Chapter 5

HER2-positive metastatic breast cancer: second-line treatment

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Introduction

The human epidermal growth factor receptor 2 (HER2) is a transmembrane tyrosine kinase that is overexpressed in approximately 20% of invasive breast cancers, primarily due to gene amplification [1]. Over the last 15 years, several HER2-targeted therapies have been developed and have significantly improved the outcome of patients with metastatic breast cancer (MBC).

Trastuzumab was the first HER2-targeted agent to be approved by the United States Food and Drug Administration (FDA) for the treatment of both early stage and metastatic HER2-overexpressing breast cancer [2,3]. Since the approval of trastuzumab, the field has continued to develop rapidly. Lapatinib, an orally bioavailable small molecule dual HER2- and epidermal growth factor receptor (EGFR) HER1-specific tyrosine kinase inhibitor, received FDA approval in 2007 (in combination with capecitabine) for the treatment of patients with advanced or metastatic HER2-positive breast cancer who had received prior therapy with an anthracycline, a taxane, and trastuzumab, and (in combination with letrozole) for the treatment of postmenopausal patients with metastatic hormone receptor-positive, HER2-positive breast cancer for whom hormonal therapy is indicated [4]. More recently, pertuzumab, a recombinant humanized monoclonal antibody that inhibits the ligand-dependent dimerization of HER2, demonstrated an overall survival (OS) benefit when administered in combination with trastuzumab and docetaxel; it was approved in 2012 in the first-line setting for patients who have not received prior chemotherapy or anti-HER2 therapy

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[5,6]. Finally, trastuzumab emtansine (T-DM1) demonstrated an OS benefit when compared with capecitabine + lapatinib in patients who had previously been treated with trastuzumab and a taxane, and was approved in 2013 [7,8].

These recent advances have not only enabled a better treatment for patients with HER2-positive breast cancer, but have also generated additional questions regarding the order, timing, and effective use of HER2-directed therapies. In this chapter, we will discuss the current clinical data on second-line HER2-targeted agents.

Inhibiting HER2 therapeutically

HER2-amplification in breast cancer is an excellent example of the oncogene addiction hypothesis, which argues that some cancers are driven by a single oncogene that harbors an activating mutation or is overexpressed through gene amplification as a consequence of this single 'gene driver.'

Trastuzumab emtansine

The hypothesis that a HER2 antibody-cytotoxic drug conjugate would deliver the cytotoxic agent directly to the tumor cells, thereby reducing the side effects on normal cells while preserving the anti-HER2 activity of the antibody, has been confirmed. T-DM1 is an antibody drug conjugate (ADC) that incorporates the HER2-targeting antitumor properties of trastuzumab with the cytotoxic activity of the microtubule-inhibitory agent DM1 (derivative of maytansine) [8].

The challenges posed by the development of ADCs are formidable. Over the past 30 years, many cell surface proteins that have selective aberrant expression on malignant cells or are aberrantly highly expressed on the surface of malignant cells have been identified. As a result of such improvement, gemtuzumab ozogamicin was granted accelerated US FDA approval for the treatment of acute myelogenous leukemia in 2000, becoming the first commercially available ADC. However, in 2010, it was withdrawn from the market because it failed to meet its prospective efficacy target. Brentuximab ventodin reached FDA approval in 2011 for the treatment of refractory Hodgkin's lymphoma and, currently, more than 40 ADCs are in clinical trials.

The use of ADCs – cytotoxic drugs connected by chemical linkers to monoclonal antibodies specific for tumor-associated antigens – offers the potential

for the targeted delivery of potent cytotoxic drugs to cancer cells [9–11]. The development of an effective ADC includes three major challenges [12]:

- the identification of a target uniquely expressed in the cancer cells;
- a cytotoxic agent that is potent at low concentration; and
- a linker that can deliver a cytotoxic agent to the cancer cell without releasing the drug into the systemic circulation.

Antibody-drug conjugate: trastuzumab

Clinical trials have demonstrated significant improvement in disease-free survival and OS in patients with HER2-positive early breast cancer [13,14]. Similarly, in the pivotal trastuzumab trial in the first-line metastatic setting, trastuzumab + chemotherapy improved median OS compared with chemotherapy alone (25.1 vs 20.3 months; P=0.046) [5,15]. Importantly, 72% of patients randomized to receive chemotherapy alone subsequently received trastuzumab. This crossover is likely to underestimate the survival benefit associated with the addition of trastuzumab to chemotherapy in this patient population.

The mechanism by which trastuzumab exerts its actions is not fully understood. However, several mechanisms have been proposed, including inhibition of phosphoinositide-3-kinase (PI3K)/AKT and mitogen-activated protein kinase (MAPK) signaling transduction pathways [16,17]; prevention of HER2 ectodomain cleavage [18]; inhibition of angiogenesis [19]; antibody-dependent cell-mediated cytotoxicity [20,21]; and induction of apoptosis [22].

Cytotoxic drug: derivative of maytansine

Several standard chemotherapy agents that have been conjugated to monoclonal antibodies and these ADCs were found to be effective in the preclinical setting [23–25]. However, they were inefficient in the clinical setting because of their inability to achieve therapeutic levels of the cytotoxic agent within the tumor cells [26]. Maytansinoids, which are derivatives of the cytotoxic, antimitotic drug maytansine, are a class of agents that disrupt microtubule function. Maytansine and its congeners have been isolated from mosses, higher plants, and *Actinosynnema pretiosum*, an actinomycete [27]. Many of these compounds are antitumor agents of great potency and bind directly to microtubules to inhibit polymerization in a way similar to that seen with vinca alkaloids. During the 1970s, multiple Phase I and II studies investigated the efficacy of maytansine

in breast cancer. However, the non-selective toxicity prevented further clinical development and, ultimately, the compound was abandoned because it exhibited a poor therapeutic window [28–30].

However, improving the therapeutic index of maytansine through conjugation to monoclonal antibodies that mediate its targeted delivery to cancer cells was considered a promising approach. Efforts to link maytansine covalently to monoclonal antibodies led to the development of DM1, which has an in vitro cytotoxicity 3–10 times greater than maytansine and 10–200 times greater than taxanes or vinca alkaloids [31–33].

Stable linker: MCC

The linker which bridges a toxin and an antibody needs to be able to maintain molecular stability while in circulation but must also be amenable to cleavage while inside cancer cells [30]. Common linkers used in ADCs for cancer therapy include protease cleavable linkers, acid-labile hydrazones, and disulfides, which facilitate the release of the cytotoxic agent in a pH-dependent manner or by disulfide reduction [31,34]. The thioether (MCC) linker protein, to fit both requirements mentioned above, was thus selected as the conjugate linking trastuzumab to DM1 to create trastuzumab-MCC-DM1 (T-DM1), or trastuzumab emtansine (Figure 5.1) [35,36].

T-DM1 allows intracellular delivery of DM1 specifically to HER2-overexpressing cells, thereby improving the therapeutic index and minimizing exposure of normal tissue to this agent. T-DM1 is internalized upon binding to HER2-positive tumor cells and is thought to go through intracellular proteolytic degradation, in turn releasing the active maytansinoid metabolite (lysine-N-MCC-DM1) [36].

Trastuzumab emtansine clinical trials

After impressive preclinical results, a Phase I study conducted in 24 patients with advanced, heavily pretreated HER2-positive breast cancer (median of four prior chemotherapeutic agents for metastatic disease) assessed the safety and tolerability of ascending doses administered every 3 weeks [37]. The maximum tolerated dose (MTD) of T-DM1 was 3.6 mg/kg, with transient grade 4 thrombocytopenia observed as a dose-limiting toxicity. The toxicity profile was favorable, with common drug-related adverse events (AEs) being

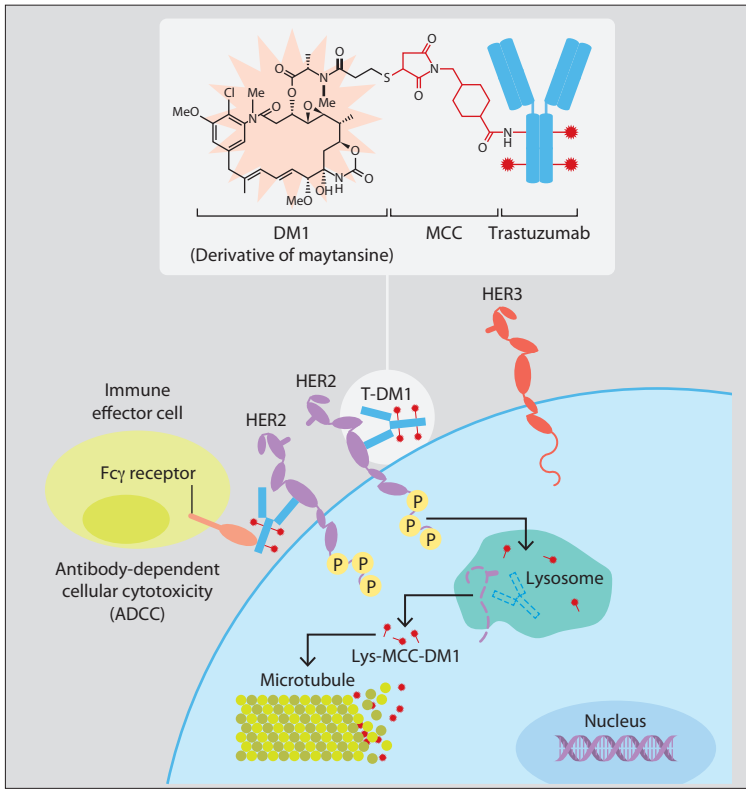


Figure 5.1 Structure and mechanism of action of trastuzumab emtansine. HER2, human epidermal growth factor receptor 2; T-DM1, trastuzumab emtansine.

thrombocytopenia, elevated transaminases, fatigue, nausea, and anemia [37]. Nearly all patients who received T-DM1 at doses >1.2 mg/kg experienced declines in platelet levels with nadirs observed at around Day 8; recovery was generally rapid (by approximately Day 15). Preliminary signs of antitumor activity were observed, with a clinical benefit result (CBR), defined as the objective response plus stable disease at 6 months, of 73% in the 15 patients treated at the MTD. Six patients had an objective partial response, five of which were later confirmed.

Based on these results, two Phase II studies of T-DM1 were conducted in heavily pretreated patients with HER2-positive MBC. The first trial was a single-arm study of 112 patients who had progressed on prior trastuzumab and chemotherapy [38]. T-DM1 was associated with an overall response rate (ORR) of 25.9% (95% CI, 18.4–34.4%). The median duration of response was

9.4 months by investigator assessment and had not yet been reached according to the independent review. The median progression free survival (PFS) was 4.6 months [38]. T-DM1 was well tolerated; most AEs were grade 1 or 2, and the most common grade ≥3 AEs were hypokalemia (8.9%), thrombocytopenia (8.0%), and fatigue (4.5%). Thrombocytopenia was not associated with serious hemorrhage, and there was no dose-limiting cardiotoxicity [38].

In the second Phase II study, T-DM1 was administered at doses of 3.6 mg/kg intravenously every 3 weeks to 110 patients with HER2-positive MBC who had previously been treated with anthracycline, trastuzumab, taxane, capecitabine, and lapatinib therapy [39]. An ORR of 34.5% (95% CI, 26.1–43.9%; all partial responses), a median duration of response of 7.2 months (95% CI, 4.6 months to not estimable), and a median PFS of 6.9 months (95% CI, 4.2–8.4 months) were seen with T-DM1 monotherapy. In patients with confirmed HER2-positive tumors (n=80), the ORR was 41.3% (95% CI, 30.4–52.8%), and the median PFS was 7.3 months (95% CI, 4.6–12.3 months). The most frequent grade ≥3 AEs were thrombocytopenia (9.1%), fatigue (4.5%), and cellulitis (3.6%) [39].

Following the successful results of the Phase II studies, EMILIA, a randomized, Phase III clinical trial, was developed to assess the efficacy and safety of TDM-1 versus capecitabine + lapatinib in nearly 991 patients with advanced HER2-positive breast cancer who had previously been treated with trastuzumab and a taxane [7]. The study had a median follow-up of approximately 13 months (19 months for OS) and showed a significantly longer median PFS in patients receiving T-DM1 compared with those receiving capecitabine + lapatinib (9.4 months vs 6.4 months; hazard ratio [HR] 0.65; 95% CI, 0.55–0.77; $P<0.001$. Median OS at the second interim analysis crossed the stopping boundary for efficacy (30.9 months vs 25.1 months; HR 0.68; 95% CI, 0.55–0.85; $P<0.001$) (Figures 5.2 and 5.3) [7]. The ORR was higher with T-DM1 (43.6% vs 30.8% with capecitabine + lapatinib; $P<0.001$). In terms of toxicity, rates of grade 3 or 4 AEs were lower for T-DM1 overall (41% vs 57%). T-DM1 was associated with higher incidences of thrombocytopenia and increased liver enzyme levels and lower incidences of diarrhea, nausea, vomiting, and palmar-plantar erythrodysthesia than capecitabine + lapatinib [7].

A recent publication of an analysis of patient-reported outcomes from EMILIA demonstrated that T-DM1 treatment resulted in a statistically significant delay in clinically meaningful symptom worsening when compared with capecitabine + lapatinib (7.1 months vs 4.6 months; HR =0.796; $P=0.012$) [40].

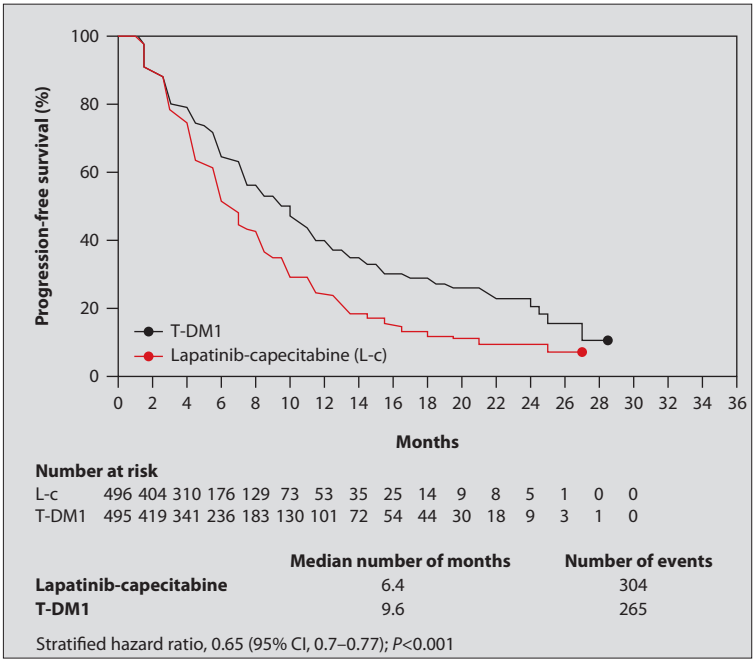
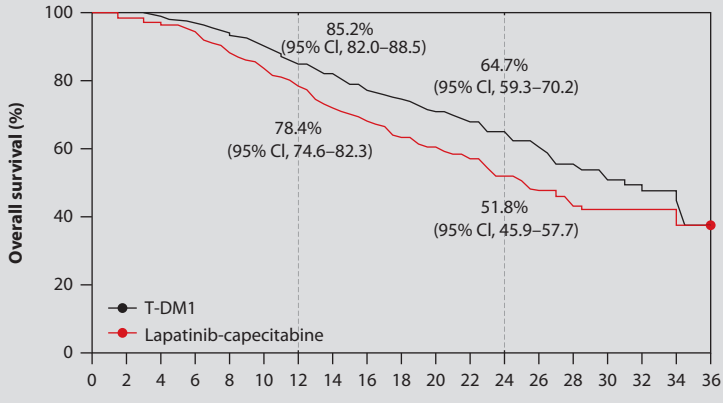


Figure 5.2 EMILIA study: progression-free survival. CI, confidence interval.; T-DM1, trastuzumab emtansine. Reproduced with permission from Verma et al [7] ©NEJM.

Brain metastasis are common in patients with HER2-positive MBC, with up to half of patients experiencing central nervous system (CNS) metastases. Guidelines for the management of CNS metastases in patients with HER2-positive breast cancer was published by ASCO [41]. In a retrospective, exploratory analysis from the EMILIA study, patients with CNS metastasis demonstrated that the rate of CNS progression in patients with HER2-positive MBC was similar for T-DM1 and for capecitabine + lapatinib, and higher overall in patients with CNS metastases at baseline compared with those without CNS metastases at baseline [42]. In patients with treated symptomatic CNS metastases at baseline, T-DM1 was associated with a significantly improved OS compared with capecitabine + lapatinib [42]. The results of EMILIA study provide solid evidence for T-DM1 as the treatment of choice in the second-line setting for HER2-positive MBC and were used as the basis for T-DM1 approval [7].

MARIANNE (NCT01120184) is a Phase III clinical trial that recruited more than 1,000 patients with HER2-positive MBC who had not received any



Number at risk

L-c	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
T-DM1	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5

	Median number of months	Number of events
Lapatinib-capecitabine	25.1	182
T-DM1	30.9	149

Stratified hazard ratio, 0.68 (95% CI, 0.55–0.85); $P<0.001$
Efficacy stopping boundary $P=0.0037$ or hazard ratio 0.73

Figure 5.3 EMILIA study. Overall survival results for lapatinib + capecitabine versus T-DM1. CI, confidence interval; T-DM1, trastuzumab emtansine. Reproduced with permission from Verma et al [7] ©NEJM.

chemotherapy in the metastatic setting. In this study, patients were randomly assigned to receive taxanes/trastuzumab, T-DM1, or T-DM1 + pertuzumab. However, this study did not include a comparator arm with taxanes, trastuzumab, and pertuzumab, which is the current standard first-line therapy for HER2-positive MBC. Approximately 37% of patients had de novo metastatic disease. As reported during the 2015 ASCO presentation, the study met the PFS noninferiority endpoint, but not the superiority endpoint [43]. OS was similar across treatment arms. The detailed data have not yet been published and the trial sponsor recently announced that the MARIANNE trial did not reach its primary endpoint [43].

The TH3RESA (NCT01419197) global trial was launched to determine the effectiveness of T-DM1 in heavily pretreated patients (beyond second-line) who had HER2-positive MBC. In this study, 606 patients with HER2-positive MBC

who previously received trastuzumab, lapatinib, and a taxane, were randomly selected to receive either T-DM1 or physician's choice of therapy [45]. The final results showed a 3-month improvement in the median PFS in the T-DM1 group. Response rates were improved in the T-DM1 group (31% in T-DM1 vs 9% in the control group). T-DM1 resulted in significant prolongation of PFS compared to treatment with physician's choice (median 6.2 months vs 3.3 months) and reduced the risk of disease progression or death by 47% (HR=0.528; $P<0.0001$). There was a suggestion of an improved overall survival rate for patients treated with T-DM1, although the data are not mature. Importantly, T-DM1 was better tolerated than other standard chemotherapies. On the basis of these results, T-DM1 is now considered a new standard treatment after multiple lines of therapy for patients who have HER2-positive MBC (Table 5.1).

There is a great interest in testing the efficacy of T-DM1 for early-stage breast cancer. An ongoing single-arm Phase II trial (NCT01196052) is evaluating the efficacy of T-DM1 in the adjuvant or neoadjuvant setting [46]. After completion of an anthracycline-based adjuvant/neoadjuvant chemotherapy regimen

Study	Patient population and sample size	Study phase	Treatment arms	Results
EMILIA [7]	Pretreated HER2$^+$ + MBC (n=991)	III	T-DM1 vs capecitabine + lapatinib	PFS: 9.6 vs 6.4 months OS: 30.9 vs 25.1 months OS: 44% vs 31%
TH3RESA [45]	Pretreated HER2$^+$ + MBC (n=602)	III	T-DM1 vs physician choice	PFS: 6.2 vs 3.3 months OS: No reached vs 14.9 months
MARIANNE [43]	First-line HER2 + MBC (n=1,092)	III	T-DM1 + placebo vs T-DM1 + pertuzumab vs trastuzumab + taxane	PFS: 14.1 vs 15.2 vs 13.7months ORR: 59.7% vs. 64.2% vs 67.9%

Table 5.1 Major completed trials of trastuzumab emtansine (T-DM1). MBC, metastatic breast cancer; PFS, progression-free survival; ORR, overall response rate; OS, overall survival.

(doxorubicin + cyclophosphamide [AC] or 5-fluorouracil + epirubicin + cyclophosphamide [FEC]), 153 patients will be treated with T-DM1 instead of the conventional taxanes/trastuzumab combination for 17 cycles.

In the ATEMPT trial (NCT01853748), 500 patients with resected stage I breast cancer will be randomly assigned to T-DM1 versus 12-week paclitaxel + trastuzumab, followed by trastuzumab regimen [47]. In the KAITLIN trial (NCT01966471), 2,500 patients will be randomly assigned after adjuvant AC/FEC to either a taxane, trastuzumab + pertuzumab, or T-DM1 + pertuzumab.

A randomized Phase III study (KATHERINE; NCT01772472) will evaluate the efficacy of T-DM1 in patients who have residual disease after neoadjuvant trastuzumab-containing regimens [48]. In this study, patients are randomly assigned to continuation of trastuzumab (standard treatment) or T-DM1. This study has a planned enrollment of more than 1,400 patients.

Finally, the KRISTINE trial (NCT02131064) will examine the combination of docetaxel, carboplatin, trastuzumab, and pertuzumab (one of the FDA-approved neoadjuvant pertuzumab-containing regimens) versus T-DM1 + pertuzumab [49]. All of these trials will provide important information relating to the integration of T-DM1 in the treatment of HER2-positive early-stage breast cancer.

Lapatinib in the metastatic setting

Lapatinib is an oral, selective, reversible small-molecule dual tyrosine kinase inhibitor of both the HER1- (ErbB1) and HER2- (ErbB2) signaling pathways. In vitro studies have confirmed that lapatinib treatment inhibits growth [50,51] and can lead to apoptosis [37] in human tumor cells overexpressing HER2 [52].

ErbB receptors form hetero- or homodimers after ligand binding, causing autophosphorylation of specific tyrosine residues within the conserved catalytic kinase domains of these receptors [53,54]. These phosphorylated tyrosine residues are docking sites for phosphotyrosine-binding domain- and Src-homology 2-containing proteins, which link activated ErbB receptors to MAPK and PI3K pathways [55]. Lapatinib treatment has been shown to inhibit the growth of HER2-overexpressing human breast cancer cells that do not respond to trastuzumab after long-term conditioning [37]. These studies also demonstrated the reduction of the volume of HER2-overexpressing human breast cancer xenografts in vivo [44].

Promising evidence of clinical activity was demonstrated in a Phase I study of lapatinib in advanced refractory solid tumors that over expressed HER1 and/or HER2 (n=67) [56]. The most common drug-related AEs were diarrhea (42%) and rash (31%). No grade 4 toxicities were reported. Four patients with trastuzumab-resistant MBC had partial responses and 24 patients experienced stable disease [56].

The activity of lapatinib monotherapy in patients with advanced HER2-positive or MBC that progressed on a first- or second-line trastuzumab-containing regimen was evaluated in a multicenter Phase II study (n=78) [57]. Lapatinib was well tolerated at either 1250 mg or 1500 mg, the median daily dose was 1467 mg (range 940–1500 mg) and the median duration of exposure was 8.4 weeks (range 1–70 weeks). The investigator-assessed ORR and CBR were 7.7% and 14.1%, respectively. In addition, five patients (6%) had stable disease for ≥24 weeks [57]. Responding patients were mostly estrogen receptor (ER)-negative/ progesterone receptor (PR)-negative. However, because the number of responders was limited, the relationship between the ER/PR relationship and response to lapatinib therapy is unclear [57].

Lapatinib was approved primarily based on results from a Phase III, randomized, open-label study comparing lapatinib + capecitabine with capecitabine alone in patients with advanced HER2-positive or MBC that had progressed after prior treatment with anthracyclines, taxanes, and trastuzumab [58]. Patients received lapatinib at 1250 mg/day continuously plus capecitabine 2000 mg/m^2 per day on Days 1–14 of a 21-day cycle or capecitabine 2500 mg/m^2 per day on Days 1–14 of a 21-day cycle. The primary endpoint was the time to tumor progression (TTP) [58]. At an interim analysis, the median TTP of the combination therapy was 8.4 months, compared with 4.4 months with capecitabine alone, a difference of 4.0 months (HR 0.49; 95% CI, 0.34–0.71; P<0.001). However, there was no significant difference in the median OS times between the two groups [58]. At the time of closure of accrual, the difference in the TTP between groups was over 50% lower, at 1.9 months (6.2 months vs 4.3 months; HR 0.57; 95% CI, 0.43–0.77; P<0.001) [59]. The OS duration also did not differ significantly between groups at this time point (15.6 months vs 15.3 months) or in the final analysis of mature survival data (75.0 vs 64.7 weeks) HR 0.87;

95% CI, 0.71–1.08; *P*=0.210) [60]. However, the study design did not allow for sufficient power to detect a survival benefit [60].

Trastuzumab-lapatinib combination therapy

Trastuzumab and lapatinib have complementary mechanism of HER2 blockade, and preclinical studies have found both increased antibody-dependent cellular cytotoxicity and enhanced induction of apoptosis in these agents [61–63]. In the metastatic setting, the combination of trastuzumab + lapatinib was assessed in the Phase III EGF104900 study: 296 patients who were pretreated with trastuzumab to receive lapatinib + trastuzumab or lapatinib alone [64]. A significant prolongation of median PFS (11.1 vs 8.1 weeks; HR 0.74; 95% CI, 0.58-0.94; *P*=0.011) and OS (14 vs 9.5 months; HR: 0.74; 95% CI, 0.57–0.7; *P*=0.026) were seen with the combination therapy versus lapatinib alone, despite significant crossover. There was a 10% improvement in the absolute OS rate at 6 months and a 15% improvement at 12 months in the lapatinib + trastuzumab arm compared with the lapatinib arm. The combination regime was well tolerated, with the most common AEs being diarrhea, nausea, fatigue, rash, and vomiting. Eleven patients given lapatinib + trastuzumab and three patients given lapatinib monotherapy experienced cardiac events [57]. This combination recently received European Medicines Agency (EMA) approval in 2013.

Conclusions

The identification and effective targeting of HER2 has redefined our approach to treating breast cancer and has raised hope that targeted therapies can effectively treat this tumor subtype with less (or even no) chemotherapy. Trastuzumab has significantly improved the prognosis for patients with HER2-positive breast cancer in the early stage as well as in the metastatic setting. However, not all patients will respond to trastuzumab and those who do not will almost inevitably experience tumor progression. The development of anti-HER2 ADCs provides further treatment options for these patients, achieving the selected delivery of potent chemotherapy coupled with HER2 inhibition. In addition, dual HER2 blockade has resulted in clinical success in both the neoadjuvant and metastatic settings. Nevertheless, many questions need to be answered:

- How can we better select the optimal HER2-blockade strategy for the individual patient? (To answer this question, we need a strong predictive biomarker, which is not available at present)
- How we can identify those patients who can be effectively treated with anti-HER2 therapy without chemotherapy?
- What is the optimal sequence of chemotherapy + anti-HER2 treatment in our current therapeutic armamentarium?
- In a financially constrained environment, how will new anti-HER2 treatments impact the cost of health care?

The future is promising, with more effective treatments in development for patients with HER2-positive breast cancer (see Chapter 6).

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