Chapter 4

HER2-positive metastatic breast cancer: first-line treatment

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Introduction

Prognoses for patients with breast cancer overexpressing the human epidermal growth factor receptor 2 (HER2) have markedly improved with the administration of anti-HER2-targeted therapy. In the last decade, trastuzumab-based therapy has become the standard first-line treatment option for patients with HER2+ metastatic breast cancer [1–5]. However, trastuzumab- and pertuzumab-based therapy is now considered the new standard of care [6]. Lapatinib in combination with capecitabine is also an approved regimen after progression on a trastuzumab-containing chemotherapy [7]. Other anti-HER2-targeted therapies, such as trastuzumab emtansine (T-DM1) and neratinib have also emerged as important treatment possibilities.

Trastuzumab-based therapy

Trastuzumab has shown to be effective in patients with metastatic HER2+ breast cancer as a first-line therapy [8,9] either alone or in combination with selected chemotherapeutic agents [1,9]. In randomized clinical trials, trastuzumab has also been proven to be beneficial when combined with taxanes (with or without platinum compounds), vinorelbine, and capecitabine [1–4,10–12]. These combination regimens are

R.H. Alvarez et al. (eds.), *Handbook of HER2-Targeted Agents in Breast Cancer*, DOI 10.1007/978-3-319-28216-9_4

recommended in the current National Comprehensive Cancer Network (NCCN) guidelines as options for first-line treatment [13].

Trastuzumab- and taxane-based first-line therapy

Trastuzumab and taxane dual-combination therapy

Pivotal trials have established the efficacy of the combination of taxanes with trastuzumab in patients with HER2-positive metastatic breast cancer (Table 4.1) [1–4,12]. In the H0648g trial, patients were allocated to receive chemotherapy alone or in combination with trastuzumab [1]. Anthracycline-naïve patients received anthracycline-based chemotherapy and patients already given anthracyclines received paclitaxel every 3 weeks. Patients in the trastuzumab-based therapy group had improvements in overall response rate (ORR), time to progression (TTP), and overall survival (OS) [1]. Additionally, in the M77001 study, docetaxel + trastuzumab showed superior clinical benefit compared with docetaxel administered as monotherapy [2,14].

Trastuzumab and taxane triple-combination therapy

Taxanes and trastuzumab have also been used in triple combinations with other agents. In a randomized Phase III trial, trastuzumab + paclitaxel + carboplatin demonstrated superior ORR (52% vs 36%, P=0.04) and progression-free survival (PFS; 10.7 months vs 7.1 months; hazard ratio [HR] 0.66; 95% CI, 0.59–0.73; P=0.03) compared with trastuzumab + paclitaxel [3]. However, the schedule of paclitacel (ie, every three weeks) was suboptimal. In another study, trastuzumab + paclitaxel + carboplatin was assessed in two different schedules (once weekly vs every three weeks); the weekly regimen had efficacy superior to that of the every-three-weeks regimen [15]. Thus, this triple combination can be considered in the clinical practice when a rapid response is warranted.

The addition of carboplatin to trastuzumab and docetaxel was not found to be superior to trastuzumab and docetaxel alone. However, one of the reasons for the inferior efficacy of this regimen was the reduced docetaxel dose in the triple-combination arm [4]. By contrast, capecitabine added to trastuzumab and docetaxel was demonstrated to have superior PFS (17.9 vs 12.8 months;

Drug combination	n	Regimen (mg/m²)	Response (%)			Median OS (m)	Median TTP (m)	Reference
			ORR	SD	PD			
Taxanes with or without trastuzumab	92	P 175 mg/m² q3wk + T 4 mg/kg loading, then 2 mg/kg/wk	41*	NR	NR	22.1	6.9*	[1]
	96	P 175 mg/m² q3wk	17	NR	NR	18.4	3.0	
	92	D 100 mg/m² q3wk + T 4 mg/kg loading, then 2 mg/kg/wk	61*	27	NR	31.2*	11.7*	[2]
	94	D 100 mg/m² q3wk	34	44	NR	22.7	6.1	
Triple therapy with taxanes and trastuzumab	112	T 8 mg/kg loading then 6 mg/kg + D 75 mg/m² q3wk + X 950 mg/m² b.i.d days 1–14 q3wk	70.5	25	3.6	0.75†	18.6*	[12]
	110	T 8 mg/kg loading then 6 mg/kg + D 100 mg/m² q3wk	72.7	16.4	9.1	0.66†	13.6	
	132	D 75 mg/m² q3wk + C AUC 6 mg/mL/min q3wk (8 cycles) + T 4 mg/kg loading then 2 mg/kg/wk, then T 6 mg/kg/wk alone until PD	72	15	8.3	37.4	10.4	[4]
	131	D 100 mg/m² q3wk + T 4 mg/kg loading then 2 mg/kg/wk, then T 6 mg/kg/wk alone until PD	72	18	8.4	37.1	11.0	
	98	T 4 mg/kg loading then 2 mg/kg/wk + 6 cycles: P 175 and C AUC6 q3wk, then T 2 mg/kg/wk alone until PD	52*	38	10	35.7	NR	[3]
	98	T 4 mg/kg loading then 2 mg/kg/wk + 6 cycles P 175 mg/m² q3wk, then T 2 mg/kg/wk alone until PD	36	43	21	32.2	NR	

Table 4.1 Trastuzumab- and taxane-based therapy as a first-line treatment strategy. AUC, area under the curve; b.i.d, twice daily; C, carboplatin; D, docetaxel; m, months; NR, not reported; ORR, overall response rate; OS, overall survival; P, paclitaxel; PD, progressive disease; q3wk, every 3 weeks; SD, stable disease; T, trastuzumab; TTP, time to progression; wk, weeks; X, capecitabine. *Statistically significant difference between treatment arms. †2-year survival probability.

HR 0.73; *P*=0.045) and longer TTP (18.6 vs 13.6 months; HR 0.70; *P*=0.033) versus trastuzumab + docetaxel, although ORR and OS rates were similar [12].

Other combinations involving trastuzumab and taxanes

Other combinations containing taxanes have been investigated and have demonstrated efficacy in the first-line setting. In two Phase II clinical trials, gemcitabine and trastuzumab were combined with either taxanes or platinum compounds, achieving an ORR of 52.5% and 66%, respectively [16,17].

Trastuzumab- and vinorelbine-based first-line therapy

In preclinical studies, vinorelbine was demonstrated to act synergistically with trastuzumab [18]. Given the high response rates with manageable toxicity observed with vinorelbine and trastuzumab in Phase II trials, two Phase III randomized studies investigated the combination of trastuzumab with either taxanes or vinorelbine [11,19].

The TRAVIOTA trial compared trastuzumab + weekly vinorelbine or taxane (paclitaxel or docetaxel) therapy and demonstrated comparable efficacy between both arms. However, as a consequence of poor accrual, the study was closed prematurely, with 81 evaluable patients instead of the original target of 250 [20]. Subsequently, the HERNATA trial has confirmed a role for vinorelbine + trastuzumab as an alternative first-line therapy combination [11]. In this Phase III clinical trial, the ORR was 59.3% in both the docetaxel + trastuzumab and vinorelbine + trastuzumab arms; the median TTP was 12.4 versus 15.3 months (HR 0.94; *P*=0.67) and the median OS was 35.7 versus 38.8 months (HR 1.01; *P*=0.98). The combination of vinorelbine and trastuzumab had significantly fewer adverse effects than docetaxel and trastuzumab [11].

Trastuzumab- and anthracycline-based first-line therapy

In the H0648g pivotal trial, the combination of trastuzumab with anthracycline-based chemotherapy was associated with a high rate (27%) of cardiac toxicity [1,21]. Liposomal forms of doxorubicin have been shown to provide efficacy similar to that of conventional doxorubicin with greater cardiac safety [22–24]. Several trials have evaluated pegylated and non-pegylated liposomal doxorubicin (NPLD) in combination with trastuzumab with or without taxanes [25–30]. For example, in the first-line setting, a Phase I/II trial investigating the combination of

NPLD, paclitaxel, and trastuzumab showed a general ORR of 98.1% and a median TTP of 22.1 months in the patients with metastatic disease (TTP not reached at time of publication in those with locally advanced nonoperable breast cancer) [27]. However, a recent randomized Phase III trial did not demonstrate significant clinical improvement with the addition of NPLD to paclitaxel and trastuzumab as first-line therapy [31]. The median PFS was 16.1 versus 14.5 months (HR 0.84; P=0.174) and the median OS was 33.6 versus 28.9 months (HR 0.79; P=0.083) for the arms with and without NPLD, respectively. Interestingly, for patients with estrogen receptor (ER)- and progesterone receptor-negative tumors, PFS was 20.7 months for those given NPLD and 14.0 months for those who were not (HR 0.68; 95% CI, 0.47–0.99). The incidence of congestive heart failure (New York Heart Association Class III/IV) was 3% with the arm that included NPLD [31].

Pertuzumab

Given that resistance to trastuzumab is common, new anti-HER2-targeted therapies with complementary and/or synergistic mechanisms of action have been investigated. One such therapy, pertuzumab, has dramatically changed the landscape of first-line HER2-positive breast cancer therapy. Pertuzumab is a HER2-targeted recombinant humanized monoclonal antibody that inhibits the ligand-dependent dimerization of HER2-HER3 [32]. Compared with trastuzumab, which binds to an epitope near the subdomain IV of HER2 [33], pertuzumab binds to HER2 at an epitope near the center of domain II (Figure 4.1) [34]. By blocking HER2 from interaction with itself or HER1, HER3, or HER4, pertuzumab hampers the activation of multiple HER signaling pathways [34].

Therapeutic efficacy

Pertuzumab was shown to be well tolerated and clinically active in Phase I trials in patients with advanced solid malignancies [35–37]. In the context of HER2-positive breast cancer, a dual anti-HER2 combination regimen containing pertuzumab and trastuzumab was initially investigated [38–40]. In the BO17929 study, all 66 patients had experienced progression on prior trastuzumab-based therapy. Treatment with pertuzumab + trastuzumab led to an ORR of 24.2%, a complete response rate of 7.6%, and a clinical benefit rate (CBR; total number of

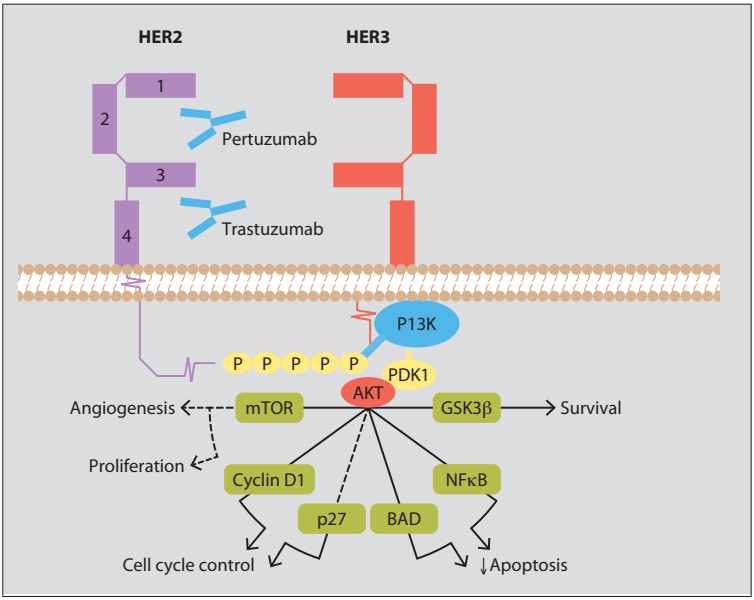

Figure 4.1 Pertuzumab- and trastuzumab-based therapy in HER2-positive metastatic breast cancer. Pertuzumab, a HER dimerization inhibitor, binds to an epitope on the subdomain II of HER2, preventing its ability to pair with other HER family members (HER1, HER3, and HER4) and with itself. By contrast, trastuzumab binds to an epitope on the subdomain IV of HER2. While blocking the formation of dimers, pertuzumab prevents the activation of key intracellular signaling pathways. AKT, protein kinase B; GSK3β, glycogen synthase kinase 3 beta; mTor, mammalian target of rapamycin; NFκB, nuclear factor kappa beta; P13K, phosphatidylinositol 3-kinase; PDK1, phosphoinositide-dependent kinase 1.

objective responses plus stable disease for >6 months) of 50%; median PFS was 5.5 months [38]. A separate cohort of the BO17929 study was designed to investigate the impact of reintroducing trastuzumab in patients who had progressed on both trastuzumab and pertuzumab monotherapy. The combination of pertuzumab and trastuzumab was shown to have superior activity versus pertuzumab monotherapy (ORR 17.6% vs 3.4%; CBR 41.2% vs 10.3%) [39].

First-line use of pertuzumab-based treatment in HER2-positive metastatic breast cancer

Pertuzumab and trastuzumab were tested in combination with docetaxel as first-line therapy in the randomized Phase III Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) registration study [6]. This study enrolled 808 patients (median age 54 years) with centrally confirmed HER2-positive metastatic or locally recurrent breast cancer and randomized them in a 1:1 ratio to receive

trastuzumab, docetaxel, and pertuzumab (n=402) or trastuzumab, docetaxel, and placebo (n=406). The primary endpoint, PFS (assessed independently), was significantly prolonged in the pertuzumab-containing arm (median PFS 18.5 months vs 12.4 months in the control arm; HR 0.62; 95% CI, 0.51–0.75; *P*<0.001) [6]. In addition, the ORR was superior for the pertuzumab-containing arm (80.2% vs 69.3%; *P*<0.001).

The confirmatory analysis of OS was reported after a median follow-up of 50 months [6]. In this final interim analysis, the combination of pertuzumab, trastuzumab, and docetaxel significantly improved OS for patients with HER2-positive metastatic breast cancer compared with trastuzumab and docetaxel (median OS 56.5 vs 40.8 months: HR 0.68; 95% CI, 0.56–0.84; *P*=0.001) [41]. Full efficacy results for CLEOPATRA can be found in Table 4.2 [6,41].

An exploratory post-hoc efficacy analysis was performed in elderly patients enrolled in the CLEOPATRA study (age ≥65 years). The pertuzumab-containing arm showed improved efficacy for the independently assessed PFS regardless of the patient's age (<65 years: median PFS 17.2 months vs 12.5 months for the control arm [HR 0.65, 95% CI, 0.53–0.80]; ≥65 years: median PFS 21.6 vs 10.4 months [HR 0.52, 95% CI, 0.31–0.86]) [42].

Based on the results of the CLEOPATRA study, the combination of pertuzumab + trastuzumab + a taxane has been incorporated into clinical practice

Study	n	Regimen (mg/m²)	Response (%)*					Median PFS (m)	Median OS (m)
			CR	PR	OR	SD	PD		
CLEOPATRA [6,41]	402	T 8 mg/kg loading then 6 mg/kg q3wk + D 75 mg/m² q3wk + P 840 mg q3wk followed by 420 mg q3wk	5.5	74.6	80.2	14.6	3.8	18.7	56.5
	406	T 8 mg/kg loading then 6 mg/kg q3wk + D 75 mg/m² q3wk + placebo	4.2	65.2	69.3	20.8	8.3	12.4	40.8

Table 4.2 Pertuzumab-based therapy as a first-line treatment for HER2-positive breast cancer. CR, complete response; D, docetaxel; m, months; NR, not reported; OR, objective response; OS, overall survival; P, pertuzumab; PD, progressive disease; PFS, progression-free survival; PR, partial response; q3wk, every 3 weeks; SD, stable disease; T, trastuzumab. *Overall response, as assessed at an independent review facility.

guidelines as a preferred first-line treatment for patients with HER2-positive metastatic breast cancer [13]. The efficacy and safety of an alternative option based on weekly paclitaxel in combination with trastuzumab and pertuzumab was confirmed in a single-arm, Phase II study [43].

Tolerability

In the BO17929 study, the administration of pertuzumab + trastuzumab was generally well tolerated [38,39]. The majority of the adverse events were grade 1 or 2; the most common were diarrhea (64% of patients), fatigue (33%), nausea (27%), and rash (26%) [38]. In the CLEOPATRA study, the most common adverse events were more frequent in the pertuzumab arm than in the control arm (diarrhea, 66.8% vs 46.3%; alopecia, 60.9% vs 60.5%; neutropenia, 52.8% vs 49.6%) [6]. These adverse events were generally grades 1 and 2. The incidence of grade 3 or 4 febrile neutropenia in all geographic areas was approximately 10% for both treatment groups; however, for patients in Asia, the incidence of grade 3 or 4 febrile neutropenia was significantly higher in the pertuzumab arm (26% vs 12% for the control arm) [6].

Treatment with pertuzumab combined with trastuzumab [36,37] or with trastuzumab and docetaxel [6] was not associated with an increase in adverse cardiac events. In the CLEOPATRA study, left ventricular systolic dysfunction at any grade was shown to be more frequent in the control arm than in the pertuzumab arm (8.6% vs 6.6%) [6]. A specific analysis of safety in the elderly population (based on a cut-off age of 65 years) was performed and the incidence of diarrhea, dysgeusia, and fatigue was higher for those aged ≥65 years in both arms. By contrast, the incidence of neutropenia and febrile neutropenia was less frequent for those in that age group [42]. For patients with good performance status, pertuzumab should be used irrespective of the patient's age.

Advantages of using trastuzumab and pertuzumab for the treatment of HER2-positive breast cancer

The robust activity of pertuzumab and trastuzumab administered in combination has been demonstrated in several HER2-positive tumor models [44,45]. In the clinic, the combination of pertuzumab and trastuzumab appears to be more effective than pertuzumab monotherapy [39]. Thus, pertuzumab has

been recognized as the first HER-dimerization inhibitor with a mechanism of action complementary to that of trastuzumab, which allows for a more complete blockade of HER2-driven signaling pathways. Pertuzumab-based therapy is now considered the new standard of care for the first-line treatment of HER2-positive metastatic breast cancer [6,46].

Other first-line anti-HER2 combination strategies

Given the interactions between HER2 and other molecular pathways, there is a compelling rationale for combining pertuzumab with other therapeutic approaches and simultaneously targeting multiple pathways [10].

T-DM1 an anti-HER2 antibody-drug conjugate that combines trastuzumab ('T') with the highly potent cytotoxic antimicrotubule (maytansinoid) emtansine ('DM1'), targets HER2-expressing cells to specifically deliver the cytotoxic agent [47]. As a first-line therapy, T-DM1 showed superior efficacy versus trastuzumab + docetaxel in terms of PFS (14.2 vs 9.2 months; HR 0.59; 95% CI 0.36–0.97; *P*=0.035) and also had a favorable safety profile [48]. Pertuzumab and T-DM1 may have synergistic and complementary mechanisms of action.

The randomized Phase III study (MARIANNE) investigated the role of pertuzumab in combination with T-DM1 as another first-line strategy for dual HER2 blockade [49]. In this multicenter trial, which has PFS as a primary endpoint, patients were randomized to receive T-DM1 + pertuzumab, T-DM1 + placebo, or trastuzumab + a taxane [49]. The interim analysis of the MARIANNE trial showed that patients with HER2-positive metastatic breast cancer treated with T-DM1 + pertuzumab had similar PFS compared with those treated with trastuzumab plus a taxane-based chemotherapy. After a median follow-up of 35 months, both T-DM1-containing regimens showed noninferior PFS, but not superiority, over trastuzumab + taxane. The median PFS was 15.2 months in the T-DM1 plus pertuzumab arm (HR 0.87, 95% CI, 0.69, 1.08; *P*=0.14), 14.1 months with T-DM1 alone (HR 0.91, 95% CI, 0.73, 1.13; *P*=0.31) compared with 13.7 months with trastuzumab + taxane [49]. The overall survival data were not yet reached. Though the trial met its noninferiority endpoint, showing a similar PFS in the first-line setting between the two combination therapies along with T-DM1 alone, it failed to demonstrate that T-DM1 outperforms trastuzumab + chemotherapy.

The mammalian target of rapamycin (mTOR), an important protein kinase that regulates multiple signaling pathways, is involved in trastuzumab resistance [50,51]. Everolimus is an oral inhibitor of mTOR, which has been investigated in trastuzumab-resistant HER2-positive metastatic breast cancer [51]. In patients previously treated with trastuzumab and taxanes, the addition of everolimus to trastuzumab and paclitaxel was safe and well tolerated and demonstrated promising efficacy [52].

In the previously reported BOLERO-3, everolimus added to trastuzumab and vinorelbine significantly improved PFS for patients with trastuzumab-resistant previously treated cancer [53]. In the first-line setting, the BOLERO-1 Phase III trial evaluated the combination of everolimus with trastuzumab and paclitaxel [54]. The primary endpoint was investigator-assessed PFS in the whole population and in the hormone-negative subpopulation. The study enrolled 719 patients [54]. In the full study population, PFS was comparable between the arms: 14.95 months with the addition of everolimus and 14.49 months with placebo (HR=0.89; P=0.1166). In the hormone receptor–negative subpopulation, however, everolimus-treated patients achieved a median PFS of 20.27 months vs 13.08 months with placebo (HR=0.66; P=0.0049) [54].

Ongoing first-line studies

In the first-line setting, several ongoing studies are investigating pertuzumab with other anti-HER2-targeted therapies and cytotoxic chemotherapeutic agents [49, 52, 55–69]. In addition, new anti-HER2 agents (eg, neratinib, dasatinib) are being investigated as first-line strategies and might change the paradigm for the treatment of patients with HER2-positive breast cancer. Table 4.3 illustrates the current clinical trials that are enrolling HER2-positive breast cancer patients for treatment in the first-line.

HER2/hormone receptor co-positive tumors

Given the crosstalk between the ER and HER pathways and the associated endocrine therapy resistance of HER2-positive tumors [70,71], the concomitant inhibition of both ER and HER2 pathways has been posited to be a more effective treatment strategy than ER inhibition alone. In fact, the combination of aromatase inhibitors with anti-HER2 therapies is an option for some patients who coexpress both HER2 and the ER, although its efficacy seems to be inferior

Clinical trial / NCT ID	Phase of development	Regimen	Primary objective(s)	Estimated enrollment
Pertuzumab-based therapy				
PERUSE (pertuzumab global safety study) [55]	IIIb	Pertuzumab + trastuzumab + taxane	Safety and tolerability	1500
NCT01491737 [56]	II	Trastuzumab + AI ± pertuzumab + chemotherapy*	PFS	250
		Trastuzumab + AI ± chemotherapy*		
EORTC (NCT01597414) (elderly patients) [57]	II	Pertuzumab + trastuzumab†	PFS	80
		Pertuzumab + trastuzumab + metronomic chemotherapy†		
NCT01565083 [58]	II	Pertuzumab + trastuzumab + vinorelbine	ORR	210
NCT01276041 (0 or 1 prior treatment in the metastatic setting) [59]	II	Pertuzumab + trastuzumab + paclitaxel	6 months progression-free	69
NCT01730833 [60]	II	Pertuzumab + trastuzumab + albumin-stabilized nanoparticle formulation of paclitaxel	PFS and ORR	45
HELENA (NCT01777958) [61]	Observational	Pertuzumab + trastuzumab after adjuvant trastuzumab	PFS	478
Miscellaneous				
NEFERTT (NCT00915018) [62]	II	Trastuzumab + paclitaxel	PFS	480
		Neratinib + paclitaxel		

Table 4.3 Ongoing clinical trials for the treatment of HER2-positive breast cancer in the first-line setting (*continues overleaf*). AI, aromatase inhibitor; NCT ID, National Clinical Trials Identifier (ClinicalTrials.gov); ORR, overall response rate; OS, overall survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine. *Induction chemotherapy at the investigator's discretion. †After progression, patients will be given the option of receiving T-DM1.

Clinical trial / NCT ID	Phase of development	Regimen	Primary objective(s)	Estimated enrollment (n)
Miscellaneous (continued)				
NCT01306942 [63]	I/II	Dasatinib + trastuzumab + paclitaxel	Phase I: maximum tolerated dose and recommended Phase II dose Phase II: ORR	60
NCT00520975 [64]	III	Induction: trastuzumab + placebo + paclitaxel ± carboplatin Maintenance: trastuzumab + placebo	PFS	489
		Induction: trastuzumab + bevacizumab + paclitaxel ± carboplatin Maintenance: trastuzumab + bevacizumab		
ICORG (NCT01526369) [65]	III	Paclitaxel + trastuzumab	PFS	600
		Paclitaxel + trastuzumab + lapatinib		
NCT00496366 [66]	II	Lapatinib + capecitabine	ORR	11
NCT01835236 [67]	II	Pertuzumab + trastuzumab (first- line) → T-DM1 (second-line)	OS at 24 months	208
		Pertuzumab + trastuzumab + paclitaxel (or vinorelbine) (first-line) → T-DM1 (second-line)		
NCT01269346 [68]	II	Eribulin + trastuzumab	ORR	52
NCT00033514 [69]	I/II	Erlotinib + trastuzumab	ORR	58

Table 4.3 Ongoing clinical trials for the treatment of HER2-positive breast cancer in the first-line setting (*continued*).

to that of chemotherapy plus anti-HER2-targeted therapy. For example, in the first-line setting, the addition of lapatinib to letrozole was evaluated in 1286 patients with metastatic breast cancer. In the HER2/hormonal receptor co-positive subgroup (n=219), adding lapatinib was associated with an important increase in the median PFS (8.2 vs 3.0 months; *P*=0.019), ORR (28% vs 15%; *P*=0.021); and CBR (48% vs 29%; *P*=0.003) [72].

In another study, trastuzumab and anastrozole combination therapy was compared with anastrozole monotherapy in 208 postmenopausal patients and showed a superior median PFS (4.8 vs 2.4 months; *P*=0.0016) and CBR (42.7% vs 27.9%; *P*=0.026) [73]. Median OS rates were 28.5 and 23.9 months in the combination and single-agent arms, respectively (*P*=0.325). Both combination therapies involving lapatinib + letrozole and trastuzumab + anastrozole were manageable and well tolerated [72,73].

Conclusions

Anti-HER2-targeted agents combined with chemotherapy are the current standard of care for the first-line treatment of patients with HER2-positive breast cancer (Table 4.4). Pertuzumab provides a more comprehensive inhibition of HER2-driven signaling pathways and has mechanistic advantages when combined with trastuzumab. Based on the outstanding results of the CLEOPATRA study, pertuzumab + trastuzumab + docetaxel should be offered as a preferred first-line treatment for patients with HER2-positive metastatic breast cancer.

References

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Regimen	Content	Frequency
Pertuzumab + trastuzumab + docetaxel	Pertuzumab 840 mg IV followed by 420 mg IV Trastuzumab 8 mg/kg IV as a 90-minute infusion D1 followed by 6 mg/kg IV as a 30-minute infusion weekly Docetaxel 75 mg/m^2 IV D1	Every 3 weeks
Pertuzumab + trastuzumab + paclitaxel	Pertuzumab 840 mg IV followed by 420 mg IV Trastuzumab 4 mg/kg IV as a 90-minute infusion D1 followed by 2 mg/kg IV as a 30-minute infusion weekly *or* Trastuzumab 8 mg/kg IV as a 90-minute infusion D1 followed by 6 mg/kg IV as a 30-minute infusion weekly Paclitaxel 80 mg/m^2 IV D1	Every 3 weeks Weekly
Paclitaxel + trastuzumab	Paclitaxel 90 mg/m^2 IV D1 Trastuzumab 4 mg/kg IV as a 90-minute infusion D1 followed by 2 mg/kg IV as a 30-minute infusion weekly *or* Trastuzumab 8 mg/kg IV as a 90-minute infusion D1 followed by 6 mg/kg IV as a 30-minute infusion every 3 weeks	Weekly
Docetaxel + trastuzumab	Docetaxel 80–100 mg/m^2 IV D1 or Docetaxel 35 mg/m^2 IV D1 Trastuzumab 4 mg/kg IV as a 90-minute infusion D1 followed by 2 mg/kg IV as a 30-minute infusion weekly *or* Trastuzumab 8 mg/kg IV as a 90-minute infusion D1 followed by 6 mg/kg IV as a 30-minute infusion every 3 weeks	Every 3 weeks or weekly
Paclitaxel + carboplatin + trastuzumab	Paclitaxel 175 mg/m^2 IV D1 Carboplatin AUC6 IV D1 or Paclitaxel 80 mg/m^2 IV D1, 8, 15 Carboplatin AUC2 IV D1, 8, 1	Every 3 weeks
Paclitaxel + carboplatin + trastuzumab	Trastuzumab 4 mg/kg IV as a 90-minute infusion D1 followed by 2 mg/kg IV as a 30-minute infusion weekly or Trastuzumab 8mg/kg IV as a 90-minute infusion D1 followed by 6 mg/kg as a 30-minute infusion every 3 weeks	28-day cycle
Vinorelbine + trastuzumab	Vinorelbine 25 mg/m^2 IV D1 Trastuzumab 4 mg/kg IV as 90-minute infusion D1 followed by 2 mg/kg IV as a 30-minute infusion weekly	Weekly
Lapatinib + letrazole	Lapatinib 1500 mg PO daily Letrozole 2.5 mg PO daily	Continuous

Table 4.4 HER2-targeted therapy for HER2-positive metastatic breast cancer in the first-line setting. AUC, area under the curve; D, day; IV, intravenous; PO, orally.

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