The Oncologist®

Breast Cancer

Advances in First-Line Treatment for Patients with HER-2$^+$ Metastatic Breast Cancer

LETICIA DE MATTOS-ARRUDA, JAVIER CORTES

Medical Oncology Department, Vall D′Hebron University Hospital, Barcelona, Spain

Key Words. Metastatic breast cancer • HER-2$^+$ • Trastuzumab • First-line treatment

Disclosures: Javier Cortes: Roche, Eisai, Celgene, Novartis (C/A); Roche, Eisai, Celgene, Cephalon (H). The other author indicated no financial relationships.

Section Editors: **Gabriel Hortobágyi**: Allergan, Genentech, Sanofi, Novartis (C/A); Novartis (RF); **Kathleen Pritchard:** Novartis, Roche, AstraZeneca, Pfizer, Abraxis, Boehringer-Ingelheim (C/A), (RF).

Reviewer "A": Roche, Novartis, AstraZeneca (C/A); Roche, GlaxoSmithKline (RF).

Reviewer "B": Ziopharm, MabVax, Johnson & Johnson, Novartis, AB Sciences, Eisai, Infinity, Imclone, Genentech, Roche, Geron, Abbott, Medivation, Astellas, and Exelexis (RF).

Reviewer "C": Roche (C/A); Roche, GlaxoSmithKline (H).

Reviewer "D": GlaxoSmithKline (RF).

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the optimal strategies to treat HER-2$^+$ metastatic breast cancer patients in the first-line setting and after recurrence with adjuvant trastuzumab.
2. Identify the current first-line therapeutic options for HER-2$^+$ metastatic breast cancer, including HER-2/hormone receptor copositive tumors.
3. Discuss the most important advances for HER-2$^+$ metastatic breast cancer and the potential of novel anti-HER-2 therapies.

CME This article is available for continuing medical education credit at CME.TheOncologist.com.

ABSTRACT

Background. **The prognosis for breast cancer patients overexpressing human epidermal growth factor receptor (HER)-2 has changed with anti–HER-2–targeted therapy. Although anti–HER-2 therapy with trastuzumab and chemotherapy is the standard first-line treatment, the best therapeutic regimen has yet to be defined, and new strategies are evolving.**

Methods. **A literature review of well-established and recently published trials, reviews, and ongoing clinical trials addressing first-line treatment for HER-2$^+$ metastatic breast cancer patients was performed.**

Results. **Taxanes are the agents most commonly used in combination with trastuzumab, but other chemotherapy drugs, such as anthracyclines, vinorelbine, and gemcitabine and triple-combination therapies including platinum compounds, capecitabine, and taxanes have been studied. The combination of aromatase inhibitors with anti–HER-2 therapies is a new therapeutic option for some patients who coex-**

Correspondence: Javier Cortes, M.D., Ph.D., Medical Oncology Department, Vall d'Hebron University Hospital, Paseo Vall d'Hebrón 119–129, 08035 Barcelona, Spain. Telephone: 34-93-274-6085; Fax: 34-93-274-6059; e-mail: jacortes@vhio.net Received September 11, 2011; accepted for publication March 8, 2012; first published online in ***The Oncologist*** *Express* on April 20, 2012.
1083-7159/2012/$20.00/0 http://dx.doi.org/10.1634/theoncologist.2011-0187

press HER-2 and hormone receptors, although its activity observed in randomized clinical trials seems to be inferior to that of chemotherapy plus anti–HER-2 therapies. In addition, new anti–HER-2 therapies have shown activity in HER-2$^+$ tumors, both alone and in combination with trastuzumab.

Conclusions. **Trastuzumab plus chemotherapy is the current standard of care for the upfront treatment of HER-2$^+$ breast cancer patients, though other anti–HER-2–targeting agents may appear as new standards in the upcoming years.** ***The Oncologist*** 2012;17:631–644

Introduction

Breast cancer is the most common tumor type in women [1]. Metastatic breast cancer (MBC) is an incurable disease, and systemic treatment aims to prolong survival, control disease progression, alleviate symptoms, and enhance patient quality of life. Although early detection and improvements in therapy have augmented survival rates by ~1% per annum in recent years, the 5-year survival rates for stage IV cancer remain <25% [2].

The human epidermal growth factor receptor (HER) family of receptors has been proposed as a target in cancer therapy. This family comprises four receptors, HER-1 to HER-4. The receptors are inactive as monomers, but binding of a ligand to the extracellular domain induces the formation of receptor homodimers and heterodimers. This results in phosphorylation of the tyrosine kinase, which consequently triggers a complex and multilayered network of inter-related signaling pathways that are involved in the control of several cellular processes such as apoptosis, migration, growth, adhesion, and differentiation (Fig. 1) [3–5].

The overexpression or HER-2 or amplification of *HER-2*, which occurs in 15%–20% of invasive breast cancers, is of clinical importance. Of note, HER-2 has been validated as a prognostic factor and also as a predictive biomarker for HER-2–targeting therapy [6, 7]. MBC patients with HER-2$^+$ tumors are known to have aggressive disease and a poor prognosis, with shorter overall survival (OS) and disease-free survival times [6]. Trastuzumab (Herceptin®; Genentech, Inc., South San Francisco, CA), a recombinant humanized anti–HER-2 monoclonal antibody that targets the extracellular domain of HER-2 with high affinity, was developed in the early 1990s and was the first clinically available HER-targeting treatment. Trastuzumab, when combined with chemotherapy, produces not only a higher overall response rate (ORR) and longer time to disease progression (TTP) but also a longer OS time [8, 9], and it has become the standard treatment for patients with HER-2$^+$ MBC [10]. In fact, the natural history of HER$^+$ breast tumors has been dramatically modified by trastuzumab. Dawood and colleagues retrospectively compared the prognoses of patients with HER-2$^-$ MBC and HER-2$^+$ MBC, with and without the addition of first-line trastuzumab treatment [11]. Patients with HER-2$^+$ disease who received trastuzumab had better outcomes than those with HER-2$^-$ disease (44% lower risk for death). However, other anti–HER-2 drugs and new strategies have recently been shown to be active, even in patients who have received trastuzumab-based therapies, and some of these therapies are being studied as first-line treatments.

Methods

A literature review using MEDLINE and PubMed was performed to search for first-line treatment strategies in the HER-2$^+$ MBC setting. The search strategy was restricted to English-language articles of clinical trials as well as reviews highlighting first-line HER-2$^+$ MBC management (using key words such as "metastatic breast cancer," "first-line treatment," "HER2-positive," "trastuzumab," "target therapy"). Included publication years were 1987 to the present. The evaluated MBC treatments were chemotherapy, endocrine therapy, and targeted treatments alone and in combination. The main articles on trastuzumab cardiotoxicity and mechanisms of trastuzumab resistance were also included. When no specific publications highlighting first-line treatment in HER-2$^+$ patients were found, the strategy was broadened to include, using the manual search engine, annual conference presentations (i.e., the American Society of Clinical Oncology annual meetings and annual San Antonio Breast Cancer Symposium). When redundant publications were found, the most recent ones were used. In order to address some important advances in HER-2$^+$ MBC therapeutics, the U.S. National Institutes of Health database of ongoing clinical trials (http://www.ClinicalTrials.gov) was searched.

Results

Trastuzumab as First-Line Therapy

Trastuzumab was shown to be active in patients with HER-2$^+$ MBC in the first-line setting as a single agent [12, 13] and in combination with cytotoxic therapy [8, 9].

Trastuzumab and Taxane-Based Therapy

In the pivotal H0648g trial, patients were randomly selected to receive chemotherapy alone (anthracycline-based therapy in anthracycline-naïve patients or 3-weekly paclitaxel in anthracycline-pretreated patients) or in combination with trastuzumab [8]. Patients who received trastuzumab-based therapy had greater clinical benefit (Table 1). In the M77001 study, docetaxel plus trastuzumab was significantly superior to docetaxel monotherapy, and long-term follow-up showed that 22% of patients were still alive 4 years after receiving the combination therapy [9, 14]. These data established taxanes and trastuzumab as the standard first-line treatment for patients with HER-2$^+$ MBC. Whether or not trastuzumab alone is equivalent to the standard docetaxel and trastuzumab combination as first-line treatment was explored in the HERTAX trial. The purpose of that study was to compare the initial use of docetaxel plus trastuzumab with sequential trastuzumab followed by docetaxel treatment. Although the median progression-free survival (PFS) times were 9.4 months for patients in

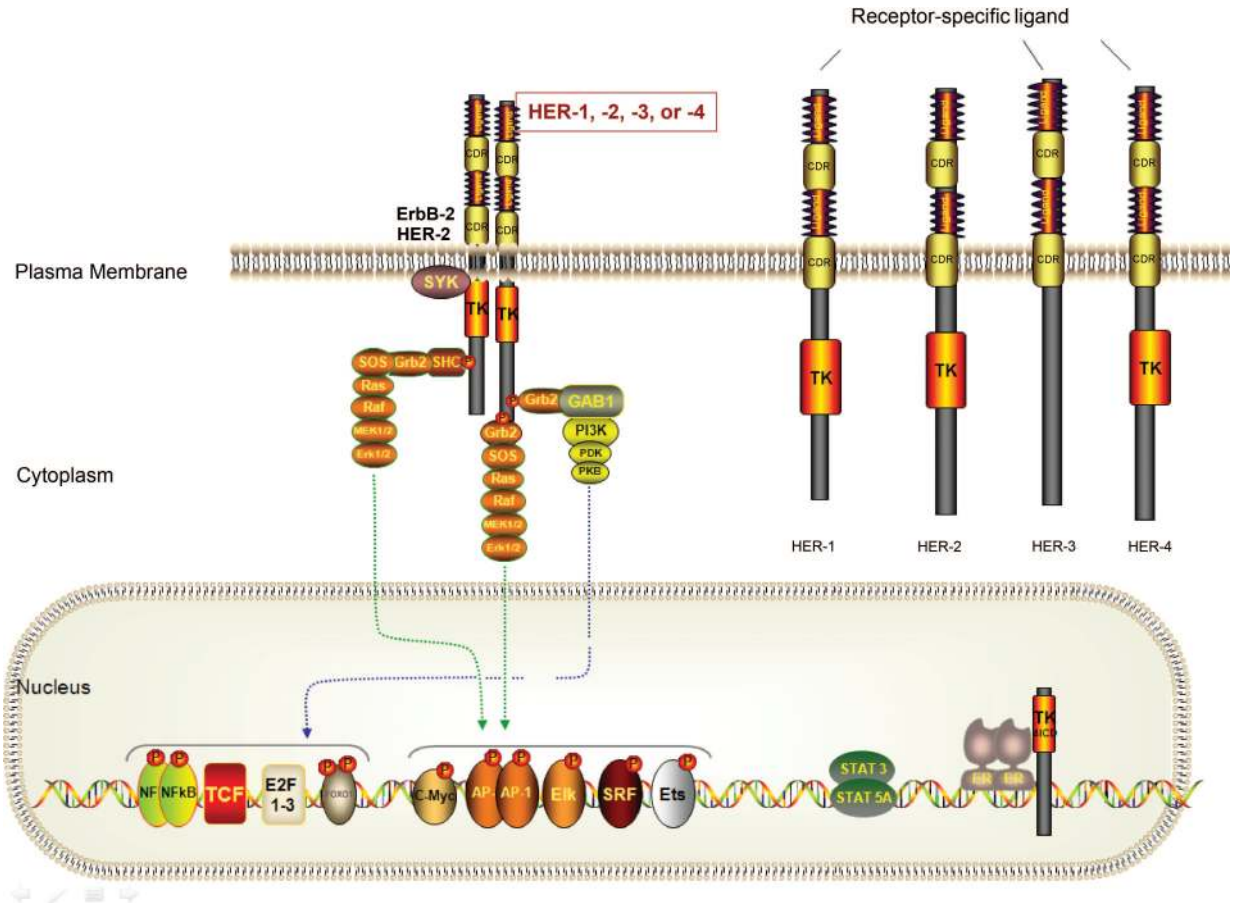

Figure 1. Schematic representation of HER signaling. The ligand-induced formation of different homo- and heterodimers and the recruitment of various downstream adaptor and effector proteins allow the activation of numerous signal transduction pathways.

Abbreviations: AO-1, activator protein 1; CDR, complementary determining regions; E2F, 17-β-estradiol factor; ERK, extracellular signal–related kinase; HER, human epidermal growth factor receptor; MEK, mitogen-activated protein kinase/ERK kinase; NFκB, nuclear factor κB; PDK, 3-phosphoinositide-dependent protein kinase; PI3K, phosphoinositide 3-kinase; PKB, protein kinase B; SOS, son of sevenless; SRF, serum response factor; STAT, signal transducer and activator of transcription; TCF, T-cell factor; TK, tyrosine kinase.

the combination arm and 3.9 months for patients in the monotherapy arm ($p = .0001$), and the median PFS time for patients in the sequential arm was 9.9 months ($p = .22$), definitive conclusions cannot be drawn because of the small study size [15].

Trastuzumab and Vinorelbine-Based Therapy

Based on the high activity observed with vinorelbine and trastuzumab in small phase II trials, randomized studies aimed to compare taxanes with vinorelbine, both in combination with trastuzumab [16–18]. The TRAVIOTA trial, designed to compare trastuzumab plus weekly vinorelbine with taxane therapy, showed equivalent efficacy between arms. Because of poor accrual, the study was closed prematurely with 81 evaluable patients instead of the original target of 250 [16]. Recently, the HERNATA trial confirmed the role of vinorelbine plus trastuzumab versus docetaxel plus trastuzumab as an alternative first-line therapy combination. In that study, the TTP (median, 12.4 months versus 15.3 months), ORR (59.3% in both arms), and OS time (median, 35.7 months versus 38.8 months) did not differ between arms. More patients in the docetaxel arm were forced to discontinue treatment as a result of toxicity (20% versus 7%; $p < .001$) [17].

Trastuzumab in Triple-Combination Therapy

Taxanes and trastuzumab in triple combinations have shown higher ORRs in randomized phase III trials (Table 1). Combination regimens containing trastuzumab, a taxane, and a platinum agent have shown benefit in the first-line setting, confirming preclinical data that demonstrated synergistic or additive interactions of these agents with trastuzumab in breast cancer cell lines [19]. Whereas the addition of carboplatin to trastuzumab plus paclitaxel resulted in a superior ORR and PFS interval, as reported by Robert et al. [20], the Breast Cancer International Group 007 trial did not show a benefit with the addition of carboplatin to trastuzumab plus docetaxel [21]. Noteworthy is the fact that, in the former study, the dose of

Table 1. Trastuzumab and taxane-based therapy as a first-line treatment

Study	*n*	Regimen (doses in mg/m^2)	Response (%)					Median OS (mos)	Median TTP (mos)
			CR	PR	OR	SD	PD		
Comparison of taxanes with and without trastuzumab									
Slamon et al. [8]	101	P, 175 q3wk + T, 4 mg/kg loading then 2 mg/kg per wk	8	34	41[a]	NR	NR	22.1	6.9[a]
		P, 175 q3wk	2	15	17	NR	NR	18.4	3.0[a]
Marty et al. [9]	92	D, 100 q3wk + T, 4 mg/kg loading then 2 mg/kg/wk	7	54	61[a]	27	NR	31.2[a]	11.7[a]
	94	D, 100 q3wk	2	32	34	44	NR	22.7[a]	6.1[a]
Triple therapy with taxanes and trastuzumab									
Wardley et al. [25]	112	T, 8 mg/kg loading then 6 mg/kg + D, 75 q3wk + X, 950 BID days 1–14 q3wk	23.2	47.3	70.5	25	3.6	0.75[b]	18.3[a]
	110	T, 8 mg/kg loading then 6 mg/kg + D, 100 q3wk	16.4	56.4	72.7	16.4	9.1	0.66[b]	13.6[a]
Valero et al. [21]	132	D, 75 mg/m^2 q3wk + C, AUC = 6 q3wk (8 cycles) + T, 4 mg/kg loading then 2 mg/kg per wk then T, 6 mg/kg until PD	17	55	72	15	8.3	37.4	10.3
	131	D, 100 q3wk + T, 4 mg/kg loading then 2 mg/kg per wk then T, 6 mg/kg until PD	18	54	72	18	8.4	37.1	11.0
Robert et al. [20]	98	T, 4 mg/kg loading then 2 mg/kg per wk + 6 cycles P (175) and C (AUC = 6) q3wk, followed by T wk alone	10	42	52[a]	38	10	35.7	NR
	98	T, 4 mg/kg loading then 2 mg/kg per wk + 6 cycles P (175) q3wks followed by T wk alone	3	33	36	43	21	32.2	NR

[a]Statistically significant difference between groups ($p < .05$).
[b]2-year survival probability.
Abbreviations: AUC, area under the curve; BID, twice day; C, carboplatin; CR, complete response; D, docetaxel; NR, not reported; OS, overall survival; P, paclitaxel; PD, progresive disease; PR, partial response; q3wk, every 3 weeks; SD, stable disease; T, trastuzumab; TTP, time to progression; wk, weeks, X capecitabine.

paclitaxel was maintained in both arms, and in the latter study the lower dose of docetaxel in the triple-combination arm could have contributed to its lack of efficacy. To optimize such combinations, the North Central Cancer Treatment Group study 983252 evaluated the efficacy and tolerability of two different schedules of paclitaxel–carboplatin–trastuzumab [22]. All outcomes were better when paclitaxel was administered in a weekly regimen rather than every 3 weeks. Although toxicity has been a major concern, such a triple combination can be considered in clinical practice when a rapid response is mandatory.

Gemcitabine and trastuzumab have been explored with taxanes and with platinum compounds [23, 24], achieving ORRs of 52.5% and 66%, respectively, in two phase II clinical trials. Both regimens can be considered active in the first-line scenario; however, they are associated with more hematologic toxicity than with other approaches. Moreover, the MO16419 CHAT (Capecitabine, Herceptin®, and Taxotere®) study showed that the addition of capecitabine to trastuzumab and docetaxel yielded a superior PFS outcome (hazard ratio [HR], 0.72; $p = .045$) and longer TTP (HR, 0.70; $p = .033$), although ORRs and OS times were similar [25].

Trastuzumab and Anthracycline-Based Therapy

Anthracyclines are considered one of the most active agents for MBC, especially in the HER-2$^+$ population [26]. It is known that the combination of trastuzumab with doxorubicin or epirubicin and cyclophosphamide is associated with a high rate of cardiac toxicity (27% incidence of cardiac events in the H0648g trial) [8, 27]. In fact, cardiac toxicity, manifested as symptomatic congestive heart failure (CHF) or asymptomatic left ventricular ejection fraction (LVEF) decline, is an impor-

tant adverse effect of trastuzumab that has been attributed to blockade of HER-2 signaling in cardiac myocytes and appears to be reversible and manageable. Of note, in the pivotal trial, 63 patients had documented symptomatic or asymptomatic cardiac dysfunction. Forty-four of those 63 patients received standard medical treatment, with an improvement in 33 patients (75%) [8].

The incidence of severe CHF observed in the large adjuvant trastuzumab trials was in the range of 0%–4% (Table 2) [18, 28–33]. Importantly, results from those studies vary and direct comparisons among trials are difficult, mostly because of differences in cardiac event definitions, inclusion/exclusion criteria, monitoring schedules, and the timing of trastuzumab administration.

Liposomal forms of doxorubicin provide efficacy similar to that of conventional doxorubicin with a significantly lower risk for cardiotoxicity and CHF [34–36]. Non-pegylated liposomal doxorubicin (NPLD) and pegylated liposomal doxorubicin (PLD) have been evaluated in combination with trastuzumab alone and with trastuzumab plus taxanes [37–42].

In a phase I–II trial, a high ORR of 98.1% and a median TTP (not reached in locally advanced breast cancer patients and 22.1 months in MBC patients) were observed among 54 patients treated with NPLD, paclitaxel, and trastuzumab at the recommended doses (50 mg/m^2 every 3 weeks for NPLD and 80 mg/m^2 per week for paclitaxel) [39]. There was no treatment-related CHF with this triple combination; however, 12 patients (17%) developed asymptomatic declines in LVEF, and in eight of those patients, the LVEF recovered to >50% after a median of 9 weeks (range, 3–38 weeks).

A phase II study assessed the cardiac safety and clinical efficacy of PLD, docetaxel, and trastuzumab in HER-2$^+$ MBC patients [41]. A response rate of 45.7% was reported, and the median PFS and OS times were 10.6 months and 31.8 months, respectively. In that study, some patients with HER-2$^-$ disease were treated with the same schedule without trastuzumab. Interestingly, cardiotoxicity was similar in both cohorts of patients, with rates of 25% and 24.4% ($p = .99$) in the HER-2$^+$ and HER-2$^-$ populations, respectively.

Mechanisms of Trastuzumab Resistance

Most HER-2$^+$ breast cancer patients who initially respond to trastuzumab subsequently become refractory and experience disease progression [43]. A comprehensive understanding of HER-2 biology and the molecular mechanisms underlying primary and acquired trastuzumab resistance is crucial to develop new pharmacological strategies and to improve HER-2$^+$ patients' clinical outcomes. Several possible mechanisms of trastuzumab resistance were identified in preclinical and retrospective studies, including loss of antibody binding, increased downstream signaling, and activation of alternative growth factor pathways.

However, most of these have not yet been validated in prospective clinical trials. Although it is not the aim of this manuscript to review in detail the different mechanisms to overcome trastuzumab resistance, Table 3 summarizes some of the strategies that are being explored [44–71]. As an example, trastuzumab resistance may be driven by the activation of alternative signaling pathways such as through HER-3. Inhibition of HER-3 signaling via the blockage of HER-2–HER-3 heterodimerization by pertuzumab and other anti–HER-3–targeting therapies under clinical development is being pursued. Notably, p95HER-2 is a truncated form of HER-2 that lacks the extracellular domain (and the binding site for trastuzumab) but conserves an intact intracellular domain with strong kinase activity. It was recently demonstrated that expression of p95HER-2 also correlates with de novo resistance to trastuzumab-based therapy [44]. Seeking alternative anti–HER-2 therapeutic strategies, Scaltriti and colleagues investigated the activity of lapatinib, a small molecule that inhibits both epidermal growth factor receptor (EGFR) and HER-2 phosphorylation, in p95HER-2$^+$ tumors. Lapatinib was proven to be efficacious in inhibiting tumor growth in several trastuzumab-resistant p95HER-2 preclinical models. Lapatinib-based therapy was equally effective in p95HER-2$^+$ and p95HER-2$^-$ patients, differing from trastuzumab-based therapy [44]. Although these data seem encouraging and deserve further translational and clinical investigation, recent neoadjuvant trials (the Chemotherapy plus trastuzumab, lapatinib or both [CHER-LOB] and GeparQuattro trials) have produced inconclusive data regarding p95HER-2 status [72, 73]. A randomized phase II trial will be launched to evaluate if combination lapatinib-based therapy is more active than trastuzumab-based therapy in patients with p95HER-2$^+$ tumors.

Lapatinib as First-Line Therapy

Lapatinib as a Single Agent

Lapatinib (Tykerb®/Tyverb®; GlaxoSmithKline, Brentford, U.K.) is a potent, selective, oral, reversible small-molecule dual tyrosine kinase inhibitor (TKI) of both the HER-1 and HER-2 signaling pathways. Based on pharmacokinetic data, the EGF20009 study was designed to assess two different doses of lapatinib (500 mg twice daily and 1,500 mg once daily) in patients with HER-2$^+$ MBC as first-line agents [74]. In total, 138 patients were treated. The ORRs and clinical benefit rates (CBRs) for the two treatment groups were not significantly different (22% versus 26%; $p = 0.691$ and 29% versus 33%; $p = 0.714$ for 1,500 mg and 500 mg, respectively), and the median TTP was 7.9 weeks in both groups. The most common adverse events related to lapatinib did not differ between treatment schedules and mainly consisted of grade 1 or 2 diarrhea (36%), rash (27%), pruritus (18%), and nausea (10%).

Lapatinib and Taxane-Based Therapy

The combination of paclitaxel and lapatinib was also tested in clinical trials. Pharmacokinetic interaction between lapatinib and paclitaxel resulted in a higher plasma concentration of both drugs by 20%–25%, although a predictable and manageable safety profile was demonstrated [75, 76].

A phase III randomized trial evaluated the efficacy of 3-weekly paclitaxel with or without lapatinib in patients with HER-2$^-$ or HER-2 status unknown MBC [59]. No statistically significant differences were observed between groups. Inter-

Table 2. Trastuzumab cardiac safety data

	NSABP B-31[28][a]		N9831 [29][a]			HERA [30]		BCIRG 006 [31]			FinHER [18]		PACS-04 [32]	
Treatment arms	**AC-P**	**AC-PT**	**AC-P**	**AC-P-T**	**AC-PT**	**Observation**	**T**	**AC-D**	**AC-DT**	**DCa-T**	**Ch**	**Ch-T**	**Observation**	**T**
Patients	872	932	664	710	570	1,719	1,682	1,073	1,074	1,075	116	115	268	260
Previous A	100%		100%			94%		100%		0	0		100%	
LVEF baseline	≥50%		≥50%			≥55%		≥50%			median 65–66		≥50%	
LVEF asymptomatic reduction (%)	17	34	UK			2.9	9.8	10	18	8.6	10.7[b]	6.8	2.2	4.2
CHF class III–IV (%)	1.3	3.9	0.3	2.5	3.3	0	0.8	0.38	1.87	0.38	1.7	0.9	0.4	1.7
Cardiac deaths	1	0	1	1	0	1	0	0	0	0	0	0	0	0

Abbreviations: A, anthracycline; BCIRG, Breast Cancer International Research Group; C, cyclophosphamide; Ca, Carboplatin; Ch, chemotherapy; CHF, congestive heart failure; D, docetaxel; FinHER, Finnish Herceptin®; HERA, Herceptin® Adjuvant; LVEF, left ventricular ejection fraction; NSABP, National Surgical Adjuvant Breast and Bowel Project; P, paclitaxel; PACS, trastuzumab versus observation after adjuvant chemotherapy; T, trastuzumab; UK, unknown.
[a]Combined review of cardiac data from both trials showed 2% symptomatic heart failure events for T-based therapy and 0.45% for Ch arm [33].
[b]LVEF decrease >20%.

estingly, 86 patients (15%) were considered to have centrally defined HER-2$^+$ tumors. Although this was not the primary objective of the trial, treatment with paclitaxel and lapatinib resulted in a statistically significant longer TTP (36.4 weeks versus 25.1 weeks for paclitaxel alone versus the combination therapy; $p = .005$) and greater ORR (63.3% versus 37.8%; $p = .023$). The addition of lapatinib to paclitaxel resulted in higher incidences of grade 3 rash (4% versus 0%) and grade 3 diarrhea (15% versus 1%). Fatal adverse events were observed in 2.7% and 0.6% of patients in the combination and single-agent arms, respectively.

Lapatinib and trastuzumab, although targeting distinct domains of HER-2, demonstrated a synergistic interaction in preclinical studies [77, 78] and better clinical outcomes than with lapatinib alone in trastuzumab-refractory patients [79]. A phase I study assessed the safety and efficacy of adding lapatinib to paclitaxel and trastuzumab in three different dose cohorts [80]. The ORR for all patients was 75% and was similar among all cohorts. However, a higher incidence of severe gastrointestinal events (grade 3 diarrhea, 50%–62%) was observed when lapatinib was administered at higher doses. Pharmacokinetic interaction between lapatinib and paclitaxel was observed in all cohorts of patients. This three-drug combination is being explored in patients with primary tumors.

HER-2–Hormone Receptor Copositive Tumors

Estrogen receptor (ER) and/or progesterone receptor expression occurs in ~50% of HER-2$^+$ breast cancers [81, 82]. Crosstalk between the ER and HER pathways promotes endocrine therapy resistance [83, 84]. For this reason, inhibiting both the HER-2 and ER pathways at the same time should be a more effective treatment strategy than ER inhibition alone (Fig. 2).

Letrozole, an aromatase inhibitor (AI), was evaluated in combination with trastuzumab in a phase II trial that showed, for the first time, efficacy data in terms of durable responses [82]. Two large randomized, first-line trials evaluating the combination of AIs with anti–HER-2 therapies in patients with advanced HER-2$^+$ breast cancer were published. Lapatinib in combination with letrozole was compared with letrozole alone in 1,286 patients with MBC (EGF30008 study) [85, 86]. Notably, the primary objective of that trial was to assess the PFS interval in the HER-2$^+$ population. In the HER-2–hormone receptor copositive subgroup (219 patients), the addition of lapatinib to letrozole was associated with a significantly longer median PFS time than with letrozole alone (8.2 months versus 3.0 months; $p = 0.019$), greater ORR (28% versus 15%; $p = .021$), and higher CBR (48% versus 29%; $p = .003$). The most common grade 3 or 4 adverse events included diarrhea and rash, and these were more common in the lapatinib–letrozole arm (diarrhea, 10% versus 1%; rash, 1% versus 0%).

The TrAstuzumab in Dual HER2 ER-Positive Metastatic breast cancer trial evaluated the benefit of adding trastuzumab to anastrozole therapy versus anastrozole alone in 208 postmenopausal patients [87]. The combination was significantly more effective in regard to the median PFS interval (4.8 months versus 2.4 months; $p = .0016$), the primary objective of the trial, and the ORR (20.3% versus 6.8%; $p = .018$). The median OS times were 28.5 months and 23.9 months in the combination and single-agent arms, respectively ($p = .325$). Nevertheless, the crossover of 70% of patients from the anastrozole arm to trastuzumab-based therapy upon disease progression bears mentioning. The combination therapy was manageable and well tolerated.

Optimization of First-Line Treatment for Patients With HER-2$^+$ MBC

A New Loading Dose Schedule of Trastuzumab

In the standard weekly or 3-weekly regimen, the steady-state concentration of trastuzumab is reached after ~18 weeks of

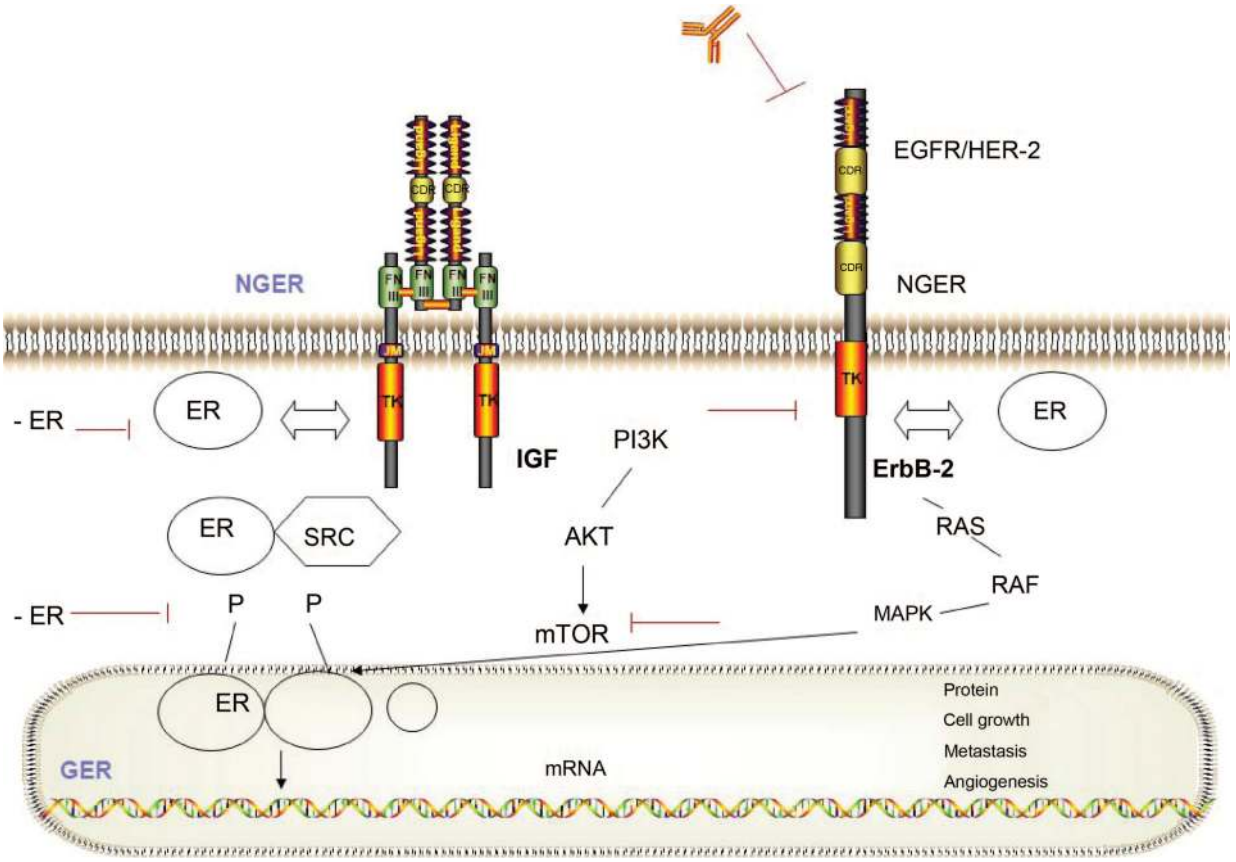

Figure 2. Crosstalk between the ER and HER family signaling pathways in breast cancer. NGER and GER activities may be greater in tumors with overexpression of EGFR and HER-2. Anti-ER and anti-HER therapies may reduce the crosstalk and overcome rous sarcoma oncogene.

Abbreviations: CDR, complementary determining regions; EGFR, epidermal growth factor receptor; ER, estrogen receptor; GER, genomic estrogen receptor; HER, human epidermal growth factor receptor; IGF, insulin-like growth factor; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NGER, nongenomic estrogen receptor; PI3K, phosphatidylinositol 3-kinase; SRC, rous sarcoma oncogene.

therapy. In patients receiving treatment who have earlier progression, trastuzumab administration might be discontinued before serum levels reach steady-state concentrations. For this purpose, a loading dose schedule of trastuzumab was studied [88]. A total of 72 patients received a loading dose of 6 mg/kg i.v. trastuzumab monotherapy over 90 minutes on days 1, 8, and 15 of cycle 1, followed by a 3-weekly maintenance dose of 6 mg/kg. That study demonstrated that higher than established steady-state trastuzumab serum concentrations can be reached during cycle 1 of the 3-weekly schedule. In 47 patients with measurable disease, the ORR was 23.4%, and stable disease was observed in 27.7% of patients; interestingly, the median TTP was 7.7 months. This schedule was well tolerated, and no unexpected adverse events were noted. Therefore, achieving higher trastuzumab levels very early in the course of therapy, similar to those observed at steady state, could be of benefit for patients. This new trastuzumab schedule could be considered in the design of new clinical trials, particularly in the neoadjuvant setting.

New Anti–HER-2 Agents Might Improve the Outcomes for Patients With HER-2$^+$ MBC

Novel anti–HER-2 therapies are needed to overcome acquired trastuzumab resistance and to improve patient outcomes. There is a strong rationale for simultaneously targeting multiple pathways considering the interactions between HER-2 and other molecular pathways. Exciting new anti–HER-2–targeted drugs and combinations are being studied in the first-line setting of MBC (Table 4) [89–93], after showing promising results in trastuzumab-pretreated patients [61, 89].

Neratinib. Neratinib (HKI-272), a potent, oral, irreversible pan-HER TKI (i.e., HER-1, HER-2, and HER-4) produced an ORR of 56% and median PFS interval of 40 weeks in a trastuzumab-naïve population [95]. To better define the role of neratinib in first-line treatment, a phase III trial is being conducted comparing neratinib plus paclitaxel with the standard trastuzumab and paclitaxel regimen [90]. In

Table 3. Trastuzumab mechanisms of resistance and novel therapeutic approaches to HER-2$^+$ breast cancer

Mechanism of resistance	Example/target	Agent class	Drugs
Loss or prevention of trastuzumab binding to HER-2 [44–49]	MUC4 CD44–hyaluronan polymer complex		Trastuzumab resistance reversed with knockdown of MUC4 in breast cancer cells
	Truncated receptor p95	TKI	Lapatinib
	Downregulation of HER-2 expression		
	Increased circulating HER-2 ECD: competition for binding		
Upregulation of downstream signaling pathways of HER-2 [50] [51, 52]	PTEN loss of function and/or *PI3K/AKT* mutations	PI3K Inhibitor	BEZ235, BGT226
		mTOR Inhibitor	XL147
		Inhibition of AKT signaling	GDC-0941
			CCI-779 (temsirolimus)
			RAD001 (everolimus)
			AP23573
			Perifosine
			GDC0068
Alternative growth factor receptor signaling pathways [53–63]	IGF-1R	IGF-1R inhibitor	CP-751871
	MET	MET inhibitor	NVP-AEW541
	PCDGF		MK-0646
	ß1-/ß4-integrin	mAb	XL880
	EGFR	(HER-2/HER-3)	Pertuzumab
	HER-3	mAb (HER-2/HER-3)	Pertuzumab
		Pan-HER TKI	Neratinib
		mAb	AMG 888
		TKI	MM-121
			Lapatinib
			HKI-272
			CI-1033 (PD183805, Canertinib)
			PKI-166
			EKB-569
			BIBW-2992
			BMS-599626
			AEE788
Other strategies [64–71]	Decreasing the expression of protein processing of HER-2 and other signaling components	HSP90 inhibitor	KOS-953 (17-AAG)
		HDAC inhibitor	KOS-1022
		Proteasome inhibitor	AUY922
			LAQ824
			SAHA (Vorinostat)
			Bortezomib
	Increasing toxicity of trastuzumab to HER-2$^+$ cells	Antibody–drug conjugate	T-DM1
	Increasing immunity against HER-2$^+$ cells	Immunotherapy	Anti–HER-2 therapeutic vaccine
		Monoclonal antibody Trifunctional bispecific: target HER-2 and CD3	Ertumaxomab
		Genetically engineered Fc of mAb	Enhanced FcγRIII receptor binding on effector cells

Abbreviations: ECD, extracellular domain; EGFR, epidermal growth factor receptor; HDAC, histone deacetylase; HER, human epidermal growth factor receptor; HSP90, heat shock protein 90; IGF-1R, insulin growth factor 1 receptor; mAb, monoclonal antibody; MET, mesenchymal–epithelial transition factor; mTOR, mammalian target of rapamycin; MUC4, membrane associated glycoprotein mucin-4; PCDGF, PC-cell derived growth factor; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; TKI, tyrosine kinase inhibitor.

Table 4. Phase III clinical trials with new anti–HER-2 agents as first-line treatments

ClinicalTrials.gov identifier	Regimen	Estimated *n* of patients	Primary objective
NCT00915018 [90]	Neratinib + paclitaxel Trastuzumab + paclitaxel	1,200	PFS
NCT00567190 [91]	Trastuzumab + docetaxel + pertuzumab Trastuzumab + docetaxel+ placebo	808	PFS
NCT01120184 [92]	T-DM1 + pertuzumab T-DM1 + pertuzumab-placebo Trastuzumab + taxane	1,092	PFS
NCT00876395 [93]	Everolimus + trastuzumab + paclitaxel Trastuzumab + paclitaxel	717	PFS
NCT00391092 [94]	Bevacizumab + trastuzumab + docetaxel Trastuzumab +docetaxel	424	PFS

Abbreviations: HER, human epidermal growth factor receptor; PFS: progression-free survival.

addition, a new generation of irreversible inhibitors of EGFR and a HER-2 TKI, BIBW 2992, are in early phases of clinical development [96].

Pertuzumab. To achieve more powerful blockade of the HER-2 signaling pathway, trastuzumab in combination with pertuzumab, a HER-2–targeted monoclonal antibody that prevents HER-2 dimerization, has shown encouraging results in patients with prior progression on trastuzumab therapy [97]. The observed ORR was 24.2%, and adverse events, most of them grade 1 or 2, included diarrhea, fatigue, and nausea. Importantly, a recently published phase III randomized trial in the first-line setting (CLEOPATRA study) that assessed trastuzumab and docetaxel with either pertuzumab or placebo demonstrated dramatic results in terms of the PFS time (18.5 months versus 12.4 months; $p < .001$), consistent across predefined subgroups. There was a higher response rate (80.2% versus 69.3%; $p = .001$) and also a trend toward a longer survival time for the dual HER-2 blockade. There was no difference in the incidence of cardiac adverse events; although patients in the pertuzumab arm had higher incidences of diarrhea, rash, mucosal inflammation, and febrile neutropenia, these were mainly grades 1 and 2 [91].

The concept of complete HER-2 blockade with various regimens containing trastuzumab, lapatinib, and pertuzumab led to interesting results in at least five phase II–III studies in the neoadjuvant setting [72, 98–101]. High rates of pathologic complete response (pCR) were observed with various regimens with trastuzumab and lapatinib (the neoALLTO [Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation], GeparQuinto, CHER-LOB trials) and with trastuzumab and pertuzumab (the NeoSphere and TRYPHAENA trials). Chemotherapy-free regimens also led to pCRs in a remarkable number of cases (16.8% with trastuzumab plus pertuzumab in the NeoSphere trial) [98]. A randomized phase II study (TRYPHAENA) investigating the combination of pertuzumab and trastuzumab with or without an anthracycline-based chemotherapy regimen reached its primary endpoints (safety and tolerability), regardless of which chemotherapy scheme was chosen [101].

Trastuzumab-DM1. Trastuzumab-MCC-DM1 (T-DM1) is a first-in-class anti–HER-2 antibody–drug conjugate that combines the biological activity of trastuzumab with a highly potent antimicrotubule agent (DM1) and specifically targets HER-2–expressing cells, conferring selectivity to the cytotoxic agent and thus increasing the therapeutic index [102]. A phase II study of T-DM1 as a single agent revealed clinical activity (ORR, 25.9%) in patients with HER-2^+ MBC who had progressed while receiving trastuzumab-based chemotherapy [69]. The most common adverse events were grade 1 or 2 and consisted of fatigue, nausea, and headache. The observed grade 3 or 4 adverse events were thrombocytopenia, hypocalemia, and fatigue. In the first-line setting, T-DM1 was compared with trastuzumab plus docetaxel and was associated with robust efficacy. A significantly longer PFS interval (14.2 months versus 9.2 months; $p = .0353$) and greater rate of durable response (median duration, not reached versus 9.5 months) were observed for T-DM1, whereas the ORR did not differ between arms (64.2% versus 58.0%). A lower rate of adverse events grade ≥3 (46.4% versus 89.4%) confirmed the better tolerability of T-DM1 [103]. A phase III study of T-DM1 plus pertuzumab or T-DM1 plus placebo versus trastu-

zumab plus a taxane in first-line treatment is currently recruiting patients [92].

Everolimus. The mammalian target of rapamycin (mTOR) is involved in the cellular processes that contribute to the development and progression of breast cancer [104]. Consequently, various mTOR inhibitors have been developed and studied in combination with chemotherapy. In patients previously treated with trastuzumab, the addition of everolimus to trastuzumab (with or without paclitaxel) was clinically active, and the toxicity was acceptable. Partial responses were observed in 19% and 15% of patients treated with the three or two agents, respectively, and the median TTP were 6 months and 3.9 months, respectively [105, 106]. Based on these previous data, the BOLERO 1 phase III trial is evaluating the combination of everolimus with trastuzumab and paclitaxel as a first-line MBC treatment [93].

Bevacizumab. Overexpression of HER-2 is associated with the upregulation of vascular endothelial growth factor (VEGF) in breast cancer cells. Clinical evidence suggests that VEGF may be involved in the aggressive phenotype of HER-2$^+$ breast cancers [107]. This rationale supports the use of combination therapies targeting both HER-2 and VEGF. Bevacizumab, a VEGF-specific angiogenesis inhibitor, in combination with trastuzumab, showed promising results in a phase II study as a first-line therapy [108]. The ORR was 48% and the median TTP was 9.2 months. Although 32% of patients experienced a decrease in LVEF, all events were asymptomatic and either grade 1 or 2. There was one event (grade 4) detected in a patient who had previously received anthracyclines. The recent phase III Averel trial, which evaluated the efficacy and safety of docetaxel and trastuzumab with or without bevacizumab, met its primary endpoint. The investigator-assessed PFS interval was an average of 3 months longer for HER-2$^+$ patients who received bevacizumab in the first-line setting (13.7 months versus 16.5 months; HR, 0.82; $p = .0775$). No difference was seen in the OS times (38.3 months versus 38.5 months; HR, 1.01; $p = .9543$). A potential predictive role for high plasma VEGF-A levels could be inferred by an exploratory analysis [94].

HER-2$^+$ MBC After Progression on Adjuvant Trastuzumab-Based Therapy

Trastuzumab represents the standard therapy for the adjuvant treatment of HER-2$^+$ breast cancer patients [18, 31, 109–111]. Unfortunately, an important number of patients experience progression during or after trastuzumab adjuvant therapy and, for those patients, the standard of care is unclear. Furthermore, it is not yet established when a tumor should be considered as trastuzumab sensitive, refractory, or resistant; many oncologists consider an interval of 1 year between the end of adjuvant trastuzumab and relapse. The Finnish Herceptin® trial suggested that docetaxel administered concomitantly with trastuzumab is more effective than vinorelbine plus trastuzumab, each followed by 5-fluorouracil, epirubicin, and cyclophosphamide, as adjuvant treatment of HER-2$^+$ early breast cancer [18].

Considering that the HER-2 status might change in up to 30% of recurring or MBC cases [112–115], its accurate assessment should be pursued because treatment options could change in a proportion of cases. Therefore, HER-2 retesting represents a clinically relevant strategy whenever feasible. Another potential approach is the substitution of blood for tumor-tissue analysis because some bloodborne circulating biomarkers (e.g., cell-free DNA [cfDNA] and circulating tumor cells) have shown promise as noninvasive and real-time alternatives to biopsies. The recent detection of *HER-2* amplification in plasma cfDNA in primary breast cancer and MBC patients, as shown by Page et al. [116], might pave the way for routine blood sampling for *HER-2* amplification.

There are many strategies under development for HER-2$^+$ breast cancer patients, such as novel TKIs, new monoclonal antibodies combined with chemotherapy, and inhibitors of multiple signaling pathways [117]. The management and the choice of HER-2–based therapy after progression in the adjuvant setting depends on patient characteristics, tumor biology, and previous treatments [118]. Currently, trastuzumab remains the only anti–HER-2 agent approved in combination with non-anthracycline chemotherapy for the first-line treatment of MBC patients. Lapatinib with letrozole was recently approved for the treatment of postmenopausal women who coexpress hormone receptors and HER-2 and for whom hormonal therapy is indicated [85]. Lapatinib in combination with capecitabine showed a higher ORR (22% versus 14%; $p = .09$), longer median TTP (8.4 months versus 4.4 months; $p < .001$), and fewer cerebral metastases than with capecitabine monotherapy [119] in patients who were progressing on trastuzumab-based therapy. Based on these findings, the combination was approved for second-line therapy for patients previously treated with an anthracycline, a taxane, and trastuzumab, and this might be an attractive option for patients progressing on treatment or just after finishing adjuvant trastuzumab.

One attractive chemotherapy-free approach is the combination of trastuzumab and lapatinib. A phase III trial demonstrated a significantly longer median PFS interval (12 weeks versus 8.1 weeks; $p = .008$) with trastuzumab plus lapatinib than with lapatinib monotherapy in patients with previous exposure to trastuzumab, an anthracycline, and a taxane [79]. Although there was no difference in the ORRs (10.3% versus 6.9%; $p = .46$), the CBR was superior for the combination arm (24.7% versus 12.4%; $p = .01$). A trend toward a longer OS time was observed for patients in the anti–HER-2 combination arm (HR, 0.75; 95% confidence interval, 0.53–1.07; $p = .106$).

The administration of trastuzumab beyond disease progression on trastuzumab also showed positive results in the phase III German Breast Group 26/Breast International Group

03–05 trial [120]. Patients who received further trastuzumab plus capecitabine, compared with capecitabine alone, showed a significantly greater ORR (48% versus 27%; $p = .0115$) and longer TTP (8.2 months versus 5.6 months; $p = .0338$).

Conclusions

Although trastuzumab-based therapy is the standard first-line therapy for patients with HER-2$^+$ MBC, the optimal schedule remains to be defined. Taxanes have emerged as the drugs most commonly used in combination with trastuzumab, and they are used in the control arm of all randomized phase III trials. However, some important considerations have been raised. First, platinum compounds have been shown to improve the response rate and PFS time in combination with paclitaxel and trastuzumab; nevertheless, adverse events remain a major issue in patients for whom quality of life is a primary consideration. Second, the role of anthracyclines has not been completely elucidated. A recently completed phase III trial, designed to compare weekly paclitaxel and trastuzumab with or without NPLD, will reveal anthracyclines' potential role in this clinical scenario. Third, more "friendly" regimens, such as vinorelbine with trastuzumab, have shown promising activity and might be an appealing alternative to taxanes in an important subgroup of patients, especially in those with previous exposure to neo- or adjuvant chemotherapy and with cumulative long-term toxicities. Fourth, it is important to note that, although the addition of trastuzumab or lapatinib to hormonal therapy led to a significantly longer PFS interval, these clinical trials were not designed to determine the optimal treatment for patients with HER-2–hormone receptor copositive tumors. HER-2$^+$ tumors appear to be resistant to hormonal therapy; thus, chemotherapy in combination with trastuzumab should still be considered the standard of care. Nevertheless, there might be a small subgroup of patients who might benefit from AIs in combination with trastuzumab or lapatinib for avoiding unnecessary chemotherapy-related toxicity [121, 122].

On the other hand, it is very likely that other targeted agents will have a role in the treatment of patients with HER-2$^+$ MBC. Lapatinib, pertuzumab, neratinib, trastuzumab-DM1, bevacizumab, and everolimus are the most well-established agents in this setting, and they may emerge as new standards of care in the forthcoming years. Although the optimal sequence, duration, and number of lines of anti–HER-2 treatment is not yet clear, data from retrospective studies have shown that continued HER-2–directed therapy is a valuable option [123, 124]. Retreatment with trastuzumab or lapatinib-based therapies after disease progression on T-DM1 [123] (and also treatment with trastuzumab after progression on lapatinib) seems to benefit patients [124]. Definitively, HER-2$^+$ breast cancer patients will receive anti–HER-2 therapies as part of their treatment.

Acknowledgment

Leticia De Mattos-Arruda is a recipient of an ESMO Translational Research Fellowship.

Author Contributions

Conception/Design: Javier Cortes, Leticia De Mattos-Arruda
Provision of study material or patients: Javier Cortes, Leticia De Mattos-Arruda
Collection and/or assembly of data: Javier Cortes, Leticia De Mattos-Arruda
Data analysis and interpretation: Javier Cortes, Leticia De Mattos-Arruda
Manuscript writing: Javier Cortes, Leticia De Mattos-Arruda
Final approval of manuscript: Javier Cortes, Leticia De Mattos-Arruda

References

1. Smigal C, Jemal A, Ward E et al. Trends in breast cancer by race and ethnicity: Update 2006. CA Cancer J Clin 2006;56:168–183.

2. Hayat MJ, Howlader N, Reichman ME et al. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) program. ***The Oncologist*** 2007;12:20–37.

3. Mendelsohn J, Baselga J. Status of epidermal growth factor receptor antagonists in the biology and treatment of cancer. J Clin Oncol 2003;21:2787–2799.

4. Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. Nat Rev Mol Cell Biol 2001;2:127–137.

5. Atalay G, Cardoso F, Awada A et al Novel therapeutic strategies targeting the epidermal growth factor receptor (EGFR) family and its downstream effectors in breast cancer. Ann Oncol 2003;14:1346–1363.

6. Slamon DJ, Clark GM, Wong SG et al. Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987;235:177–182.

7. Mass RD, Press MF, Anderson S et al. Evaluation of clinical outcomes according to HER2 detection by fluorescence in situ hybridization in women with metastatic breast cancer treated with trastuzumab. Clin Breast Cancer 2005;6:240–246.

8. Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783–792.

9. Marty M, Cognetti F, Maraninchi D et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: The M77001 study group. J Clin Oncol 2005;23:4265–4274.

10. Jackisch C. HER-2-positive metastatic breast cancer: Optimizing trastuzumab-based therapy. ***The Oncologist*** 2006;11(suppl 1):34–41.

11. Dawood S, Broglio K, Buzdar AU et al. Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: An institutional-based review. J Clin Oncol 2010;28:92–98.

12. Vogel CL, Cobleigh MA, Tripathy D et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 2002;20:719–726.

13. Baselga J, Carbonell X, Castaneda-Soto NJ et al. Phase II study of efficacy, safety, and pharmacokinetics of trastuzumab monotherapy administered on a 3-weekly schedule. J Clin Oncol 2005;23:2162–2171.

14. Marty M, Cognetti F, Maraninchi D et al. Superior long-term survival benefits of trastuzumab plus docetaxel compared to docetaxel alone in patients with HER2-positive metastatic breast cancer: Patients surviving more than 4 years in the M77001 study. Presented at the 29th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 14–17, 2006.

15. Hamberg P, Bos MM, Braun HJ et al. Randomized phase II study comparing efficacy and safety of combination-therapy trastuzumab and docetaxel vs. sequential therapy of trastuzumab followed by docetaxel alone at progression as first-line chemotherapy in patients with HER2+ metastatic breast cancer: HERTAX trial. Clin Breast Cancer 2011;11:103–113.

16. Burstein HJ, Keshaviah A, Baron AD et al. Trastuzumab plus vinorelbine or taxane chemotherapy for HER2-overexpressing metastatic breast cancer: The trastuzumab and vinorelbine or taxane study. Cancer 2007;110:965–972.

17. Andersson M, Lidbrink E, Bjerre K et al. Phase III randomized study comparing docetaxel plus trastuzumab with vinorelbine plus trastuzumab as first-line therapy of metastatic or locally advanced human epidermal growth factor receptor 2-positive breast cancer: The HERNATA study. J Clin Oncol 2011;29:264–271.

18. Joensuu H, Bono P, Kataja V et al. Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: Final results of the FinHer Trial. J Clin Oncol 2009;27:5685–5692.

19. Pegram MD, Konecny GE, O'Callaghan C et al. Rational combinations of trastuzumab with chemotherapeutic drugs used in the treatment of breast cancer. J Natl Cancer Inst 2004;96:739–749.

20. Robert N, Leyland-Jones B, Asmar L et al. Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. J Clin Oncol 2006;24:2786–2792.

21. Valero V, Forbes J, Pegram MD et al. Multicenter phase III randomized trial comparing docetaxel and trastuzumab with docetaxel, carboplatin, and trastuzumab as first-line chemotherapy for patients with HER2-gene-amplified metastatic breast cancer (BCIRG 007 study): Two highly active therapeutic regimens. J Clin Oncol 2011;29:149–156.

22. Perez EA, Suman VJ, Rowland KM et al. Two concurrent phase II trials of paclitaxel/carboplatin/trastuzumab (weekly or every-3-week schedule) as first-line therapy in women with HER2-overexpressing metastatic breast cancer: NCCTG study 983252. Clin Breast Cancer 2005;6:425–432.

23. Fountzilas G, Christodoulou C, Tsavdaridis D et al. Paclitaxel and gemcitabine, as first-line chemotherapy, combined with trastuzumab in patients with advanced breast cancer: A phase II study conducted by the Hellenic Cooperative Oncology Group (HeCOG). Cancer Invest 2004;22:655–662.

24. Yardley DA, Burris HA 3rd, Simons L et al. A phase II trial of gemcitabine/carboplatin with or without trastuzumab in the first-line treatment of patients with metastatic breast cancer. Clin Breast Cancer 2008;8:425–431.

25. Wardley AM, Pivot X, Morales-Vasquez F et al. Randomized phase II trial of first-line trastuzumab plus docetaxel and capecitabine compared with trastuzumab plus docetaxel in HER2-positive metastatic breast cancer. J Clin Oncol 2010;28:976–983.

26. Gennari A, Sormani MP, Pronzato P et al. HER2 status and efficacy of adjuvant anthracyclines in early breast cancer: A pooled analysis of randomized trials. J Natl Cancer Inst 2008;100:14–20.

27. Seidman A, Hudis C, Pierri MK et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol 2002;20:1215–1221.

28. Rastogi P, Jeong J, Geyer CE et al. Five year update of cardiac dysfunction on NSABP B-31, a randomized trial of sequential doxorubicin/cyclophosphamide (AC)→paclitaxel (T) vs. AC→T with trastuzumab(H). J Clin Oncol 2007;25(18 suppl):LBA513.

29. Perez EA, Suman VJ, Davidson NE et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol 2008;26:1231–1238.

30. Procter M, Suter TM, de Azambuja E et al. Longer-term assessment of trastuzumab-related cardiac adverse events in the Herceptin Adjuvant (HERA) trial. J Clin Oncol 2010;28:3422–3428.

31. Slamon D, Eiermann W, Robert N et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011;365:1273–1283.

32. Spielmann M, Roché H, Delozier T et al. Trastuzumab for patients with axillary-node-positive breast cancer: Results of the FNCLCC-PACS 04 trial. J Clin Oncol 2009;27:6129–6134.

33. Russell SD, Blackwell KL, Lawrence J et al. Independent adjudication of symptomatic heart failure with the use of doxorubicin and cyclophosphamide followed by trastuzumab adjuvant therapy: A combined review of cardiac data from the National Surgical Adjuvant Breast and Bowel Project B-31 and the North Central Cancer Treatment Group N9831 clinical trials. J Clin Oncol 2010;28:3416–3421.

34. Harris L, Batist G, Belt R et al. Liposome-encapsulated doxorubicin compared with conventional doxorubicin in a randomized multicenter trial as first-line therapy of metastatic breast carcinoma. Cancer 2002;94:25–36.

35. Batist G, Ramakrishnan G, Rao CS et al. Reduced cardiotoxicity and preserved antitumor efficacy of liposome-encapsulated doxorubicin and cyclophosphamide compared with conventional doxorubicin and cyclophosphamide in a randomized, multicenter trial of metastatic breast cancer. J Clin Oncol 2001;19:1444–1454.

36. O'Brien ME, Wigler N, Inbar M et al. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. Ann Oncol 2004;15:440–449.

37. Theodoulou M, Campos SM, Batist G et al. TLC D99 (D, Myocet) and Herceptin (H) is safe in advanced breast cancer (ABC): Final cardiac safety and efficacy analysis. Proc Am Soc Clin Oncol 2002;21:216.

38. Amadori D, Milandri C, Comella G et al. A phase I/II trial of non-pegylated liposomal doxorubicin, docetaxel and trastuzumab as first-line treatment in HER-2-positive locally advanced or metastatic breast cancer. Eur J Cancer 2011;47:2091–2098.

39. Cortes J, Di Cosimo S, Climent MA et al. Nonpegylated liposomal doxorubicin (TLC-D99), paclitaxel, and trastuzumab in HER-2-overexpressing breast cancer: A multicenter phase I/II study. Clin Cancer Res 2009;15:307–314.

40. Chia S, Clemons M, Martin LA et al. Pegylated liposomal doxorubicin and trastuzumab in HER-2 overexpressing metastatic breast cancer: A multicenter phase II trial. J Clin Oncol 2006;24:2773–2778.

41. Wolff AC, Wang M, Li H et al. Phase II trial of pegylated liposomal doxorubicin plus docetaxel with and without trastuzumab in metastatic breast cancer: Eastern Cooperative Oncology Group trial E3198. Breast Cancer Res Treat 2010;121:111–120.

42. Karabelis A, Kosmas C, Mylonakis N et al. Paclitaxel (P), pegylated liposomal doxorubicin (PLD) and trastuzumab as 1st-line chemotherapy (chemo) in HER2/neu-positive (+) metastatic breast cancer (MBC). J Clin Oncol 2006;24(18 suppl):10663.

43. Nahta R, Yu D, Hung MC et al. Mechanisms of disease: Understanding resistance to HER2-targeted therapy in human breast cancer. Nat Clin Pract Oncol 2006;3:269–280.

44. Scaltriti M, Chandarlapaty S, Prudkin L et al. Clinical benefit of lapatinib-based therapy in patients with human epidermal growth factor receptor 2-positive breast tumors coexpressing the truncated p95HER2 receptor. Clin Cancer Res 2010;16:2688–2695.

45. Nagy P, Friedländer E, Tanner M et al. Decreased accessibility and lack of activation of ErbB2 in JIMT-1, a Herceptin-resistant, MUC4-expressing breast cancer cell line. Cancer Res 2005;65:473–482.

46. Pàlyi-Krekk Z, Barok M, Isola J et al. Hyaluronan-induced masking of ErbB2 and CD44-enhanced trastuzumab internalisation in trastuzumab resistant breast cancer. Eur J Cancer 2007;43:2423–2433.

47. Lu Y, Li X, Liang K et al. Epidermal growth factor receptor (EGFR) ubiquitination as a mechanism of acquired resistance escaping treatment by the anti-EGFR monoclonal antibody cetuximab. Cancer Res 2007;67:8240–8247.

48. Anido J, Scaltriti M, Bech Serra JJ et al. Biosynthesis of tumorigenic HER2 C-terminal fragments by alternative initiation of translation. EMBO J 2006;25:3234–3244.

49. Scaltriti M, Rojo F, Ocaña A et al. Expression of p95HER2, a truncated form of the HER2 receptor, and response to anti-HER2 therapies in breast cancer. J Natl Cancer Inst 2007;99:628–638.

50. Junttila TT, Akita RW, Parsons K et al. Ligand-independent HER2/HER3/PI3K complex is disrupted by trastuzumab and is effectively inhibited by the PI3K inhibitor GDC-0941. Cancer Cell 2009;15:429–440.

51. Andre F, Campone M, O'Regan R et al. Phase I study of everolimus plus weekly paclitaxel and trastuzumab in patients with metastatic breast cancer pretreated with trastuzumab. J Clin Oncol 2010;28:5110–5115.

52. Leighl NB, Dent S, Clemons M et al. A phase 2 study of perifosine in advanced or metastatic breast cancer. Breast Cancer Res Treat 2008;108:87–92.

53. Nahta R, Yuan LX, Zhang B et al. Insulin-like growth factor-I receptor/human epidermal growth factor receptor 2 heterodimerization contributes to trastuzumab resistance of breast cancer cells. Cancer Res 2005;65:11118–11128.

54. Shattuck DL, Miller JK, Carraway KL 3rd et al. Met receptor contributes to trastuzumab resistance of Her2-overexpressing breast cancer cells. Cancer Res 2008;68:1471–1477.

55. Tripathy D, Mukhopadhyay P, Verma U et al. Targeting of the chemokine receptor CXCR4 in acquired trastuzumab resistance. Presented at the 30th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 13–16, 2007.

56. Kim WE, Serrero G. PC cell-derived growth factor stimulates proliferation and confers trastuzumab resistance to Her-2-overexpressing breast cancer cells. Clin Cancer Res 2006;12:4192–4199.

57. Thoms J, Sabri S, Deschenes J et al. Increased b1 integrin expression is a predictor of trastuzumab resistance in HER-2 overexpressing metastatic breast cancer patients. Presented at the 30th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 13–16, 2007.

58. Agus DB, Akita RW, Fox WD et al. Targeting ligand-activated ErbB2 signaling inhibits breast and prostate tumor growth. Cancer Cell 2002;2:127–137.

59. Di Leo A, Gomez HL, Aziz Z et al. Phase III, double-blind, randomized study comparing lapatinib plus paclitaxel with placebo plus paclitaxel as first-line treatment for metastatic breast cancer. J Clin Oncol 2008;26:5544–5552.

60. Wong KK, Fracasso PM, Bukowski RM et al. A phase I study with neratinib (HKI-272), an irreversible pan ErbB receptor tyrosine kinase inhibitor, in patients with solid tumors. Clin Cancer Res 2009;15:2552–2558.

61. Roy V, Perez EA. Beyond trastuzumab: Small molecule tyrosine kinase inhibitors in HER-2-positive breast cancer. ***The Oncologist*** 2009;14:1061–1069.

62. Chandarlapaty S, Sawai A, Scaltriti M et al. AKT inhibition relieves feedback suppression of receptor tyrosine kinase expression and activity. Cancer Cell 2011;19:58–71.

63. Wong H, Leung R, Kwong A et al. Integrating molecular mechanisms and clinical evidence in the management of trastuzumab resistant or refractory HER-2+ metastatic breast cancer. ***The Oncologist*** 2011;16:1535–1546.

64. Zsebik B, Citri A, Isola J et al. Hsp90 inhibitor 17-AAG reduces ErbB2 levels and inhibits proliferation of the trastuzumab resistant breast tumor cell line JIMT-1. Immunol Lett 2006;104:146–155.

65. Modi S, Stopeck A, Linden H et al. HSP90 inhibition is effective in breast cancer: A phase II trial of tanespimycin (17-AAG) plus trastuzumab in patients with HER2-positive metastatic breast cancer progressing on trastuzumab. Clin Cancer Res 2011;17:5132–5139.

66. Disis ML, Goodell V, Schiffman K et al. Humoral epitope-spreading following immunization with a HER-2/neu peptide based vaccine in cancer patients. J Clin Immunol 2004;24:571–578.

67. Kiewe P, Hasmïller S, Kahlert S et al. Phase I trial of the trifunctional anti-HER2 x anti-CD3 antibody ertumaxomab in metastatic breast cancer. Clin Cancer Res 2006;12:3085–3091.

68. Lazar GA, Dang W, Karki S et al. Engineered antibody Fc variants with enhanced effector function. Proc Natl Acad Sci U S A 2006;103:4005–4010.

69. Burris HA 3rd, Rugo HS, Vukelja SJ et al. Phase II study of the antibody drug conjugate trastuzumab-DM1 for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer after prior HER2-directed therapy. J Clin Oncol 2011;29:398–405.

70. Fuino L, Bali P, Wittmann S et al. Histone deacetylase inhibitor LAQ824 down-regulates Her-2 and sensitizes human breast cancer cells to trastuzumab, Taxotere, gemcitabine, and epothilone B. Mol Cancer Ther 2003; 2:971–984.

71. Cardoso F, Durbecq V, Laes JF et al. Bortezomib (PS-341, Velcade) increases the efficacy of trastuzumab (Herceptin) in HER-2-positive breast cancer cells in a synergistic manner. Mol Cancer Ther 2006;5:3042–3051.

72. Guarneri V, Frassoldati A, Bottini A et al. Final results of a phase II randomized trial of neoadjuvant anthracycline-taxane chemotherapy plus lapatinib, trastuzumab, or both in HER2-positive breast cancer (CHER-LOB trial). J Clin Oncol 2011;(29 suppl):507.

73. Loibl S, Bruey J, Von Minckwitz G et al. Validation of p95 as a predictive marker for trastuzumab-based therapy in primary HER2-positive breast cancer: A translational investigation from the neoadjuvant GeparQuattro study. J Clin Oncol 2011;(29 suppl):530.

74. Gomez HL, Doval DC, Chavez MA et al. Efficacy and safety of lapatinib as first-line therapy for ErbB2-amplified locally advanced or metastatic breast cancer. J Clin Oncol 2008;26:2999–3005.

75. Crown JP, Burris HA, Jones S et al. Safety and tolerability of lapatinib in combination with taxanes (T) in patients with breast cancer (BC). J Clin Oncol 2007; 25(18 suppl):1027.

76. Jones SF, Burris HA 3rd, Yardley DA et al. Lapatinib (an oral dual kinase inhibitor) plus weekly or every 3 week paclitaxel. Presented at the 27th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 8–11, 2004.

77. Konecny GE, Pegram MD, Venkatesan N et al. Activity of the dual kinase inhibitor lapatinib (GW572016) against HER-2-overexpressing and trastuzumab-treated breast cancer cells. Cancer Res 2006;66:1630–1639.

78. Scaltriti M, Verma C, Guzman M et al. Lapatinib, a HER2 tyrosine kinase inhibitor, induces stabilization and accumulation of HER2 and potentiates trastuzumab-dependent cell cytotoxicity. Oncogene 2009;28:803–814.

79. Blackwell KL, Burstein HJ, Storniolo AM et al. Randomized study of lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. J Clin Oncol 2010;28:1124–1130.

80. Esteva FJ, Franco S, Hagan MK et al. Updated efficacy and safety assessment of first-line therapy with lapatinib, trastuzumab, and paclitaxel in HER2+ metastatic breast cancer. J Clin Oncol 2010;28(15 suppl): 1046.

81. Konecny G, Pauletti G, Pegram M et al. Quantitative association between HER-2/neu and steroid hormone receptors in hormone receptor-positive primary breast cancer. J Natl Cancer Inst 2003;95:142–153.

82. Marcom PK, Isaacs C, Harris L et al. The combination of letrozole and trastuzumab as first or second-line biological therapy produces durable responses in a subset of HER2 positive and ER positive advanced breast cancers. Breast Cancer Res Treat 2007;102:43–49.

83. Osborne CK, Shou J, Massarweh S et al. Crosstalk between estrogen receptor and growth factor receptor pathways as a cause for endocrine therapy resistance in breast cancer. Clin Cancer Res 2005;11:865s–870s.

84. Arpino G, Wiechmann L, Osborne CK et al. Crosstalk between the estrogen receptor and the HER tyrosine kinase receptor family: Molecular mechanism and clinical implications for endocrine therapy resistance. Endocr Rev 2008;29:217–233.

85. Johnston S, Pippen J Jr, Pivot X et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. J Clin Oncol 2009;27: 5538–5546.

86. Schwartzberg LS, Franco SX, Florance A et al. Lapatinib plus letrozole as first-line therapy for HER-2+ hormone receptor-positive metastatic breast cancer. ***The Oncologist*** 2011;15:122–129.

87. Kaufman B, Mackey JR, Clemens MR et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: Results from the randomized phase III TAnDEM study. J Clin Oncol 2009;27:5529–5537.

88. Leyland-Jones B, Colomer R, Trudeau ME et al. Intensive loading dose of trastuzumab achieves higher-than-steady-state serum concentrations and is well tolerated. J Clin Oncol 2010;28:960–966.

89. Chandarlapaty S, Modi S. Targeted therapy for human epidermal growth factor receptor 2-positive breast cancer: Can there be too many active drugs? J Clin Oncol 2011;29:3111–3113.

90. ClinicalTrials.gov. Study Evaluating Neratinib Plus Paclitaxel VS Trastuzumab Plus Paclitaxel In ErbB-2 Positive Advanced Breast Cancer (NEFERTT). Available at http://ClinicalTrials.gov/ct2/show/NCT00915018, accessed August 16, 2011.

91. Baselga J, Cortés J, Kim SB et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109–119.

92. ClinicalTrials.gov. A Study of Trastuzumab Emtansine (T-DM1) Plus Pertuzumab/Pertuzumab Placebo Versus Trastuzumab [Herceptin] Plus a Taxane in Patients With Metastatic Breast Cancer (MARIANNE). Available at http://ClinicalTrials.gov/ct2/show/NCT01120184, accessed August 16, 2011.

93. ClinicalTrials.gov. Everolimus in Combination With Trastuzumab and Paclitaxel in the Treatment of HER2 Positive Locally Advanced or Metastatic Breast Cancer (BOLERO-1). Available at http://ClinicalTrials.gov/ct2/show/NCT00876395, accessed August 16, 2011.

94. Gianni L, Romieu G, Lichinitser M et al. First results of AVEREL, a randomized phase III trial to evaluate bevacizumab (BEV) in combination with trastuzumab (H) + docetaxel (DOC) as first-line therapy for HER2-positive locally recurrent/metastatic breast cancer (LR/mBC). Presented at the 34th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 6–10, 2011.

95. Burstein HJ, Sun Y, Dirix LY et al. Neratinib, an irreversible ErbB receptor tyrosine kinase inhibitor, in patients with advanced ErbB2-positive breast cancer. J Clin Oncol 2010;28:1301–1307.

96. Hickish T, Wheatley D, Lin N et al. Use of BIBW 2992, a novel irreversible EGFR/HER2 tyrosine kinase inhibitor (TKI), to treat patients with HER2-positive metastatic breast cancer after failure of treatment with trastuzumab. J Clin Oncol 2009;7(15 suppl):1023.

97. Baselga J, Gelmon KA, Verma S et al. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. J Clin Oncol 2010;28:1138–1144.

98. Gianni L, Pienkowski T, Im Y-H et al. Neoadjuvant pertuzumab (P) and trastuzumab (H): Antitumor and safety analysis of a randomized phase II study ('NeoSphere'). Presented at the 33rd Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 8–12, 2010.

99. Baselga J, Bradbury I, Eidtmann H et al. First results of the NeoALTTO trial (BIG 01–06 / EGF 106903): A phase III, randomized, open label, neoadjuvant study of lapatinib, trastuzumab, and their combination plus paclitaxel in women with HER2-positive primary breast cancer. Presented at the 33rd Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 8–12, 2010.

100. Untch M, Loibl S, Bischoff J et al. Lapatinib vs trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy: Primary efficacy endpoint analysis of the GEPARQUINTO study (GBG 44). Presented at the 33rd Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 8–12, 2010.

101. Schneeweiss A, Chia S, Hickish T et al. Neoadjuvant pertuzumab and trastuzumab concurrent or sequential with an anthracycline-containing or concurrent with an anthracycline-free standard regimen: A randomized phase II study (TRYPHAENA). Presented at the 34th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 6–10, 2011.

102. Lewis Phillips GD, Li G, Dugger DL et al. Targeting HER2-positive breast cancer with trastuzumab-DM1, an antibody-cytotoxic drug conjugate. Cancer Res 2008;68:9280–9290.

103. Hurvitz SA, Dirix L, Kocsis J et al. Trastuzumab emtansine (T-DM1) versus trastuzumab + docetaxel in previously untreated HER2-positive metastatic breast cancer (MBC): Primary results of a randomized, multicenter, open-label phase II study (TDM4450g/BO21976) [abstract 5.001]. Presented at the ESMO-ECCO European Multidisciplinary Cancer Congress, Stockholm, Sweden, September 23–27, 2011.

104. Shaw RJ, Cantley LC. Ras, PI(3)K and mTOR signalling controls tumour cell growth. Nature 2006; 441:424–430.

105. Dalenc F, Campone M, Hupperets P et al. Everolimus in combination with weekly paclitaxel and trastuzumab in patients (pts) with HER2-overexpressing metastatic breast cancer (MBC) with prior resistance to trastuzumab and taxanes: A multicenter phase II clinical trial. J Clin Oncol 2010;28(15 suppl):1013.

106. Morrow PK, Wulf GM, Ensor J et al. Phase I/II study of trastuzumab in combination with everolimus (RAD001) in patients with HER2-overexpressing metastatic breast cancer who progressed on trastuzumab-based therapy. J Clin Oncol 2011;29:3126–3132.

107. Konecny GE, Meng YG, Untch M et al. Association between HER-2/neu and vascular endothelial growth factor expression predicts clinical outcome in primary breast cancer patients. Clin Cancer Res 2004; 10:1706–1716.

108. Hurvitz SA, Pegram MD, Lin L-S et al. Final results of a phase II trial evaluating trastuzumab and bevacizumab as first line treatment of HER2-amplified advanced breast cancer. Presented at the 32nd Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 2009;9–13.

109. Piccart-Gebhart MJ, Procter M, Leyland-Jones B

et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005;353: 1659–1672.

110. Gianni L, Dafni U, Gelber RD et al. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: A 4-year follow-up of a randomised controlled trial. Lancet Oncol 2011;12:236–244.

111. Perez EA, Romond EH, Suman VJ et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: Joint analysis of data from NCCTG N9831 and NSABP B-31. J Clin Oncol 2011;29:3366–3373.

112. Zidan J, Dashkovsky I, Stayerman C et al. Comparison of HER-2 overexpression in primary breast cancer and metastatic sites and its effect on biological targeting therapy of metastatic disease. Br J Cancer 2005;93:552–556.

113. Gong Y, Booser DJ, Sneige N. Comparison of HER-2 status determined by fluorescence in situ hybridization in primary and metastatic breast carcinoma. Cancer 2005;103:1763–1769.

114. Santinelli A, Pisa E, Stramazzotti D et al. HER-2 status discrepancy between primary breast cancer and metastatic sites. Impact on target therapy. Int J Cancer 2008;122:999–1004.

115. Guarneri V, Giovannelli S, Ficarra G et al. Comparison of HER-2 and hormone receptor expression in primary breast cancers and asynchronous paired metastases: Impact on patient management. ***The Oncologist*** 2008;13:838–844.

116. Page K, Hava N, Ward B et al. Detection of HER2 amplification in circulating free DNA in patients with breast cancer. Br J Cancer 2011;104:1342–1348.

117. Geuna E, Milani A, Redana S et al. Hitting multiple targets in HER2-positive breast cancer: Proof of principle or therapeutic opportunity? Expert Opin Pharmacother 2011;12:549–565.

118. Metzger-Filho O, Vora T, Awada A. Management of metastatic HER2-positive breast cancer progression after adjuvant trastuzumab therapy—current evidence and future trends. Expert Opin Investig Drugs 2010; 19(suppl 1):S31–S39.

119. Geyer CE, Forster J, Lindquist D et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006;355: 2733–2743.

120. von Minckwitz G, du Bois A, Schmidt M et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: A German Breast Group 26/Breast International Group 03–05 study. J Clin Oncol 2009;27: 1999–2006.

121. Cortes J, Baselga J. How to treat hormone receptor-positive, human epidermal growth factor receptor 2-amplified breast cancer. J Clin Oncol 2009;27:5492–5494.

122. Cortés J, Saura C, Bellet M et al. HER2 and hormone receptor-positive breast cancer—blocking the right target. Nat Rev Clin Oncol 2010;8:307–311.

123. Olson EM, Lin NU, DiPiro PJ et al. Responses to subsequent anti-HER2 therapy after treatment with trastuzumab-DM1 in women with HER2-positive metastatic breast cancer. Ann Oncol 2012;23:93–97.

124. Gori S, Montemurro F, Spazzapan S et al. Retreatment with trastuzumab-based therapy after disease progression following lapatinib in her2-positive metastatic breast cancer. Ann Oncol 2011 Oct 29 [Epub ahead of print].

Marcia Deans

Phelps Lake – Grand Tetons National Park, Wyoming