Optimizing (neo)adjuvant treatment of HER2-positive breast cancer

Reva K. Basho and Heather L. McArthur

Ther Adv Med Oncol
2018, Vol. 10: 1–13
DOI: 10.1177/1758835918775697

Abstract: The development of human epidermal growth factor 2 (HER2)-directed therapy has resulted in significant improvement in outcomes for patients with early-stage HER2-overexpressing (HER2+) breast cancer. In recent years, newer HER2-directed agents and novel treatment strategies have been developed with ongoing improvements in overall outcomes. However, with the addition of newer agents, there is an increasing need to risk stratify patients to maximize efficacy and minimize toxicity of treatment. De-escalation of therapy with the potential to shorten the duration of adjuvant therapy and minimize chemotherapy administration in patients with favorable disease can be considered. On the other hand, escalation of therapy with the addition of novel HER2-directed agents and extended duration of therapy in patients at high risk of relapse can help improve long-term cure rates. Herein, we discuss recent developments in neoadjuvant and adjuvant strategies for the treatment of potentially curable HER2+ breast cancer.

Keywords: adjuvant, breast cancer, HER2+ breast cancer, neoadjuvant, targeted therapy

Received: 1 December 2017; revised manuscript accepted: 12 April 2018.

Correspondence to:
Reva K Basho
Breast Medical Oncology, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, 8700 Beverly Boulevard AC 1053, Los Angeles, CA 90048, USA
Reva.Basho@cshs.org

Heather McArthur
Breast Medical Oncology, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA

Introduction

Amplification of the human epidermal growth factor 2 (HER2) neu gene or overexpression of the HER2 protein is observed in approximately 20–25% of all breast cancers and has historically been associated with early relapse and poor prognosis.[1–3] However, with the successful development of HER2-directed therapies within the past two decades, first in the palliative and then the curative-intent settings, breast cancer-specific outcomes are now dramatically improved for affected women.[4] HER2 is a transmembrane protein with tyrosine kinase activity encoded by the *ERBB2* gene. Ligand-dependent and independent signaling through HER2 results in cell proliferation and tumor growth.

Trastuzumab (Herceptin®; Genentech, Inc.) is a humanized recombinant monoclonal antibody that binds to the extracellular domain of HER2 and inhibits downstream signaling. Although the administration of trastuzumab as monotherapy in the metastatic setting has been associated with modest response rates,[5] it synergizes with many conventional cytotoxic agents, and co-administration with chemotherapy has resulted in significant improvements in disease-free survival (DFS) and overall survival (OS) in early-stage HER2-overexpressing (HER2+) breast cancer.[6–10] A Cochrane systematic review of eight randomized, controlled adjuvant trastuzumab trials enrolling 11,991 patients, confirmed fewer cancer recurrences [DFS hazard ratio (HR) 0.60; 95% confidence interval (CI) 0.50–0.71] and deaths (OS HR 0.66; 95% CI 0.57–0.77) in the groups treated with trastuzumab.[11]

Overall, four randomized pivotal trials initially reported on adjuvant trastuzumab for localized HER2+ breast cancer (NSABP B31, NCCTG N9831, HERA, BCIRG 996).[6–8] All four studies evaluated adjuvant chemotherapy and 12 months of adjuvant trastuzumab therapy, administered concurrently or sequentially with chemotherapy. The 12 months duration of adjuvant trastuzumab therapy was chosen somewhat arbitrarily without pre-existing preclinical or clinical evidence. When the United States Food and Drug Administration

Table 1. Final reported DFS and OS benefit of adjuvant trastuzumab in randomized pivotal trials.

Study	Treatment	N	DFS (%)	P Value	OS (%)	P Value
HERA[12]	CT alone CT-H	1697 1702	63 69	<0.0001	73 79	0.0005
BCIRG 006[8]	AC-D AC-DH DCH	1073 1074 1075	67.9 74.6 73.0	<0.001 0.04	78.7 85.9 83.3	<0.001 0.04
NCCTG N9831/ NSABP B-31[6]	AC-T AC-TH	2018 2028	62.2 73.7	<0.001	75.2 84	<0.001

AC, adriamycin and cyclophosphamide; CT, chemotherapy; D, docetaxel; DCH, docetaxel, carboplatin, and trastuzumab; DFS, disease-free survival; DH, docetaxel and trastuzumab; H, trastuzumab; OS, overall survival; T, paclitaxel; TH, paclitaxel and trastuzumab.

(US FDA) approved adjuvant trastuzumab in 2006, 12 months of adjuvant therapy became the standard of care due to the absence of data from other durations.

Since that time, several trials have investigated modifications to his strategy. Shorter duration of trastuzumab and less intensive chemotherapy regimens have been evaluated with the goals of de-escalating therapy and minimizing toxicity, particularly for patients with lower risk disease. On the other hand, regimens incorporating dual HER2 targeted therapies have also been evaluated with the goal of maximizing efficacy in patients with high-risk disease. Herein, we discuss recent developments in neoadjuvant and adjuvant strategies for the treatment of curable HER2+ breast cancer.

Longer duration of adjuvant trastuzumab

Overall, four pivotal, randomized trials evaluated 12 months of adjuvant trastuzumab therapy (Table 1). The HERceptin Adjuvant (HERA) trial was unique in that women were randomized to initiate adjuvant trastuzumab after completion of adjuvant chemotherapy, while the other trials assessed the administration of trastuzumab concurrently with chemotherapy and then as monotherapy to complete 1 year. Furthermore, women in HERA were randomly assigned to receive 1 year, 2 years, or no adjuvant trastuzumab.

Initial results from HERA showed efficacy of adjuvant trastuzumab compared with the observation group. However, an updated report indicated that 2 years of adjuvant trastuzumab did not result in further DFS or OS benefit when compared with 1 year of trastuzumab.[7,13] The final efficacy analysis of the HERA trial was reported after a median follow up of 11 years in 5102 women (N = 1697 in the chemotherapy alone arm, N = 1702 in the chemotherapy followed by 1 year of trastuzumab arm, and N = 1700 in the chemotherapy followed by 2 years of trastuzumab arm).[12] It was found that 2 years of adjuvant trastuzumab did not result in improved DFS compared with 1 year of trastuzumab (HR 1.02; 95% CI 0.89–1.17).

In all studies of trastuzumab and other HER2-directed agents, cardiac toxicity has been a concern, particularly when combined with anthracycline-based chemotherapy. In HERA, extended cardiac monitoring with annual measurement of left ventricular ejection fraction (LVEF) up to 10 years after randomization showed more secondary cardiac events in the 2-year trastuzumab group [122 (7%)] compared with the 1-year trastuzumab group [74 (4%)]. Together, these findings from HERA support the current practice of adjuvant trastuzumab administration for 1 year to maximize efficacy and minimize cardiac toxicity.

Shorter duration of adjuvant trastuzumab

However, the optimal duration of adjuvant trastuzumab is not known. Other studies have evaluated shorter durations of administration. The Finland Herceptin (FinHer) trial evaluated 9 weekly adjuvant trastuzumab infusions administered concurrently with adjuvant chemotherapy.[9] At a median follow up of 5 years, women with HER2+ disease who received trastuzumab had a

trend toward improved distant DFS with a HR favoring trastuzumab that was similar to those reported in the North American and HERA studies (HR 0.65; 95% CI 0.38–1.12). The median LVEF of trastuzumab-treated patients remained unchanged during the 5-year follow up with only one trastuzumab-treated patient diagnosed with heart failure. However, all patients on the study received 9 weeks of trastuzumab therapy, and there was no direct comparison with the standard longer duration of 12 months.

There have been two non-inferiority trials that randomly assigned patients with early-stage HER2+ breast cancer to receive 6 months or 12 months of adjuvant trastuzumab.[14,15] The Protocol for Herceptin as Adjuvant therapy with Reduced Exposure (PHARE) study was a phase III, randomized non-inferiority study in which 3384 patients with HER2+ early breast cancer were randomly assigned to continue or stop adjuvant trastuzumab therapy after completion of 6 months of treatment.[14] After a median follow up of 3.5 years, the trial was unable to show non-inferiority of 6 months of adjuvant trastuzumab therapy. There were 175 DFS events in the 12-month group compared with 219 in the 6-month group. However, significantly more patients in the 12-month group experienced a cardiac event than in the 6-month group, 96 (5.7%) of 1690 patients *versus* 32 (1.9%) of 1690 patients ($p < 0.0001$).

Similarly, the Hellenic Oncology Research Group (HORG) study was a randomized non-inferiority study that compared 6 *versus* 12 months of adjuvant trastuzumab started concurrently with taxane chemotherapy in 481 patients with early-stage HER2+ disease. After 4 years of median follow up, there were 17 (7.1%) and 28 (11.7%) disease relapses in the 12- and 6-month groups, respectively ($p = 0.08$). These studies both concluded that despite the potentially higher rates of cardiac events, 12 months of adjuvant trastuzumab should remain the standard of care over 6 months.

Several studies have evaluated even shorter durations of trastuzumab compared with the standard 12 months. The ECOG-ACRIN E2198 trial was a pilot study that evaluated 12 weeks *versus* 12 months of adjuvant trastuzumab therapy started concurrently with anthracycline- and taxane-based chemotherapy in 227 patients with axillary node-positive HER2+ breast cancer.[16] The primary endpoint was safety, particularly congestive heart failure (CHF). DFS and OS were secondary endpoints. Very few patients experienced CHF (four in the 1-year trastuzumab group and three in the 12-week group). 5-year DFS was comparable between the two arms (76% in the 12-week group and 73% in the 1-year group; $p = 0.3$).

The Short-HER study was a phase III, multicenter, randomized non-inferiority trial evaluating 9 weeks (short group) *versus* 12 months (long group) of adjuvant trastuzumab therapy started concurrently with adjuvant taxane chemotherapy in 1254 patients with early-stage HER2+ breast cancer.[17] In this study, the CI of the 5-year DFS crossed a prespecified non-inferiority margin of 1.29 based on frequentist analysis (85.4% short group *versus* 87.5% long group; HR 1.15; 90% CI 0.91–1.46). Thus, based on the frequentist analysis, non-inferiority of the shorter treatment approach could not be claimed, but according to a preplanned Bayesian analysis, non-inferiority is likely (78% probability). The 5-year OS was similar between the two groups (95.0% short group *versus* 95.1% long group; HR 1.06; 90% CI 0.73–1.55).

Interestingly, when subgroup analysis of DFS was conducted in the Short-HER study, a significant improvement with longer duration was seen in stage III *versus* stage I–II patients, (HR 2.30, 90% CI 1.35–3.94, $p < 0.001$). Similarly, when patients with four of more positive lymph nodes were compared with patients with 0–3 positive lymph nodes, a significant improvement with longer duration was seen (HR 2.25, 90% CI 1.33–3.83, $p < 0.001$). There were significantly more cardiac events in the long group compared with the short group: 90 *versus* 32, respectively (HR 0.32, 95% CI 0.21–0.50, $p < 0.0001$).

In the randomized phase III Synergism or Long Duration (SOLD) study, 2176 patients with node-positive or high-risk node-negative HER2+ breast cancer were randomly assigned to receive 9 weeks *versus* 12 months of adjuvant trastuzumab therapy started concurrently with adjuvant taxane chemotherapy.[18] All patients also received anthracycline-based therapy. The primary endpoint was DFS, and distant DFS and OS were secondary endpoints. The study reported a significantly better 5-year DFS in the 12-month group compared with the 9-week group (90.5% *versus* 88.0%; HR 1.39; 90% CI 1.12–1.72). However, distant DFS (94.2% *versus* 93.2%; HR 1.24; 90% CI 0.93–1.65) and OS (95.9% *versus* 94.7%; HR 1.36;

CI 0.98–1.89) did not differ significantly between the two groups. Interestingly, when the subset of patients who received a docetaxel dose of 80 mg/m^2 was compared with those who received a dose of 100 mg/m^2, the patients receiving the lower dose but not the higher dose had a significantly improved DFS with longer duration of trastuzumab. Fewer cardiac adverse events were observed in the 9-week arm compared with the 12-month arm (2% *versus* 3.9%; $p = 0.012$).

Because these studies have been unable to demonstrate non-inferiority of shorter durations of trastuzumab, 12 months of adjuvant trastuzumab therapy remains the standard of care despite the potential of increased cardiac toxicity. However, as demonstrated by the Short-HER study, there may be a subset of patients with favorable disease characteristics in whom the duration of adjuvant trastuzumab can be significantly shortened, potentially avoiding cardiac complications in a curative disease setting. Longer follow up from the reported studies and data from an additional trial evaluating 12 months *versus* 6 months (PERSEPHONE, ClinicalTrials.gov identifier: NCT00712140) of adjuvant trastuzumab may help further assess subgroups of patients in whom shorter duration may be safely considered. Chemotherapy dosing with shorter durations of trastuzumab therapy also warrants further investigation as suggested by the SOLD study. Further, as the use of dual HER2-directed therapy increases, the optimal duration of combined therapies will need to be evaluated.

Treatment of small, node-negative disease: retrospective data

Historically, small (≤1 cm) HER2+ tumors without nodal involvement have been considered to have low risk for disease recurrence. As a result, patients with node-negative tumors ≤1cm in size were largely excluded from pivotal adjuvant trastuzumab trials, and patients with larger node-negative disease were underrepresented: 0% in NSABP B-31, 14.5% in N9831, and about a third each in BCIRG 006 and HERA.[6–8] However, recent evidence suggests that the biology of a tumor may be more important than its size at diagnosis, and sub-centimeter HER2+ tumors carry a higher risk of recurrence than their HER2-negative counterparts.[19–21]

A retrospective analysis of 965 patients with node-negative tumors, 1 cm or smaller, conducted at MD Anderson Cancer Center reported that 5-year distant recurrence-free survival was significantly worse in patients with HER2+ disease compared with HER2-negative disease (86.4% *versus* 97.2%; $p < 0.0001$).[19] Similarly, in a nationwide population-based study in Finland, 852 patients with node-negative breast cancers, 2 cm or smaller (including 49 T1a, 264 T1b, and 539 T1c tumors) from the Finnish Cancer Registry were included.[20] None of the patients with T1a tumors recurred, but patients with T1b grade 2 or 3 tumors had a significantly decreased 9-year distant DFS when the HER2 protein was overexpressed (67% *versus* 95%; $p = 0.003$). A third retrospective study evaluated 150 patients with node-negative HER2+ tumors, 1 cm or smaller, and compared outcomes to a matched, HER2-negative cohort.[21] After a median follow up of 4.6 years, HER2 overexpression was associated with worse DFS (HR 2.4; $p = 0.09$).

On the basis of these retrospective analyses, the benefit of adjuvant trastuzumab has been assessed in small, node-negative tumors. In the first retrospective analysis to report on the impact of trastuzumab in lower risk disease, 261 women with HER2+ node-negative, 2 cm or smaller tumors treated at Memorial Sloan Kettering Cancer Center were evaluated.[22] Overall, two cohorts of patients from the pre- and post-trastuzumab eras were compared ($N = 106$ and 155, respectively). The 3-year distant recurrence-free survival was significantly improved with administration of trastuzumab (100% *versus* 95%; $p = 0.007$). The two groups were balanced with respect to age, size of tumor, and hormone receptor status, but 97% of the trastuzumab cohort received chemotherapy compared with only 57% of patients in the no trastuzumab cohort.

A similar multicenter retrospective analysis was performed in 75 patients with node-negative HER2+ tumors, 1 cm or smaller to evaluate the efficacy of adjuvant trastuzumab in these patients.[23] Adjuvant chemotherapy was administered in 33 (44%) of patients. Anthracycline-based (A), taxane-based (T), and A/T combinations were chosen for 54%, 4% and 42%; respectively. Almost all of the patients who received chemotherapy also received adjuvant trastuzumab ($N = 31$; 41%). No recurrences occurred in patients who received trastuzumab, while three occurred in patients who did not receive trastuzumab or chemotherapy. Based on these data, the investigators concluded that patients with HER2+, node-negative disease with tumors 1 cm or smaller are at risk of

recurrence and should be treated with adjuvant trastuzumab.

A meta-analysis of patient-level data from five randomized, phase III adjuvant trastuzumab trials (NSABP B31, NCCTG N9831, HERA, PACS 04, FinHER; total $N = 4220$) confirmed that trastuzumab improved DFS and OS for patients with HER2+ tumors less than or equal to 2 cm in size.[24] The study also confirmed that trastuzumab was beneficial in both hormone receptor (HR)-positive and HR-negative disease with primary tumor less than or equal to 2 cm. In HR-positive disease, the recurrence rate after 8 years was 17.3% in women who received trastuzumab *versus* 24.3% in women who did not (HR 0.70; $p < 0.001$). Mortality was 7.8% in women who received trastuzumab *versus* 11.6% in women who did not (HR 0.68; $p = 0.005$). In HR-negative disease, the recurrence rate after 8 years was 24.0% in women who received trastuzumab *versus* 33.4% in women who did not (HR 0.70; $p < 0.001$). Mortality was 12.4% in women who received trastuzumab *versus* 21.2% in women who did not (HR 0.60; $p = 0.005$).

These retrospective analyses suggest that chemotherapy and HER2-directed therapy should be considered in all patients with small, node-negative HER2+ tumors due to their higher risk of recurrence. However, the chemotherapy backbone that is used is often influenced by potential toxicities given the overall smaller absolute benefit derived from treatment compared with patients with more locally advanced disease. Standard adjuvant regimens such as doxorubicin and cyclophosphamide followed by paclitaxel and trastuzumab (AC-TH) or docetaxel, carboplatin, and trastuzumab (TCH) may be considered too toxic in this setting.

Treatment of small, node-negative disease: prospective data

Recently, a prospective, single-arm, multicenter study, the Adjuvant Paclitaxel and Trastuzumab (APT) trial, evaluated a regimen of adjuvant paclitaxel and trastuzumab delivered weekly for 12 weeks in 410 patients with node-negative HER2+ tumors, 3 cm or smaller.[25] In the total study population, 2.2% of patients had tumors that measured 0.1 cm or less (T1mi), 49.5% of the patients had tumors that measured 1 cm or less (16.7% T1a and 30.5% T1b), 41.6% had tumors that measured between 1 cm and 2 cm (T1c), and 8.9% of the patients had tumors that measured between 2 cm and 3 cm (T2). The overall 3-year invasive DFS was 98.7% (95% CI 97.6–99.8). An updated 7-year follow up reported a DFS of 93.3%.[26] The 7-year DFS was 94.6% for HR-positive patients and 90.7% for HR-negative patients. The overall incidence of serious toxic events was low. During 12 weeks of combined therapy, 13 patients (3.2%) reported grade 3 neuropathy. No grade 4 neurotoxic effects were reported. Overall, two patients (0.5%) had grade 3 systolic dysfunction of the left ventricle, but both recovered after discontinuation of trastuzumab.

On the basis of this study, the regimen of adjuvant weekly paclitaxel and trastuzumab for 12 weeks has quickly become a widely accepted standard regimen for patients with small, node-negative HER2+ breast cancers. However, some controversies remain. It is unclear from these data whether there is a size threshold for initiating trastuzumab-based systemic therapy. Given that a higher percentage of patients with T1b tumors compared with T1a tumors were evaluated in this prospective and other retrospective analyses, the argument for systemic therapy is stronger in patients with T1b tumors, but the data also support therapy in patients with T1a tumors. Further, the most effective regimen and the size threshold and biologic risk profile for various regimens is unknown. Although the regimen of paclitaxel and trastuzumab had low incidence of recurrence in patients with small, node-negative HER2+ tumors, it has not been compared with other widely used regimens containing polychemotherapy or additional HER2-directed agents.

Another prospective, single-arm phase II study evaluated four cycles of docetaxel and cyclophosphamide with trastuzumab in 493 patients with early-stage HER2+ breast cancer. Of those, 391 (79.3%) had node-negative disease and 3-year DFS for these patients was 97.8% (95% CI 95.6–98.9).[27] Although cross-trial comparisons are discouraged, this 3-year DFS is very similar to that reported with paclitaxel and trastuzumab in the APT trial, implying a limited role for the addition of cyclophosphamide to a taxane in the management of small, node-negative HER2+ tumors. However, data are not available comparing the APT regimen with other chemotherapeutic and HER2-directed agents, and toxicity and

individual disease risk should also be considered when making treatment decisions.

Studies evaluating chemotherapy-free adjuvant regimens in this population are also ongoing. Results are awaited from the ATEMPT trial [ClinicalTrials.gov identifier: NCT01853748], which has completed accrual. The study randomly assigned women with stage I, HER2+ breast cancer in a 3:1 fashion to receive adjuvant ado-trastuzumab emtansine (T-DM1; Kadcyla®; Genentech, Inc.), an antibody-drug conjugate of trastuzumab, or the paclitaxel plus trastuzumab regimen used in the APT trial. This study was designed to compare clinically relevant toxicities between the two arms and to also examine DFS among those patients receiving T-DM1. Other studies of chemotherapy-free regimens are evaluating dual HER2-directed agents and are focused in the neoadjuvant space; they are detailed below.

Dual HER2-directed therapy

Despite the tangible effects of adjuvant trastuzumab therapy, about 30% of patients with HER2+ disease relapse.[28] Several additional HER2-directed agents have been developed and evaluated in combination with trastuzumab-based therapy with the goal of improving long-term cure rates. To expedite evaluation, these agents have first been evaluated in the neoadjuvant setting with assessment of pathologic complete response (pCR) rates as a potential surrogate for long-term efficacy. Overall, these agents have shown significant promise in the neoadjuvant setting with improvement in pCR rates, but these findings have not consistently translated into meaningful improvements in DFS and OS when evaluated in the adjuvant setting. There is ongoing debate regarding the optimal use of these agents.

Lapatinib

Lapatinib (Tykerb®, GlaxoSmithKline) is an orally bioavailable dual tyrosine kinase inhibitor of HER2 and epidermal growth factor receptor (EGFR). It was the first agent to be evaluated in combination with trastuzumab as dual HER2-directed therapy. Table 2 summarizes the neoadjuvant studies of combined lapatinib and trastuzumab. Overall, the combination of lapatinib plus trastuzumab with chemotherapy resulted in numerically higher pCR rates as compared with trastuzumab plus chemotherapy, but the difference in the pCR rates was statistically significant only in the NeoALTTO and the CHER-LOB trials.

Given the consistently improved pCR rates with the combination of trastuzumab and lapatinib across these trials, the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) trial was designed to evaluate the combination adjuvantly in 8381 patients with early breast cancer.[36] The study randomly enrolled patients in one of four arms: trastuzumab alone, trastuzumab plus concomitant lapatinib, sequential trastuzumab and lapatinib, or lapatinib alone. Therapy was started concurrently with or sequentially after chemotherapy and continued for 12 months. The lapatinib only arm was closed early due to futility to detect non-inferiority of lapatinib to trastuzumab, and the patients in this group were offered trastuzumab. After median follow up of 4.5 years, there was no significant improvement in DFS with concomitant trastuzumab and lapatinib (HR 0.84; 97.5% CI 0.70–1.02) or sequential trastuzumab followed by lapatinib (HR 0.96; 97.5% CI 0.80–1.15) compared with trastuzumab alone. The incidence of cardiac toxicity was low in all arms, occurring in 0.25–0.97% of patients, but there was increased overall toxicity in the combination arms, particularly diarrhea, rash, and hepatotoxicity.

Similarly, the NeoALTTO trial also evaluated survival of patients randomly allocated to receive neoadjuvant trastuzumab, lapatinib, or their combination.[30] The designated HER2-directed therapy was continued adjuvantly to complete 1 year. The study was not powered for this purpose, and event-free survival (EFS) and OS were secondary endpoints. The 3-year EFS (HR 0.78; 95% CI 0.47–1.28) and OS (HR 0.62; 95% CI 0.30–1.25) did not differ significantly between the combination group and the trastuzumab alone group. Again, the incidence of cardiac events was low across treatment groups, but the overall toxicity was increased in the combination arm.

In summary, dual HER2 inhibition with trastuzumab plus lapatinib does not offer significant advantage in DFS or OS over trastuzumab alone, and the combination is associated with greater toxicity

Table 2. Randomized trials evaluating neoadjuvant trastuzumab (H) and lapatinib (L) with chemotherapy in HER2+ breast cancer.

Study	Treatment arm	*N*	pCR (%)	*p*-value
NSABP B-41[29]	H	181	49.4	
	L	174	47.4	0.78
	H + L	174	60.2	0.056
NeoALTTO[30]	H	149	29.5	
	L	154	24.7	0.34
	H + L	152	51.3	0.0001
CALGB 40601[31]	H	120	46	
	L	67	32	
	H + L	118	56	0.13
TRIO-US B07[32]	H	34	47	
	L	36	25	0.14
	H + L	58	52	0.45
EORTC 10054[33]	H	53	52	
	L	23	36	
	H + L	52	56	
CHER-LOB[34]	H	36	25.0	
	L	39	26.3	
	H + L	46	46.7	0.019
Holmes and colleagues[35]	H	26	54	
	L	29	45	
	H + L	23	74	

HER2, human epidermal growth factor 2; HER2+, HER2-overexpressing; L, lapatinib; pCR, pathologic complete response; H, trastuzumab.

and cost. As a result, 1 year of trastuzumab remained the standard of care after trials of combined therapy with lapatinib.

Pertuzumab

Pertuzumab (Perjeta®; Genentech, Inc.) is a HER2-directed humanized monoclonal antibody with a distinct binding site than trastuzumab. Pertuzumab conferred OS benefit when combined with taxane-based chemotherapy and trastuzumab in the first line palliative setting in the CLEOPATRA study.[37] The addition of pertuzumab to taxane-based chemotherapy with trastuzumab in the preoperative setting was evaluated in in two phase II clinical trials (NeoSphere and TRYPHAENA) and resulted in significant improvement in pCR rates. The OS benefit in the metastatic setting together with the pCR improvements in the neoadjuvant setting

ultimately led to US FDA approval in 2013 for neoadjuvant administration in combination with trastuzumab and taxane-containing regimens for tumors greater than 2 cm in size or node-positive disease.[38,39]

The NeoSphere study was a randomized, multicenter, phase II trial that compared neoadjuvant docetaxel plus either trastuzumab, pertuzumab, or both trastuzumab and pertuzumab in women with early-stage, locally advanced, or inflammatory HER2+ breast cancer.[38] In a fourth arm, a chemotherapy-free regimen of pertuzumab and trastuzumab was administered. A total of 417 patients with HER2+ tumors 2 cm or larger in size were enrolled, and the primary endpoint was pCR. All patients were treated postoperatively with fluorouracil, epirubicin, and cyclophosphamide, and patients in the chemotherapy-free neoadjuvant arm also received postoperative docetaxel. The addition of pertuzumab to trastuzumab and docetaxel resulted in significantly higher pCR rate (45.8% *versus* 29.0%; $p = 0.014$). The addition of pertuzumab was also shown to be relatively well tolerated. The mean maximum decrease in LVEF measurement was low (4–5%) and was balanced across treatment groups. No significant change was detected when pertuzumab was added to trastuzumab. The study was not powered to demonstrate an EFS benefit, but an exploratory analysis at 5-year follow up showed a numerical trend in favor of the docetaxel/trastuzumab/pertuzumab arm compared with docetaxel/trastuzumab (84% *versus* 81%; HR 0.69; 95% CI 0.34–1.40).[40]

TRYPHAENA was a three-arm study enrolling 225 patients with HER2+ tumors 2 cm or larger.[39] It primarily aimed to evaluate the cardiac safety of three pertuzumab and trastuzumab-containing regimens. Overall, two of the three arms contained anthracycline-based chemotherapy while the third did not. pCR rates were similarly high among the three treatment arms (notably, 66.2% for docetaxel/carboplatin/trastuzumab/ pertuzumab and 57.3% for fluorouracil/epirubicin/cyclophosphamide followed by docetaxel/trastuzumab/ pertuzumab). No long-term data from this study are currently available, but the tested regimens appeared to be well tolerated from a cardiac perspective with only two patients overall experiencing symptomatic left ventricular systolic dysfunction.

The phase III GeparSepto study aimed to assess the non-inferiority of the pCR rate with neoadjuvant nanoparticle albumin-bound paclitaxel-based chemotherapy compared with a solvent-based paclitaxel regimen.[41] All patients with HER2+ disease in this study ($N = 396$) received both pertuzumab and trastuzumab.[42] Overall, the pCR rate for the HER2+ subset was 57.8%: 71% in the HER2+/HR-negative cohort and 49.7% in the HER2+/HR-positive cohort. LVEF decreases from baseline were uncommon (2% of patients overall), providing further evidence of the activity and tolerability of pertuzumab/trastuzumab-based therapy.

Similar to lapatinib, after improvements in pCR rates were seen with combined trastuzumab and pertuzumab-based therapy in the neoadjuvant setting, the combination was evaluated in the adjuvant setting to evaluate long-term efficacy. The Adjuvant Pertuzumab and Trastuzumab in Early Her2+ Breast Cancer (APHINITY) study was a phase III, randomized, double-blind, placebo-controlled trial evaluating the combination of chemotherapy and trastuzumab with or without pertuzumab in the adjuvant setting.[43] To date, it is the only study evaluating long-term invasive DFS with the combination. Overall, 4805 patients with HER2+ breast cancer patients with node-positive or high-risk, node-negative disease (tumor size greater than 1 cm, histologic or nuclear grade 3, negativity for estrogen and progesterone receptors, or age younger than 35 years) were randomly assigned to receive 12 months of either pertuzumab or placebo added to standard adjuvant chemotherapy plus 1 year of treatment with trastuzumab. The majority of patients had node-positive (63%) and HR-positive (64%) disease. The 3-year invasive DFS was 94.1% in the pertuzumab group compared with 93.2% in the placebo group ($p = 0.045$). In patients with node-positive disease, the 3-year invasive DFS was 92.0% in the pertuzumab group compared with 90.2% in the placebo group (HR 0.77; $p = 0.02$). In patients with node-negative disease, the 3-year invasive DFS was 97.5% in the pertuzumab group compared with 98.4% in the placebo group (HR 1.13; $p = 0.64$). Primary cardiac events were rare, occurring in 17 patients (0.7%) in the pertuzumab group and 8 patients (0.3%) in the placebo group. Grade 3 or higher diarrhea occurred almost exclusively during chemotherapy and was more frequent with pertuzumab than with placebo (9.8% *versus* 3.7%).

Thus, similar to lapatinib, the significant improvement in pCR after neoadjuvant administration of pertuzumab combined with trastuzumab-based therapy did not translate into major improvements in long-term outcomes when pertuzumab was added to adjuvant systemic therapy. However, unlike lapatinib, a small benefit was seen, particularly in node-positive patients. The incremental benefit comes at the cost of added toxicity, largely diarrhea. Further, pertuzumab is frequently used neoadjuvantly after its recent US FDA approval in this setting, and the incremental benefit of adjuvant use after neoadjuvant administration is unknown. However, based on the findings of the APHINITY study, pertuzumab was also US FDA-approved for use in the adjuvant setting concurrently with trastuzumab for 1 year.

Several studies have also evaluated chemotherapy-free regimens containing pertuzumab in the neoadjuvant setting. In the phase II I-SPY 2 study, 83 women with HER2+ breast cancer with tumors measuring 2.5 cm or larger were randomly assigned to receive either neoadjuvant T-DM1 plus pertuzumab (52 patients) or neoadjuvant trastuzumab and paclitaxel (31 patients) for 12 weeks.[44] All patients subsequently received four cycles of standard combination chemotherapy with doxorubicin and cyclophosphamide, followed by surgery. More women in the T-DM1 group (52%) compared with the control group (22%) reached the primary endpoint of estimated pCR. Separately, the study evaluated neoadjuvant paclitaxel in combination with trastuzumab and pertuzumab ($N = 44$) *versus* paclitaxel plus trastuzumab ($N = 31$) followed by four cycles of doxorubicin and cyclophosphamide, and reported improvement of pCR with the addition of pertuzumab (54% *versus* 22%).[45] Unfortunately, the trial was not designed to compared T-DM1 plus pertuzumab with paclitaxel/trastuzumab/pertuzumab, and therefore conclusions regarding the efficacy chemotherapy-free regimen containing pertuzumab remained unanswered.

The Adjuvant Dynamic marker-Adjusted Personalized Therapy (ADAPT) trial evaluated 12 weeks of several neoadjuvant chemotherapy-free regimens.[46,47] In 134 HER2+/HR-negative patients, 12 weeks of neoadjuvant trastuzumab and pertuzumab, with or without paclitaxel, was evaluated. The pCR rate was significantly higher with the addition of chemotherapy (90.5% *versus* 33.7%; $p < 0.001$).[47] Similarly, the randomized phase III KRISTINE study evaluated a neoadjuvant chemotherapy-free regimen (T-DM1 and pertuzumab) *versus* docetaxel/carboplatin/trastuzumab/pertuzumab in 444 patients with stage II–III HER2+ breast cancer.[48] Again, the pCR rate was higher in the chemotherapy-containing arm (55.7% *versus* 44.4%; $p = 0.0155$). The incidence of grade 3 or higher adverse events was also higher in the chemotherapy-containing arm (64% *versus* 13%). It is interesting to note that in both of these studies, a subset of patients was able to achieve pCR without administration of chemotherapy, and it is important to better identify these subsets in future studies to minimize toxicity in the right group of patients. Biomarker analysis is ongoing to better identify patients who might be more likely to achieve pCR without chemotherapy in the KRISTINE study. Results are also awaited from large, phase III studies of adjuvant T-DM1, with or without pertuzumab, which might further be able to characterize patients who may benefit equally from a chemotherapy-free HER2-directed regimen (KATHERINE, ClinicalTrials.gov identifier: NCT01772472 and KAITLIN, ClinicalTrials.gov identifier: NCT01966471).

Neratinib

Neratinib (Nerlynx®; Puma Biotechnology) is an irreversible small-molecule inhibitor of the ERBB/HER kinase family (EGFR, HER2, and HER4). Neratinib has shown promising activity in metastatic HER2+ breast cancer.[49] Therefore, it has also been evaluated in the neoadjuvant setting. In the I-SPY-2 study, 57 patients with HER2+ disease received neoadjuvant paclitaxel and oral neratinib for 12 weeks and 22 patients received neoadjuvant paclitaxel and trastuzumab for 12 weeks.[50] All patients subsequently received four cycles of standard combination chemotherapy with doxorubicin and cyclophosphamide, followed by surgery. The estimated rate of pCR was 39% in the neratinib group *versus* 23% in the trastuzumab group. Among patients with HER2+/HR-negative disease, the estimated pCR rate was 56% *versus* 33%, and among patients with HER2+/ HR-positive disease, the estimated pCR rate was 30% *versus* 17%. Unfortunately, the combination of trastuzumab and neratinib was not evaluated as dual HER2-directed therapy was not standard of care at the time of study design. There were more adverse events in the neratinib group compared with the trastuzumab group. Grade 3 or 4 diarrhea was

noted in 38% of patients in the neratinib group compared with 4% of patients in the trastuzumab group ($p < 0.001$). Several other hematologic and gastrointestinal adverse events were significantly higher in the neratinib group compared with the trastuzumab group, including grade 1 or 2 vomiting (40% *versus* 26%; $p = 0.045$), grade 1 or 2 diarrhea (96% *versus* 50%; $p < 0.001$), grade 1 or 2 abnormalities in the aspartate aminotransferase level (26% *versus* 6%; $p < 0.001$), and abnormalities in the alanine aminotransferase level of grade 1 or 2 (37% *versus* 12%; $p < 0.001$) or of grade 3 or 4 (11% *versus* 1%; $p = 0.009$). No cases of symptomatic CHF occurred during the trial.

Similarly, the NSABP FB-7 study was a phase II randomized trial evaluating neoadjuvant paclitaxel plus neratinib, trastuzumab, or the combination in 141 patients with stage IIB–IIIC HER2+ breast cancer.[51] The pCR rate was higher in patients receiving combination therapy (50.0%) compared with trastuzumab alone (38.1%). The effect was more pronounced in patients with HR-negative disease (73.7% *versus* 57.1%) compared with HR-positive disease (30.4% *versus* 29.6%). Again, toxicity including grade 3 diarrhea and transaminitis was more frequent in the combination arm.

Similar to lapatinib and trastuzumab, after improvements in pCR rates were seen with in the neoadjuvant setting, the combination of neratinib and trastuzumab was evaluated in the adjuvant setting to evaluate long-term efficacy. However, neratinib was evaluated in the extended adjuvant setting after completion of 12 months of trastuzumab. The neratinib after trastuzumab-based adjuvant therapy in patients with HER2+ breast cancer (ExteNET) is a multicenter, randomized, double-blind, placebo-controlled, phase III study evaluating DFS benefit with 1 year of adjuvant neratinib treatment after completion of 1 year of adjuvant trastuzumab therapy.[52] Overall, 2840 patient with HER2+ breast cancer with tumors 1 cm or larger who had completed neoadjuvant and adjuvant trastuzumab therapy up to 2 years before randomization were included. The study inclusion criteria were later modified to limit enrollment to patients with stage II–III disease who had completed trastuzumab therapy up to 1 year previously. Randomization was stratified by HR status, nodal status, and adjuvant trastuzumab regimen (sequential *versus* concurrent with chemotherapy). The 5-year invasive DFS rate was 90.2% in the neratinib group *versus* 87.7% in the placebo group (HR 0.73; $p = 0.0083$).[53] Prespecified subgroup analysis showed that neratinib provided greater benefit to patients with HER2+/HR-positive disease (DFS 91.2% *versus* 86.8%; HR 0.60; 95% CI 0.43–0.83) than those with HER2+/HR-negative disease (DFS 88.9% *versus* 88.8%; HR 0.95; 95% CI 0.66–1.35). The most common grade 3–4 adverse events in the neratinib group were diarrhea (grade 3, 40% and grade 4, <1% *versus* grade 3, 2% in the placebo group), vomiting (grade 3, 3% *versus* <1%), and nausea (grade 3, 2% *versus* <1%). Decreases in LVEF (⩾ grade 2) occurred in 19 (1%) patients in the neratinib group compared with 15 (1%) patients in the placebo group. OS data was not mature at the time of study reporting and is awaited. However, on the basis of this study, neratinib was granted US FDA approval for extended adjuvant use after completion of adjuvant trastuzumab therapy in July 2017.

Like pertuzumab, the addition of neratinib to trastuzumab-based therapy resulted in significant improvement in pCR when administered in the neoadjuvant setting and significant but modest improvement in DFS when administered in the adjuvant setting. Like pertuzumab, the addition of neratinib results in increased toxicity, largely diarrhea. Thus, it is increasingly important to identify patients who will benefit from additional HER2-directed agents to avoid increased toxicity in all patients, especially when considering up to 2 years of adjuvant therapy use.

Additionally, since pertuzumab gained US FDA approval for neoadjuvant and adjuvant use, it is frequently prescribed in these settings in high-risk HER2+ patients. However, neither adjuvant pertuzumab nor extended adjuvant neratinib have been extensively evaluated after administration of neoadjuvant pertuzumab, although some patients in the ExteNET study may have received preoperative pertuzumab. Thus, the efficacy and safety of using both neoadjuvant/adjuvant pertuzumab and extended adjuvant nertaninib combined with trastuzumab-based therapy is not well defined. In summary, the optimal timing and combination of dual HER-2 directed therapy in patients with high-risk disease is unknown and many questions remain unanswered.

Conclusions

There is an increasing need to risk stratify HER2+ breast cancer patients and evaluate HER2-directed therapy in a methodical manner. De-escalation of therapy with the potential to shorten the duration of adjuvant therapy, avoid chemotherapy, and minimize toxicity in patients with favorable disease is appealing to patients and physicians. On the other hand, escalation of therapy with the addition of novel HER2-directed agents and extended duration of therapy in patients at high risk of relapse can help improve long-term cure rates. Biomarker identification is necessary to better stratify patients by biological risk. Additional strategies, such as addition of immune checkpoint inhibition, are also entering the realm of HER2+ disease and need to be evaluated with biomarker correlation with the hope of identifying the ideal patient population for incorporation of new treatment strategies. Treatment of HER2+ breast cancer has overcome significant obstacles with the advent of HER-directed therapy in recent decades, but ongoing research and biomarker development is needed to continue progress in the field.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that there is no conflict of interest.

References

1. Slamon DJ, Godolphin W, Jones LA, *et al.* Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* 1989; 244: 707–712.
2. Kennecke H, Yerushalmi R, Woods R, *et al.* Metastatic behavior of breast cancer subtypes. *J Clin Oncol* 2010; 28: 3271–3277.
3. Haque R, Ahmed SA, Inzhakova G, *et al.* Impact of breast cancer subtypes and treatment on survival: an analysis spanning two decades. *Cancer Epidemiol Biomarkers Prev* 2012; 21:1848–1855.
4. Zurawska U, Baribeau DA, Giilck S, *et al.* Outcomes of HER2-positive early-stage breast cancer in the trastuzumab era: a population-based study of Canadian patients. *Curr Oncol* 2013; 20: e539–e545.
5. Baselga J, Tripathy D, Mendelsohn J, *et al.* Phase II study of weekly intravenous recombinant humanized anti-p185HER2 monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer. *J Clin Oncol* 1996; 14: 737–744.
6. Perez EA, Romond EH, Suman VJ, *et al.* Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. *J Clin Oncol* 2014; 32: 3744–3752.
7. 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.
8. Slamon D, Eiermann W, Robert N, *et al.* Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011; 365: 1273–1283.
9. 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.
10. Spielmann M, Roche 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.
11. Moja L, Tagliabue L, Balduzzi S, *et al.* Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev* 2012; 18: CD006243.
12. Cameron D, Piccart-Gebhart MJ, Gelber RD, *et al.* 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet* 2017; 389: 1195–1205.
13. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, *et al.* 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. *Lancet* 2013; 382: 1021–1028.
14. Pivot X, Romieu G, Debled M, *et al.* 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. *Lancet Oncol* 2013; 14: 741–748.
15. Mavroudis D, Saloustros E, Malamos N, *et al.* Six versus 12 months of adjuvant trastuzumab in combination with dose-dense chemotherapy for women with HER2-positive breast cancer: a multicenter randomized study by the Hellenic Oncology Research Group (HORG). *Ann Oncol* 2015; 26: 1333–1340.

16. Schneider BP, O'Neill A, Shen F, *et al*. Pilot trial of paclitaxel-trastuzumab adjuvant therapy for early stage breast cancer: a trial of the ECOG-ACRIN cancer research group (E2198). *Br J Cancer* 2015; 113: 1651–1657.

17. Conte P, Bisagni G, Frassoldati A, *et al*. 9 weeks vs 1 year adjuvant trastuzumab in combination with chemotherapy: results of the phase III multicentric Italian study Short-HER. *J Clin Oncol* 2017; 35(15 Suppl.): abstract 501.

18. Joensuu H, Fraser J, Wildiers H, *et al*. *A randomized phase III study of adjuvant trastuzumab for a duration of 9 weeks versus 1 year, combined with adjuvant taxane-anthracycline chemotherapy, for early HER2-positive breast cancer (the SOLD study)*. *Paper presented at the San Antonio Breast Cancer Symposium*, December 5–9, 2017; San Antonio, TX. Abstract GS3–04.

19. Gonzalez-Angulo AM, Litton JK, Broglio KR, *et al*. High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. *J Clin Oncol* 2009; 27: 5700–5706.

20. Joensuu H, Isola J, Lundin M, *et al*. Amplification of erbB2 and erbB2 expression are superior to estrogen receptor status as risk factors for distant recurrence in pT1N0M0 breast cancer: a nationwide population-based study. *Clin Cancer Res* 2003; 9: 923–930.

21. Curigliano G, Viale G, Bagnardi V, *et al*. Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node-negative breast cancer. *J Clin Oncol* 2009; 27: 5693–5699.

22. McArthur HL, Mahoney KM, Morris PG, *et al*. Adjuvant trastuzumab with chemotherapy is effective in women with small, node-negative, HER2-positive breast cancer. *Cancer* 2011; 117: 5461–5468.

23. Rodrigues M, Wassermann J, Albiges-Sauvin L, *et al*. Treatment of node-negative infra-centimetric HER2+ invasive breast carcinomas: a joint AERIO/REMAGUS study. *J Clin Oncol* 2009; 27(Suppl. 15): abstract 517.

24. O'Sullivan C, Bradbury I, Campbell C, *et al*. Efficacy of adjuvant trastuzumab (T) compared with no T for patients (pts) with HER2-positive breast cancer and tumors = 2cm: a meta-analysis of the randomized trastuzumab trials. *J Clin Oncol* 2014; 32(Suppl. 15): abstract 508.

25. Tolaney SM, Barry WT, Dang CT, *et al*. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *N Engl J Med* 2015; 372: 134–141.

26. Tolaney S, Barry W, Guo H, *et al*. Seven-year (yr) follow-up of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC). *J Clin Oncol* 2017; 35(Suppl. 15): abstract 511.

27. Jones SE, Collea R, Paul D, *et al*. Adjuvant docetaxel and cyclophosphamide plus trastuzumab in patients with HER2-amplified early stage breast cancer: a single-group, open-label, phase 2 study. *Lancet Oncol* 2013; 14: 1121–1128.

28. Hess KR and Esteva FJ. Effect of HER2 status on distant recurrence in early stage breast cancer. *Breast Cancer Res Treat* 2013; 137: 449–455.

29. Robidoux A, Tang G, Rastogi P, *et al*. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial. *Lancet Oncol* 2013; 14: 1183–1192.

30. Baselga J, Bradbury I, Eidtmann H, *et al*. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. *Lancet* 2012; 379: 633–640.

31. Carey LA, Berry DA, Cirrincione CT, *et al*. Molecular heterogeneity and response to neoadjuvant human epidermal growth factor receptor 2 targeting in CALGB 40601, a randomized phase III trial of paclitaxel plus trastuzumab with or without lapatinib. *J Clin Oncol* 2016; 34: 542–549.

32. Hurvitz S, Miller J, Dichmann R, *et al*. Final analysis of a phase II 3-arm randomized trial of neoadjuvant trastuzumab or lapatinib or the combination of trastuzumab and lapatinib, followed by six cycles of docetaxel and carboplatin with trastuzumab and/or lapatinib in patients with HER2+ breast cancer (TRIO-US B07). *Cancer Res* 2014; 73(Suppl. 24): abstract S1–02.

33. Bonnefoi H, Jacot W, Saghatchian M, *et al*. Neoadjuvant treatment with docetaxel plus lapatinib, trastuzumab, or both followed by an anthracycline-based chemotherapy in HER2-positive breast cancer: results of the randomised phase II EORTC 10054 study. *Ann Oncol* 2015; 26: 325–332.

34. Guarneri V, Frassoldati A, Bottini A, *et al*. Preoperative chemotherapy plus trastuzumab, lapatinib, or both in human epidermal growth factor receptor 2-positive operable breast cancer: results of the randomized phase II CHER-LOB study. *J Clin Oncol* 2012; 30: 1989–1995.

35. Holmes FA, Espina V, Liotta LA, *et al*. Pathologic complete response after preoperative anti-HER2 therapy correlates with alterations in PTEN, FOXO, phosphorylated Stat5, and autophagy protein signaling. *BMC Res Notes* 2013; 6: 507.

36. Piccart-Gebhart M, Holmes E, Baselga J, *et al.* Adjuvant lapatinib and trastuzumab for early human epidermal growth factor receptor 2-positive breast cancer: results from the randomized phase III adjuvant lapatinib and/or trastuzumab treatment optimization trial. *J Clin Oncol* 2016; 34: 1034–1042.

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

38. Gianni L, Pienkowski T, Im YH, *et al.* Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012; 13: 25–32.

39. Schneeweiss A, Chia S, Hickish T, *et al.* Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol* 2013; 24: 2278–2284.

40. Gianni L, Pienkowski T, Im YH, *et al.* 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol* 2016; 17: 791–800.

41. Untch M, Jackisch C, Schneeweiss A, *et al.* Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto-GBG 69): a randomised, phase 3 trial. *Lancet Oncol* 2016; 17: 345–356.

42. Loibl S, Jackisch C, Schneeweiss A, *et al.* Dual HER2-blockade with pertuzumab and trastuzumab in HER2-positive early breast cancer: a subanalysis of data from the randomized phase III GeparSepto trial. *Ann Oncol* 2017; 28: 497–504.

43. von Minckwitz G, Procter M, de Azambuja E, *et al.* Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med* 2017; 377: 122–131.

44. DeMichele A, Moulder S, Buxton M, *et al.* Efficacy of T-DM1+pertuzumab over standard therapy for HER2+ breast cancer: results from the neoadjuvant I-SPY 2 TRIAL. *Cancer Res* 2016; 76(Suppl. 14): abstract CT042.

45. Buxton M, DeMichele A, Chia S, *et al.* Efficacy of pertuzumab/trastuzumab/paclitaxel over standard trastuzumab/paclitaxel therapy for HER2+ breast cancer: results from the neoadjuvant I-SPY 2 TRIAL. *Cancer Res* 2016; 76(Suppl. 14): abstract CT106.s

46. Harbeck N, Gluz O, Christgen M, *et al. Final analysis ocf WSG-ADAPT HER2+/HR+ phase II trial: efficacy, safety, and predictive markers for 12-weeks of neoadjuvant TDM1 with or without endocrine therapy versus trastuzumab+endocrine therapy in HER2-positive hormone-receptor-positive early breast cancer.* Paper presented at the 38th Annual CTRC-AACR San Antonio Breast Cancer Symposium, December 8–12, 2015; San Antonio, TX. Abstract S5–03.

47. Nitz U, Gluz O, Christgen M, *et al.* Final analysis of WSG-ADAPT HER2+/HR- trial: efficacy, safety, and predictive markers for 12-weeks of neoadjuvant dual blockade with trastuzumab + pertuzumab ± weekly paclitaxel in HER2+/HR- early breast cancer (EBC). *J Clin Oncol* 2016; 34(Suppl. 15): abstract 518.

48. Hurvitz S, Martin M, Symmans W, *et al.* Pathologic complete response rates after neoadjuvant trastuzumab emtansine (T-DM1) + pertuzumab vs. docetaxel + carboplatin + trastuzumab + pertuzumab (TCH+P) treatment in patients with HER2-positive (HER2+) early breast cancer (KRISTINE/TRIO-021). *J Clin Oncol* 2016; 34: abstract 500.

49. Chow LW, Xu B, Gupta S, *et al.* Combination neratinib (HKI-272) and paclitaxel therapy in patients with HER2-positive metastatic breast cancer. *Br J Cancer* 2013; 108: 1985–1993.

50. Park JW, Liu MC, Yee D, *et al.* Adaptive randomization of neratinib in early breast cancer. *N Engl J Med* 2016; 375: 11–22.

51. Jacobs S, Robidoux A and Garcia J. A phase II randomized trial evaluating neoadjuvant therapy with weekly paclitaxel (P) plus neratinib (N) or trastuzumab (T) or neratinib and trastuzumab (N+T) followed by doxorubicin and cyclophosphamide (AC) with postoperative T in women with locally advanced HER2-positive breast cancer. *Cancer Res* 2015; 76(Suppl. 4): abstract PD5–04.

52. Chan A, Delaloge S, Holmes FA, *et al.* Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2016; 17: 367–377.

53. Martin M, Holmes FA, Ejlertsen B, *et al.* Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2017; 18: 1688–1700.