29 %) patients in the placebo group compared with 148 (36 %) patients in the pertuzumab group, with increased frequencies of diarrhea, rash, mucosal inflammation, pruritus, febrile neutropenia, and dry skin but no increase in left-ventricular systolic dysfunction. After discontinuation of docetaxel, diarrhea, rash, and pruritus remained higher in pertuzumab treated patients although no episodes of febrile neutropenia were reported in either arm [27••, 28•]. The CLEOPATRA trial has led to the approval of pertuzumab in the first-line setting. Many ongoing studies of pertuzumab in combination with other cytotoxics including vinorelbine show activity [29].

Trastuzumab Emtansine (T-DM1)

T-DM1 is an antibody-drug conjugate (ADC) composed of trastuzumab, a stable thioether linker, and the cytotoxic agent DM1. DM1 is a derivative of maytansine, a microtubule inhibitor that is 25- to 4000-fold more potent than current clinically used chemotherapy agents. After T-DM1 binds to HER2 via the trastuzumab component, the HER2/T-DM1 complex undergoes internalization followed by lysosomal degradation. This results in intracellular release of DM1, which binds to tubulin, preventing microtubule polymerization and suppressing microtubule dynamic instability, and induces apoptosis after G_2/M cell cycle arrest. Concomitantly, T-DM1 retains the mechanisms of action of trastuzumab, including the disruption of the HER3/PIK/AKT signaling pathway, prevention of shedding of the extracellular domain of HER2, and activation of antibody-dependent cellular cytotoxicity (ADCC) [30].

Analysis of the pharmacokinetics profile of T-DM1 have consistently demonstrated minimal systemic exposure to free DM1, limiting toxicity to the normal cells while delivering the cytotoxic agent to the tumor cells [30].

T-DM1 in Previously Trastuzumab Treated Patients

A phase I trial of T-DM1 demonstrated an astonishing clinical benefit rate of 73 % among heavily pretreated patients at the maximal tolerated dose of T-DM1, which is currently the approved prescribing dose. Phase II trials of TDM-1 monotherapy confirmed robust activity in previously treated patients with metastatic HER2 positive breast cancer, with response rates of 25.9 % to 34.5 % [31, 32, 33•].

The phase III trial EMILIA which randomized 991 patients demonstrated superiority of T-DM1 compared with lapatinib plus capecitabine in patients with HER2-positive advanced breast cancer previously treated with trastuzumab and a taxane. The ORR was 43.6 % vs 30.8 % ($P<0.001$), median PFS was 9.6 months vs 6.4 months (HR 0.65; 95 % CI 0.55–0.77; $P<0.001$), and median OS was 30.9 months vs 25.1 months (HR 0.68; 95 % CI, 0.55–0.85; $P<0.001$) for the T-DM1 and lapatinib plus capecitabine arms, respectively. The T-DM1 benefit was consistent across all groups of patients, including those that had progressed within 6 months of adjuvant or neoadjuvant trastuzumab-based therapy [34••].

T-DM1 has an excellent toxicity profile. Thrombocytopenia is the most common dose-limiting toxicity. Other common AEs include elevated serum aminotransferase levels, fatigue, anemia, and nausea [31, 32, 33•, 34••].

T-DM1 in the First-Line Setting

A randomized phase II trial compared the efficacy and safety of T-DM1 with trastuzumab plus docetaxel (HT) in 137 patients with HER2-positive advanced breast cancer in first-line treatment. After a median follow-up of 14 months, T-DM1 treatment provided a statistically significant 41 % reduction in the risk of disease progression, with a median PFS of 14.2 months compared with 9.2 months for the HT group (HR 0.59; 95 % CI 0.36–0.97). The ORR for T-DM1 was 64.2 % vs 58.0 % for HT, but this difference was not statistically significant nor was the preliminary OS analysis. Again, T-DM1 treatment demonstrated a favorable toxicity profile, with fewer grade≥3 AE (46.4 % vs 90.9 %) than HT [35].

A phase III study of T-DM1 in the first-line setting comparing T-DM1 vs T-DM1 plus pertuzumab vs trastuzumab plus a taxane, the MARIANNE trial, is currently ongoing and results are eagerly awaited [36, 37].

Bevacizumab

The vascular endothelial growth factor (VEGF) plays a key role in tumor angiogenesis and is found to be up-regulated in HER2 positive human breast cancer cells in vitro. Preclinical studies suggest that this may be partly responsible for the biological aggressive phenotype of HER2 positive human breast cancer [38]. Bevacizumab is a humanized monoclonal antibody that targets VEGF and has been evaluated in phase II trials in combination with trastuzumab plus chemotherapy in HER2 positive metastatic breast cancer, demonstrating efficacy and feasibility [39, 40].

A phase III study, the AVEREL trial, randomized 424 patients with HER2-positive locally recurrent or metastatic breast

cancer in first-line treatment to receive docetaxel plus trastuzumab with or without bevacizumab 15 mg/kg every 3 weeks. The bevacizumab combination did not significantly improve PFS outcomes as assessed by the investigators (13.7 months for the control group and 16.5 months for the bevacizumab group; HR 0.82; 95 % CI 0.65–1.02). ORR was 74 % and 70 % for the bevacizumab and control arms, respectively (*P* 0.3492). The addition of bevacizumab increased grade≥3 febrile neutropenia and hypertension rates [41•].

Newer Targeted Agents

Inhibitors of the PI3K–AKT–mTOR Pathway

Activation of the PI3K–AKT–mTOR pathway is strongly implicated in resistance to trastuzumab therapy in HER2 positive metastatic breast cancer. Mutational activation of PIK3CA and loss of the PTEN tumor suppressor are described mechanisms of resistance to trastuzumab [42]. Several inhibitors of the PI3K pathway are currently undergoing investigation for treatment of metastatic breast cancer, including the mTOR inhibitor everolimus, the selective PI3K, and mTOR inhibitor BEZ235 [43–46], a highly selective PI3K inhibitor BKM120 [47–49], and the AKT inhibitor MK-2206 [44, 50, 51].

Everolimus

Everolimus inhibits mTOR, a protein kinase central to pathways that regulate cell growth and proliferation. Phase I and II trials demonstrated good safety profile and antitumor activity for the combination of everolimus, weekly paclitaxel, and trastuzumab in HER2 positive metastatic breast cancer patients previously resistant to trastuzumab [52, 53]. These results suggest that everolimus could restore trastuzumab sensitivity and enhance efficacy of HER2-targeted therapy.

The phase III trial BOLERO-3 randomized patients with trastuzumab resistant locally advanced or metastatic HER2 positive breast cancer to receive trastuzumab plus vinorelbine plus everolimus or placebo. In an interim analysis after 415 events, the addition of everolimus increased the median PFS from 5.78 to 7.0 months (HR 0.78, 95 % CI 0.65–0.95, *P* 0.0067) [54•].

ORR and CBR were not significantly different, and OS data was not mature yet although there were fewer events in the everolimus arm (36.3 % vs 41.1 %). In a subgroups analysis, there was greater benefit seen for patients who had received prior neoadjuvant/adjuvant trastuzumab therapy in comparison to patients that had no received prior trastuzumab early treatment. Final trial results are expected for 2014 [54•].

Small Molecule Inhibitors

Neratinib

Neratinib (PB-272) is an oral, irreversible inhibitor of HER1, HER2, and HER4. A phase II trial showed efficacy of neratinib in patients with prior trastuzumab treatment (ORR 24 % and PFS 22.3 weeks) and without prior trastuzumab exposure (56 % and PFS 39.6 weeks). Diarrhea was the most common grade≥3 toxicity observed. No neratinib-related grade≥3 cardiotoxicity was reported [55]. A phase I/II study of neratinib plus weekly paclitaxel reported a response rate of 69 % in patients with prior taxane, trastuzumab, and lapatinib therapy [56]. Although further trials have been initiated [57–62], the future place of neratinib is not known.

Afatinib

Afatinib (BIBW2992) is also an oral, irreversible inhibitor of HER1, HER2, and HER4. A phase II study in patients with metastatic HER2-positive breast cancer post trastuzumab-therapy showed 4 responses among 35 assessable patients. The most common AE included diarrhea (90.2 %) and rash (65.9 %) [63]. LUX-Breast 1 was a phase III study of vinorelbine plus either afatinib or trastuzumab for HER2-positive metastatic breast cancer, which was discontinued early due to the unlikelihood of meeting its primary objective [64].

Heat-Shock Protein 90 (HSP90) Inhibitors

HSP90 is a molecular chaperone that plays an essential role in the maturation and stabilization of several oncogenic proteins, including HER2. HER2, and p95-HER2 interact with the HSP90 chaperone protein and are degraded in tumor cells exposed to HSP90 inhibitors in tissue culture and in vivo. HER2-amplified breast cancer cell lines and xenograft models exposed to HSP90 inhibitors demonstrate HER2 and p95-HER2 degradation, inhibition of PI3K signaling and significant growth inhibition [65].

Phase I and II trials combining the HSP90 inhibitor tanespimycin with trastuzumab showed clinical benefit in HER2 positive trastuzumab-refractory breast cancer patients, with an ORR of 22 %, CBR of 59 %, median PFS of 6 months, and median OS of 17 months. The most common AE were diarrhea, fatigue, nausea, and headache [66, 67]. A second-generation HSP90 inhibitor, alvespimycin, has also been evaluated [68, 69].

MM-111

MM-111 is a novel bispecific antibody fusion protein that specifically targets the HER2/HER3 heterodimer and inhibits

binding of HER3's ligand heregulin. Preclinical data demonstrates that MM-111 potentiates antitumor activity of trastuzumab. A phase I/II study is currently ongoing to evaluate the safety and tolerability of MM-111 in combination with trastuzumab [70–72].

Central Nervous System (CNS) Disease

CNS metastases are diagnosed in 30 %–50 % of HER2 positive breast cancers [73], frequently as the first site of disease relapse/progression [74, 75]. Although local therapies improve CNS disease control they are limited by number of lesions, resecability, radiation dose, patient's performance status, and long-term side effects, such as dementia [76–78, 79•].

The ability of trastuzumab to cross the blood–brain barrier (BBB) is limited [80]. As a small-molecule TKI, lapatinib is theoretically able to penetrate the BBB and access CNS metastases [79•]. In an exploratory analysis of a phase III trial comparing lapatinib plus capecitabine to capecitabine alone in second-line treatment, the combination with lapatinib demonstrated a decreased risk of CNS relapse of 2 % compared with 6 % [81]. This same combination had an objective CNS response rate of 65.9 % in a small single-arm, phase II study, of 45 patients with previously untreated HER2 positive breast cancer CNS metastases [82].

The CEREBEL study aimed to evaluate the prophylactic impact on CNS metastases incidence of treatment with lapatinib plus capecitabine (LC) in comparison with trastuzumab plus capecitabine (TC) in HER2 positive metastatic breast cancer patients. At a pre-specified interim analysis with 475 patients, median PFS was 6.6 and 8.0 months in LC and TC arms (HR 1.3; 95 % CI: 1.0, 1.7), and median OS was 22.4 and 27.3 months (HR 1.58, 95 % CI 1.07–2.32), respectively. Based on these results, study termination was recommended [83].

In a subsequent subgroup analysis, trastuzumab naïve patients had a superior benefit from the TC treatment, with a median PFS of 10.9, compared with 6.3 months for the LC arm (HR 1.7, 95 % CI 1.15–2.5). In patients previously treated with trastuzumab, there was no significant difference, with a median PFS of 6.6 vs 6.1 for LC and TC arms, and median OS of 22.7 vs 27.3 months, respectively. The study was inconclusive for the incidence of CNS metastases as site of first relapse, its primary end-point, with a very low rate of events in both arms (3 % for LC and 5 % for TC) [83]. With the current data, there is little evidence that lapatinib has significant activity against CNS metastases. Therefore, there is a need for robust systemic therapies capable of preventing or treating CNS metastases.

Treatment Algorithms

The treatment algorithms for HER2 positive advanced breast cancer are constantly evolving and may reflect the availability of agents in specific jurisdictions.

Trastuzumab-Naïve Patients and Patients who Relapse After 12 Months of Adjuvant Trastuzumab-Based Treatment

First Line Therapy

The trials of first-line therapy published to date have not shown a clear difference in response in patients previously treated with adjuvant trastuzumab and those who are trastuzumab naïve. This may reflect inadequate numbers of patients, inclusion criteria for patients over a year from adjuvant treatment, or the lack of true biological difference.

First-line treatment choice for metastatic HER2 positive breast cancer patients is the combination of pertuzumab plus trastuzumab plus docetaxel, based on the CLEOPATRA trial [27••, 28•].

If pertuzumab is not an available treatment option, the treatment choice should include trastuzumab plus chemotherapy, based on initial trastuzumab trials [8, 21•, 84, 85].

Results from the ongoing MARIANNE study may show a role for T-DM1 in the first-line setting [36, 37].

Second Line Therapy and after

In the second-line, the choice of therapy will depend on prior exposure to anti-HER2 agents as well as the duration and quality of response. Currently, based on the results of the EMILIA trial [34••], T-DM1 is considered the standard second-line treatment option. If T-DM1 is not an available choice, lapatinib is the recommended to be the standard treatment in combination with capecitabine or trastuzumab [16, 17•, 19•, 20•]. In the third line setting outside a clinical trial, lapatinib may be a third line option as there has been efficacy shown, in particular in combination with trastuzumab. There is no phase III data on the efficacy of agents after first-line treatment with pertuzumab/trastuzumab/docetaxel, although prior trials of trastuzumab beyond progression and dual anti-HER2 therapy suggest that continued anti-HER2 therapy is optimal.

Patients who Progress During Adjuvant Trastuzumab or Within the First Year After Adjuvant Trastuzumab-Based Treatment

This group of patients has not been adequately studied and therefore adequate data is not available. These patients should be considered for experimental therapies.

Treatment of CNS Disease

Without Progressive Systemic Disease

Local treatment strategies to CNS metastases remain the standard therapy [76–78, 79•].

If there is progressive CNS disease after prior local therapy, further local treatments or systemic therapy can be considered, although CNS penetration remains an issue.

With Progressive Systemic Disease

For patients who have concurrent progressive CNS and non-CNS disease, local CNS therapy should be started and systemic therapy should be initiated or current therapy changed. The choice of systemic therapy should follow the previously described guidelines for first, second and third line discussed above, as there is no strong clinical benefit for specific therapies [83].

Conclusions

Although major progress has been achieved in the management of HER2 positive metastatic breast cancer in the past decade, not all patients attain clinical benefit from the current available treatment options. We need to further dissect the HER2 positive subtype to further understand how to optimally treat these patients.

In a continuous effort to overcome a sobering statement by Slamon in 2001 [8], "Although objective responses to some chemotherapy regimens are common, few patients with metastatic disease are cured, and treatments frequently cause substantial adverse effects," research is currently being propelled towards the finding of the ultimate anti-HER2 positive breast cancer agent: an agent with maximum spectrum of action against all HER2 positive breast tumors, everlasting response, minimal toxicity, and capable of crossing the blood–brain barrier. Finally, economic realities limit access to effective antiHER2 therapies globally.

Compliance with Ethics Guidelines

Conflict of Interest Rachel Jorge Dino Cossetti declares that she has no conflict of interest. Karen A. Gelmon has served on advisory boards for Roche, GlaxoSmithKline, Pfizer, AstraZeneca, and Amgen.

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.

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