



Recent Advances and Optimal Management of HER2-Positive Early-Stage Breast Cancer

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Abstract

With the introduction of anthracycline-based regimens, 5-year survival rates have significantly improved in patients with early-stage breast cancer. With the addition of trastuzumab, a monoclonal antibody targeting the Human Epidermal Growth Factor Receptor-2 (HER2), improvements in overall survival have been observed among patients with advanced HER2-positive disease. Subsequently, lapatinib, an orally bio available small molecule dual HER2- and EGFR/HER1-specific tyrosine kinase inhibitor, received FDA approval in combination with capecitabine for patients with advanced HER2+ breast cancer. Then pertuzumab in 2012 and ado-trastuzumab emtansine in 2013 were approved in the US and elsewhere based on evidence showing an improvement in survival outcomes in patients with mostly trastuzumab naïve or trastuzumab-exposed metastatic disease. The FDA also approved 1 year of extended adjuvant neratinib after chemotherapy and a year of trastuzumab for HER2-positive breast cancer on the basis of the ExteNET trial. The clinical benefit demonstrated by those drugs in advanced disease has triggered several adjuvant and neoadjuvant trials testing them in combination with chemotherapy, but also without conventional chemotherapy, using single or dual HER2-targeting drugs. In this article, we review the current data on the therapeutic management of HER2-positive early-stage breast cancer in the adjuvant and neoadjuvant setting. We also review the data the efficacy and safety of anthracycline-based and non-anthracycline-based adjuvant chemotherapy regimens combined with trastuzumab, and optimum chemotherapy regimens in small HER2-positive tumors.

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Received Date: 21 Mar 2019

Accepted Date: 03 Apr 2019

Published Date: 18 Apr 2019

Citation:

Batoo S, Bayraktar S, Al-Hattab E, Basu S, Okuno S, Gluck S. Recent Advances and Optimal Management of HER2-Positive Early-Stage Breast Cancer. *World J Breast Cancer Res*. 2019; 2(1): 1012.

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Introduction

Breast cancer remains one of the leading causes of cancer-related death worldwide [1]. Although chemotherapy has improved outcomes for patients, the marginal benefits achieved with cytotoxic agents seem to have reached a plateau. Fortunately, technological advances have enabled characterization of the molecular subtypes of breast cancer and this in turn has facilitated the development of molecularly targeted therapeutics for this disease [2,3]. One subtype that has been identified is distinguished by amplification of the gene encoding the Human Epidermal Growth Factor Receptor 2 (HER2). This subtype accounts for approximately 20% to 30% of invasive breast cancers, and until the discovery of effective anti-HER2 therapies (first of which is trastuzumab), was associated with reduced Disease-Free Survival (DFS), increased risk of metastases and shorter Overall Survival (OS) [4,5]. By 2005, the natural history of this breast cancer subtype in the adjuvant setting was forever changed with the release of the findings from adjuvant trials combining trastuzumab with chemotherapy, concomitantly or sequentially.

HER2 is a member of the cErbB family of Receptor Tyrosine Kinases (RTKs), which include HER1 (Epidermal Growth Factor Receptor [EGFR]), HER3, and HER4. HER2-mediated signal transduction is believed to depend largely on heterodimerization with other family members [5]. Trastuzumab is a humanized monoclonal antibody targeted against the extracellular portion of HER2. This is the first HER2-targeted agent to be approved by the United States Food and Drug Administration (FDA) for the treatment of both early stage and metastatic HER2-overexpressing (HER2+) breast cancer [6,7]. Subsequently, lapatinib, an orally bioavailable small molecule dual HER2- and EGFR/HER1-specific Tyrosine Kinase Inhibitor (TKI), received FDA approval in combination with capecitabine for patients with advanced HER2+ breast cancer [8]. Then pertuzumab in 2012 and ado-trastuzumab emtansine in 2013 were approved in the US and elsewhere based on evidence showing an improvement in survival outcomes in patients with mostly trastuzumab

Table 1: Initial adjuvant trastuzumab trials.

Study Name	Population included	No. of patients	Comparison	Median follow-up	DFS (5 years)	OS (5 years)	Drop LVEF
Trastuzumab							
NCCTG N9831 [13]	LN+ or high risk LN (-)	1087	AC → T vs	72 mo	71.8%	88.4%	0
		949	AC → T → H (52 w) vs		80.1%	89.7%	7%
		954	AC → TH (H then 40 wk more)		84.4%	91.9%	3.6
HERA [29]	LN+ or high risk LN (-)	1552	Std QT → H (52 w) vs	96 mo	75.9%	86.9%	7.2%
		1553	Std QT → H(40 w) vs		76.5%	88.7%	4.1%
		1697	Std QT → Observation		70%	84.5%	0.9%
BCIRG006 [16]	LN+ or high risk LN (-)	1073	AC → docetaxel vs	65 mo	75%	87%	11.2%
		1074	AC → Docetaxel+H vs		84%	92%	18.6%
		1075	TCH		81%	91%	9.4%
PACS04 [75]	LN+	260	FE100C or ED75 → Obser vs	62 mo	77.9%	96%	14.2%
		268	FE100C or ED75 → H		80.9%	95%	35.4%
FINHER [30]	LN+ or high risk LN (-)	58	Docetaxel → FEC vs	62 mo	74.1%	82%	10.5% (QT only)
		58	Vinorelbine → FEC vs		72%	82.8%	6.8% (QT+H)
		54	Docetaxel+H → FEC vs		92.5%	94.4%	
		61	Vinorelbine+H → FEC		75.2%	88.4%	
PHARE [26]	HER2+ early breast cancer	1690	Std QT → H (26 wk) vs	42.5 mo	91.1%	96.1%	5.7% (both)
		1690	Std QT → H (52 wk)		93.8%	94.5%	1.9% (both)

Abbreviations: LN: Lymph Nodes; AC → T: Adriamycin Cyclophosphamide Paclitaxel; FEC: 5-FU Epirubicin Cyclophosphamide; ED: Epirubicin Docetaxel; Std QT: Standard Chemotherapy; OS: Overall Survival; DFS: Disease Free Survival; LVEF: Left Ventricular Ejection Fraction

naïve or trastuzumab-exposed metastatic disease [9,10]. The FDA also approved 1 year of extended adjuvant neratinib (Nerlynx) after chemotherapy and a year of trastuzumab for HER2-positive breast cancer on the basis of the ExteNET trial [11]. The clinical benefit demonstrated by those drugs in advanced disease has triggered several adjuvant and neoadjuvant trials testing them in combination with chemotherapy, but also without conventional chemotherapy, using single or dual HER2-targeting drugs. In this article, we review the current data on the therapeutic management of HER2-positive early-stage breast cancer in the adjuvant and neoadjuvant setting.

Defining HER2 Positive Breast Cancer

A key first step in appropriately deciding on the use of HER2-targeted therapy is the accurate determination of HER2 over expression either by Immunohistochemistry (IHC) or Fluorescence *In Situ* Hybridization (FISH). The current American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines, updated in 2013, define HER2 positivity as 3+ on IHC (defined as uniform intense membrane staining of >10% of invasive tumor cells) or amplified on FISH (a HER2: Chromosome Enumeration Probe [CEP] 17 ratio of >2.0, or <2.0 plus average HER2 copy number >6 signals/cell) [12]. Although a detailed discussion of HER2 testing is beyond the scope of this chapter, we would like to note that if a patient's HER2 expression is ultimately deemed to be equivocal on both IHC and FISH, the oncologist can still consider HER2-targeted therapy, based on the patient's history, prognosis, and comorbidities.

Anti-HER-2 Therapy for Early Stage Breast Cancer

In this section we summarize the recent published results of the relevant phase III and some phase II clinical trials that constitute the theoretical framework to support our daily practice. We subdivide this

section according to the 2 clinical settings: adjuvant and neoadjuvant.

Recent advances in the adjuvant setting

Concomitant versus sequential chemotherapy/trastuzumab: While initially designed as 2 separate trials, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 and North Central Cancer Treatment Group (NCCTG) N9831 trials were jointly analyzed in 2005 due to their similar eligibility criteria and to allow an earlier evaluation of clinical outcomes. Both studies had a similar patient population, though N9831 also included women with high-risk node-negative disease defined as tumors ≥ 2 cm and positive for hormone receptors or tumors larger than 1 cm with negative hormone receptors. The NSABP B-31 compared four cycles of doxorubicin and Cyclophosphamide (AC) followed by four cycles of paclitaxel (AC-T) every three weeks to the same regimen plus trastuzumab given for 52 weeks starting concurrently with paclitaxel (AC-TH). The NCCTG N9831 randomized patients to receive four cycles of AC followed by weekly paclitaxel for 12 cycles with or without trastuzumab administered concurrently or sequentially to paclitaxel, for 52 wk (AC-T-H vs AC-TH). In a joint analysis that included patients similarly treated in the control (AC-T) and concomitant (AC-TH) arms of N9831 and of the NSABP B-31 trials, a significant improvement in DFS (HR 0.52, p<0.001) and a reduction of death by 39% (OS, HR 0.61, p<0.001) was observed with the addition of trastuzumab starting with paclitaxel versus just chemotherapy [13]. The efficacy of concurrent vs. sequential administration of trastuzumab showed a trend toward improvement in DFS in the concurrent arm; however, sequential was still better than placebo (P<0.001).

Buzdar et al., [14] examined the long-term outcomes associated with 2 different approaches to administering trastuzumab with neoadjuvant chemotherapy in patients with HER2-positive breast cancer. ACOSOG (American College of Surgeons Oncology Group) Z1041 (Alliance) was a Phase 3 trial conducted at 36 centers in the

continental United States and Puerto Rico. In this trial, women 18 years or older with invasive operable HER2-positive breast cancer were randomized to arm 1 received 500 mg/m² of fluorouracil, 75 mg/m² of epirubicin, and 500 mg/m² of Cyclophosphamide (FEC) every 3 weeks for 12 weeks followed by the combination of 80 mg/m² of paclitaxel and 2 mg/kg (except initial dose of 4 mg/kg) of trastuzumab weekly for 12 weeks. Patients randomized to arm 2 received the same combination of paclitaxel with trastuzumab weekly for 12 weeks followed by FEC every 3 weeks with weekly trastuzumab for 12 weeks. Across a median follow-up of 5.1 years, PCR, DFS, and OS did not differ with respect to sequential or concurrent administration of FEC with trastuzumab. Therefore, in current clinical practice, concurrent administration of trastuzumab with anthracyclines is avoided due to lack of additional benefit and concerns of cardiotoxicity. Published results from adjuvant trials in concomitant and sequential combination with anthracycline and non-anthracycline chemotherapy regimens are described in Table 1.

Concerns about cardiotoxicity: Cardiotoxicity is the most important adverse effect derived from treatment with trastuzumab, which is worse when combined with anthracyclines. Therefore, there has been a special interest in studying anthracycline-free regimens in order to minimize the cardiotoxicity risk [15]. The BCIRG 006 study was designed to provide information on this matter. Patients received AC followed by docetaxel (AC → T), AC followed by docetaxel with one year of trastuzumab (AC → TH), or docetaxel plus carboplatin and trastuzumab followed by trastuzumab to complete one year of therapy (TCH) [16]. After 65 months follow up, DFS was significantly improved with the addition of trastuzumab to chemotherapy (AC → T: 75%, AC → TH: 84%, and TCH 81%; HR for AC-TH was 0.64 (p<0.001) and for TCH was 0.75 (p=0.04) with a significant improvement in OS (AC → T: 87% vs AC → TH: 92%; HR=0.63, p<0.001), and TCH 91% (HR=0.77, p=0.038). Additionally, the incidence of cardiac toxicity was five times more with ACTH (2%) compared with TCH (0.4%). Reductions in LVEF, over 10% from basal measurements, were more frequently associated with AC → TH than with TCH (18.6 vs 9.4%; P<0.001). As well, the rate of symptomatic congestive heart failure favored treatment with TCH (P<0.001). Despite the apparent numerical survival advantage of the AC → TH over TCH, the BCIRG 006 trial was not powered to compare the two trastuzumab-containing arms; and more importantly, during additional follow-up, there was not a statistically significant difference between the two trastuzumab-containing regimens (P =0.21). The results of this trial not only confirmed the importance of trastuzumab for HER2-positive breast cancer, but it also greatly increased interest in the use of non-anthracycline-trastuzumab-base regimen, TCH, for adjuvant therapy.

Afterwards, several studies have evaluated concurrent administration of anthracycline-based chemotherapy and trastuzumab in the neoadjuvant setting [17-19]. In contrast to previous reports, trastuzumab plus anthracycline-based Neoadjuvant Systemic Therapy (NST) was both effective and well tolerated. Overall, the cardiotoxicity incidence in the neoadjuvant and adjuvant settings ranged from none-observed to 10.5%; and 2.0% to 3.3%, respectively [17,20-23].

In the MD Anderson Cancer Center (MDACC) trial, patients with HER2-positive breast cancer received paclitaxel followed by FEC75, with or without concurrent trastuzumab [17]. The PCR rate increased from 26% to 65% (P=0.02) with trastuzumab. An expansion cohort in the experimental arm (n=22) continued to show high rates of pCR

(54.5%) without significant cardiac toxicity [25]. In the Gepar Quattro trial concurrent administration of trastuzumab with epirubicin yielded persistent decrease in LVEF to less than 50% in only one patient [19]. In this study, although the patients who received TCH had more baseline cardiac comorbidities and cardiac risk factors, there were no differences in the baseline LVEF or magnitude of decrease in the LVEF after NST.

Another retrospective study conducted at MDACC evaluated the efficacy and safety profile of sequential paclitaxel and trastuzumab and FEC75 in combination with trastuzumab (PH-FECH) or TCH. Patients who received PH-FECH were 1.45 times more likely to have a pCR (OR: 1.45; 95% CI: 1.06 to 1.98; P=0.02) [24]. At a median follow-up of 26.8 months, there were 28 recurrences and 15 deaths. Three-year RFS rates were 93% and 71% (P<0.001), and 3-year OS rates were 96% and 86% (P=0.008) for patients who received PH-FECH and TCH, respectively. Patients who received PH-FECH had a lower risk of recurrence (HR: 0.27; 95% CI: 0.12 to 0.60; P=0.001) and death (HR: 0.37; 95% CI: 0.12 to 1.13; P=0.08) than those treated with TCH. Moreover, there were no significant differences in cardiac toxicity with respect to NST regimen received. Nonetheless, the treatment benefits need to be weighed against the risk of cardiotoxicity with optimal cardiac monitoring applied.

Duration of adjuvant trastuzumab: Adjuvant trastuzumab is recommended to be administered for 1 year and in part concomitantly with chemotherapy. The choice of this duration was arbitrary in the trials that established the current standard 12-month duration [25]. While the optimal duration remains unknown, 6 months of adjuvant trastuzumab did not lead to noninferior survival outcomes compared with 1-year administration in randomized trials, although the results tended to favor the longer duration, and 2-year administration was not superior to 1 year of administration [26-28].

HERA trial which was first reported at the 2005 Annual meeting of the American Society of Clinical Oncology tested adding one or two years of trastuzumab after completion of various standard adjuvant chemotherapy regimens [29]. HERA randomly assigned 5102 patients to begin adjuvant trastuzumab versus no adjuvant trastuzumab after chemotherapy (median time from diagnosis, 8 months). Patients with HER2-positive disease were eligible if node-positive or if node-negative disease and tumor >1 cm (T1c). At a median follow up of 4 years, one year of adjuvant trastuzumab led to a 24% reduction in recurrence (HR=0.76, p<0.0001). However, partly due to the significant cross-over (65%) from the observation arm to trastuzumab after the first results released, the OS benefit from trastuzumab in HERA became apparent when evaluated after 4 years (HR=0.85, p=0.11). A recent update after a median follow-up of 8 years confirmed the DFS (HR=0.76, p<0.0001) and OS benefit (HR=0.76, p=0.0005) from one year of trastuzumab. However, there was no incremental benefit from a longer duration of trastuzumab (two years) and more cardiac events were observed.

There is also a special interest in investigating whether treatment duration could be shortened due to concerns about cardiotoxicity. The results from SOLD, Short-HER, and PERSEPHONE trials were eagerly awaited with the expectation that they will confirm the FinHer data for the efficacy of short duration trastuzumab therapy [30]. FinHER investigators compared nine weeks of trastuzumab plus docetaxel and FEC with the same regimen followed by 1 year of trastuzumab therapy in the SOLD study [31]. Noninferiority of the 9-week treatment could not be demonstrated for DFS (HR: 1.39; 90%

Table 2: Selected clinical trials in the neoadjuvant setting for HER-2 positive breast cancer.

Study Name	Neoadjuvant chemotherapy	No. of patients	pCR%	Comments
Trastuzumab				
NOAH trial [18]	A+T → T → CMF vs A+T → T → CMF+H	117 HER2+ vs 118 HER2+	22% vs 43%	Not originally designed to test the efficacy of neoadjuvant trastuzumab use
Z1041 trial [76]	FEC → TH vs T+H → FEC+H	138 vs 142	56.5% vs 54.2%	Concurrent use of trastuzumab with anthracyclines is not better
HannaH trial [77]	Doc+H (SQ) → FEC+H vs Doc+H (IV) → FEC+H	260 vs 263	45.4% vs 40.7%	Trastuzumab can be administered subcutaneously
Lapatinib(L) +/- H				
GeparQuinto Trial [46]	ECH → TH vs. ECL → TL	309 vs 311	30.3% vs 22.7%	Lapatinib is less effective than trastuzumab
NeoALLTO trial [48]	TH vs TL vs THL	149 vs 154 vs 152	29.5% vs 24.7% vs 51.3%	Suggested that combination trastuzumab and lapatinib could be quite effective
NSABP B-41 Trial [49]	AC → TH vs AC → TL vs AC → THL	181 vs 174 vs 174	52.5% vs 53.2% vs 62%	Trastuzumab and lapatinib no better. All patients received anthracyclines
Pertuzumab				
Neosphere trial [53]	Do+H vs Do+P+H vs Do+P vs P+H	107 vs 107 vs 107 vs 96	29% vs 45.8% vs 24% vs 16.8%	Combination P+H results in better pCR and improved survival rates
Tryphaena trial [54]	FEC+HP → Do+HP vs FEC → Do+HP vs TCH+P	223 patients in total	56% vs 57% vs 64%	TCH+P is an active combination with left ventricular dysfunction occurring in 4% of patients

Abbreviations: T: Paclitaxel; H: Herceptin (trastuzumab); L: Lapatinib; F: 5-FU; E: Epirubicin; C: Cyclophosphamide; A: Adriamycin; M: Methotrexate; Do: Docetaxel; TC: Docetaxel-Cyclophosphamide

CI: 1.12 to 1.72). DFS and OS did not differ substantially between the groups. Thirty-six (3%) and 21 (2%) patients in the 1-year and the 9-week groups, respectively, had cardiac failure; the left ventricle ejection fraction was better maintained in the 9-week group.

The Short-HER, phase 3 multicentric Italian study, randomly assigned 1,254 patients with HER2-positive early breast cancer to either 9 weeks or 1 year of treatment with trastuzumab, with both groups also receiving chemotherapy. First results after a median follow-up of 6 years published in the Journal of Clinical Oncology in 2017 showed the short course was not noninferior but was associated with a reduction in the rate of severe cardiac toxicity. In the newest analysis reported at ESMO in 2018, researchers looked at whether there are subgroups of patients where a shorter course of trastuzumab may be noninferior to a longer course. They identified three prognostic groups: Low-risk (Pathologic Tumor size [pT]<2 cm and N0); Intermediate-risk (pT<2 cm and any N category); High-risk (pT>2 cm and N4+) patient population. Results showed that patients with low- and intermediate-risk had similar 5-year disease-free survival with a 9-week course of trastuzumab (88%) as with 1 year (89%; HR=1.02, 95% CI=0.78 to 1.33), but their risk of cardiac events was nearly three times lower (4.5% vs 12.8%, relative risk=2.88, 95% CI=1.85 to 4.47). Women at low and intermediate risk of relapse accounted for 89% of patients in the study. However, the study was underpowered because of difficulties in recruiting patients in a reasonable time, so noninferiority could not be claimed based on these results [32].

The PHARE trial and PERSEPHONE trials are noninferiority studies designed to evaluate adjuvant treatment length with trastuzumab for 6 months compared to one year [26]. In the PHARE trial, a total of 1691 patients were treated with trastuzumab for 12 months and 1693 for 6 months after receiving at least 4 cycles of adjuvant chemotherapy. Patients were stratified according to sequential or concurrent treatment and Estrogen-Receptor (ER) status. The primary endpoint was DFS and with a median follow-up of 42.5 months, 2-year DFS was 93.8% for the 12-month group and 91.1% for the 6-month group (HR=1.28; 95% CI, 1.05 to 1.56), concluding that 6 months of treatment did not reach the noninferiority criteria. However, cardiac events were more common in the 12-month treatment arm (5.7% vs 1.9%; P<0.001) and further

analysis is still required. The PERSEPHONE trial, by the Hellenic Oncology Research Group reported the results at ASCO 2018 annual meeting and established those 6 months of trastuzumab is not inferior to 12 months in 4-year survival without invasive or local regional recurrence or distant metastases. Nonetheless, on the basis of the current available evidence, PERSEPHONE is the only one that concludes noninferiority and it is the biggest of the trials. The results of the SOLD trial suggest longer trastuzumab therapy improves DFS but neither distant metastases nor OS. The PHARE results suggest that reducing trastuzumab duration is dangerous for women with a higher risk of metastases. On the basis of the current available evidence and until we get more data, 12 months of adjuvant treatment with trastuzumab remains the standard of care.

Adjuvant therapy for tumors smaller than 1 cm: The data on the role of trastuzumab in small node-negative tumors remain scarce. Retrospective institutional series from MDACC and Milan suggest small HER2-positive tumors prognostically have a poor long-term outcome when compared to their HER2-negative counterparts [33,34]. Subgroup analyses from several randomized trials have shown a benefit with adjuvant trastuzumab irrespective of tumor size, though its actual absolute benefit in small stage 1 tumors (like those with T1a up to 0.5 cm disease) remains unknown [35]. A large, retrospective European study compared the outcomes of patients T1a/b node-negative tumors who either received adjuvant trastuzumab-based chemotherapy or did not, and demonstrated a statistically significant 2% to 3% improvement in recurrence-free survival on the trastuzumab arm after a multivariate analysis [36]. Hormone Receptor (HR) status also proved to be noteworthy as bigger differences were seen in patients with high-risk features such as HR-negative or positive lymphatic vascular invasion. Therefore, it stands to reason that we could treat these tumors with adjuvant trastuzumab, especially if they are T1b or have other poor risk features.

A single arm multicenter trial included breast cancer patients with node-negative tumors up to 3 cm [37]. Patients received weekly treatment with paclitaxel and trastuzumab for 12 weeks, followed by 9 months of trastuzumab monotherapy. The primary end point was survival free from invasive disease. The 3-year rate of survival free from invasive disease was 98.7% (95% CI, 97.6 to 99.8). The results

suggest a low risk of cancer recurrence (less than 2% at 3 years) with a regimen in which the rate of serious toxic effects was low (with an incidence of heart failure that was only 0.5%). At ASCO 2017 annual meeting, they provided an updated analysis with 7-years DFS [38]. The 7-years DFS was 93.3% (95% CI: 90.4 to 96.2); 7-years DFS for ER+ pts was 94.6% (95% CI: 91.8 to 97.5) and for ER- pts was 90.7% (95% CI: 84.6 to 97.2). 7-years Recurrence Free Interval (RFI) was 97.5% (95% CI: 95.9 to 99.1); 7-year Breast Cancer Specific Survival (BCSS) is 98.6% (95% CI: 97.0 to 100); and 7-year OS was 95.0% (95% CI: 92.4 to 97.7). These data suggest that TH as adjuvant therapy for node-negative HER2+ breast cancer is associated with few recurrences and only 4 distant recurrences with longer follow-up. Absent randomized data, this regimen might become an option for patients with small node-negative HER2-positive disease in clinical scenarios where there is concern about the potential toxicity from established regimens.

Changing landscape of HER2-positive adjuvant therapy: Several drugs have recently been studied for adjuvant therapy of HER2-positive breast cancer: pertuzumab, ado-trastuzumab emtansine (formerly known as T-DM1), and tyrosine kinase inhibitor neratinib.

Data from metastatic trials of pertuzumab and ado-trastuzumab emtansine have led to adjuvant trials one of which is the APHINITY trial which compares standard chemotherapy (nonanthracycline or anthracycline-based) plus trastuzumab with or without pertuzumab [39,40]. The results of the APHINITY trial were presented at ASCO 2017 annual meeting [41]. In this phase III clinical trial of 4,805 women with HER2-positive breast cancer, the addition of pertuzumab to trastuzumab lowered the chance of developing invasive breast cancer by 19% compared to trastuzumab alone. At a median follow-up of almost 4 years, 171 patients (7.1%) in the pertuzumab group had developed invasive breast cancer, compared to 210 patients (8.7%) in the placebo group. At 3 years, an estimated 94.1% of patients in the pertuzumab group were free of invasive breast cancer, compared to 93.2% of patients in the placebo group. The rates of serious side effects were low and similar in both groups heart failure or heart-related death occurred in 0.7% of patients in the pertuzumab group and in 0.3% of patients in the placebo group. Severe diarrhea was more common with pertuzumab, occurring in 9.8% of patients, compared to 3.7% of those who received placebo. On December 20, 2017, the Food and Drug Administration (FDA) granted regular approval to pertuzumab for use in combination with trastuzumab and chemotherapy as adjuvant treatment of patients with HER2-positive early breast cancer. In our opinion, given that the absolute benefit from adding pertuzumab was modest, we should consider using it primarily in women with the highest risk or recurrence those with node-positive and hormone receptor negative breast cancer.

The phase III KATHERINE clinical trial compared the use of ado-trastuzumab emtansine (T-DM1) vs trastuzumab as adjuvant therapy in patients with HER2-positive early-stage breast cancer with residual invasive disease after receiving neoadjuvant chemotherapy and trastuzumab [42]. Patients were randomized either to 14 cycles of ado-trastuzumab emtansine versus 14 cycles of trastuzumab. The results were presented at 2018 San Antonio Breast Cancer Symposium and simultaneously published in The New England Journal of Medicine. The estimated percentage of patients who were free of invasive disease at 3 years was 88.3% in the T-DM1 group and 77.0% in the trastuzumab group. Invasive disease free survival was significantly higher in the T-DM1 group than in the trastuzumab

group (HR: 0.50; 95% CI: 0.39 to 0.64; $P < 0.001$). Distant recurrence as the first invasive-disease event occurred in 10.5% of patients in the T-DM1 group and 15.9% of those in the trastuzumab group. The safety data were consistent with the known safety profile of T-DM1, with more adverse events associated with T-DM1 than with trastuzumab alone. These results will likely be practice-changing and may form the foundation of a new standard of care in patients with residual invasive breast cancer following neoadjuvant therapy.

Evidence supporting activity of the oral Tyrosine Kinase Inhibitor (TKI) lapatinib in the preclinical and metastatic settings provided strong rationale for the evaluation of lapatinib alone and in combination with trastuzumab in the adjuvant/neoadjuvant settings [43-45]. Lapatinib has been evaluated in combination with chemotherapy in at least seven neoadjuvant clinical trials [46-51]. PCR rates with lapatinib were significantly inferior to trastuzumab in two trials making the head-to-head comparison. Although all of these studies demonstrated numeric improvements in PCR with dual HER2 blockade, only two of these studies demonstrated a statistically notable improvement in PCR [48,51]. The toxicity associated with lapatinib resulted in lower rates of completion of HER2-targeted therapy in several of these trials. Given its unfavorable safety profile and lack of demonstrated notable benefit in two large adjuvant studies and multiple smaller neoadjuvant studies, lapatinib is not considered appropriate therapy in the early-stage setting. That said, another TKI, neratinib, has shown promise in the adjuvant setting.

Neratinib is an irreversible pan-HER TKI with clinical efficacy in trastuzumab pre-treated HER2-positive (HER2+) metastatic breast cancer. ExteNET study examined sequential therapy with 1 year of trastuzumab followed by 1 year of neratinib in stage 2c to 3c HER2+ breast cancer patients whom had received the last dose of trastuzumab within the last 1 year before enrollment in the clinical trial [52]. In this study, eligible women with stage 1c to 3c (modified to stage 2c to 3c in February, 2010) operable breast cancer, who had completed neoadjuvant and adjuvant chemotherapy plus trastuzumab with no evidence of disease recurrence or metastatic disease at study entry were randomly assigned according to hormone receptor status (ER-positive vs ER-negative), nodal status (0 vs 1 to 3 vs or ≥ 4 positive nodes), and trastuzumab adjuvant regimen (given sequentially vs concurrently with chemotherapy), then to receive 1 year of oral neratinib 240 mg/day or matching placebo. After a median follow-up of 5.2 years (IQR 2.1 to 5.3), patients in the neratinib group had significantly fewer invasive DFS events than those in the placebo group (116 vs 163 events; stratified hazard ratio 0.73, 95% CI: 0.57 to 0.92, $p = 0.0083$). The 5-years invasive disease-free survival was 90.2% (95% CI: 88.3 to 91.8) in the neratinib group and 87.7% (85.7 to 89.4) in the placebo group. Without diarrhea prophylaxis, the most common grade 3 to 4 adverse events in the neratinib group, compared with the placebo group, were diarrhea (561 [40%] grade 3 and one [$<1\%$] grade 4 with neratinib vs 23 [2%] grade 3 with placebo), vomiting (grade 3: 47 [3%] vs five [$<1\%$]), and nausea (grade 3: 26 [2%] vs two [$<1\%$]). Treatment-emergent serious adverse events occurred in 103 (7%) women in the neratinib group and 85 (6%) women in the placebo group. No evidence of increased risk of long-term toxicity or long-term adverse consequences of neratinib-associated diarrhoea was identified with neratinib compared with placebo. This study led to FDA approval of 1 year of extended adjuvant therapy with neratinib, on July 17, 2017, to follow adjuvant trastuzumab-based therapy.

Table 3: Ongoing adjuvant/neoadjuvant clinical trials for HER-2 positive breast cancer.

Study Name	Clinicaltrials.gov identifier	Treatment Arms	End point
KAITLIN	NCT01966471	AC or FEC → T-DM1/pertuzumab	iDFS
		AC or FEC → taxane/trastuzumab/pertuzumab	
BOLD-1	NCT02625441	Taxane/trastuzumab/pertuzumab 3x → FEC 3x	iDFS
		Taxane/trastuzumab 3x → FEC 3x → trastuzumab for 1 year	
ATEMPT	NCT01853748	T-DM1 for 1 year vs. paclitaxel/trastuzumab for 12 weeks → trastuzumab for 1 year (stage 1 disease)	DFS
NeoPhoebe	NCT01816594	Trastuzumab/paclitaxel/buparlisib vs. trastuzumab/paclitaxel/placebo	pCR
GeparOcto	NCT02125344	PMCb vs. ETC	pCR
		If HER2+, also pertuzumab/trastuzumab	
Predic-HER2	NCT02568839	Docetaxel/sq trastuzumab/pertuzumab vs TDM1	pCR
		Therapy arms switched if no response after cycle 2	
TEAL	NCT02073487	T-DM1/lapatinib → nanoparticle albumin-bound paclitaxel vs. trastuzumab/pertuzumab/paclitaxel	pCR

Abbreviations: DFS: Disease-Free Survival; ETC: Epirubicin/Paclitaxel/Cyclophosphamide; FEC: Fluorouracil/Epirubicin/Cyclophosphamide; iDFS: Invasive Disease-Free Survival; pCR: Pathologic Complete Response; PMCb: Paclitaxel/Nonpegylated Liposomal Doxorubicin/Carboplatin; sq: Subcutaneous

Neoadjuvant setting

In the last decade, researchers have modernized trial design by using Pathologic Complete Response (PCR) as an endpoint, since PCR correlates to long-term outcome and is quicker than waiting, possibly for years, for data about recurrences or deaths. In that sense, researchers have been examining the impact of HER2-targeted agents on PCR in the neoadjuvant setting.

The results of the NOAH trial, a randomized phase III study, helped to give further enthusiasm to this approach [18]. The study was originally designed to compare neoadjuvant chemotherapy plus trastuzumab followed by 1-year trastuzumab to neoadjuvant chemotherapy alone in patients with locally advanced or inflammatory HER-2 positive tumors. From 238 patients originally randomized to neoadjuvant treatment with or without trastuzumab, the addition of anti-HER-2 therapy improved the PCR from 22% to 43% ($P < 0.001$). Trastuzumab also resulted in a 40% risk reduction of recurrence, progression or death when compared to chemotherapy alone.

In an attempt to improve the PCR, researchers started exploring the use of other anti-HER2 blockers alone or in combination with trastuzumab in the neoadjuvant setting. Four trials looked at combinations of trastuzumab with lapatinib or pertuzumab. The NeoALLTO international, randomized, phase III study compared the use of single agent lapatinib, trastuzumab or the combination of both in addition to paclitaxel for neoadjuvant treatment [48]. Interestingly, the combination arm showed a remarkable improvement in PCR almost duplicating the two other single agent anti-HER2 arms (51% vs 29.5% trastuzumab vs 24.7% lapatinib; $P < 0.001$). As expected the addition of lapatinib resulted in worse side effects, mainly related to diarrhea and rash. However, in contraposition to the NeoALLTO, the NSABP B-41 study showed no statistical difference with the combination of trastuzumab and lapatinib when compared to either drugs used as single agent [49]. In conclusion, single agent lapatinib either as a single agent or in combination with trastuzumab seems to be ineffective and more toxic in the adjuvant setting.

FDA has granted accelerated approval to pertuzumab for its use before surgery when combined with trastuzumab and chemotherapy. This decision was based on the results of two phase II clinical trials, NeoSphere and TRYPHAENA. The NeoSphere trial was a multicenter, open-label, randomized phase II study where 417 patients were randomized to one of four possible arms: Pertuzumab

(P) + Trastuzumab (T) + Docetaxel (Do); T+Do; P+Do or P+T alone [53]. All eligible patients then underwent surgical resection followed by adjuvant FEC and 1-year of trastuzumab. The three-drug arm (P+T+Do) showed the maximal rate of PCR (46%) and was statistically different from T+Do (29%; $P = 0.014$). Pertuzumab + docetaxel resulted in a 24% PCR and the chemotherapy-free arm had a 17% PCR. In the T+Do and P+T+Do arms, respectively, 3-years survival rates were 85% and 92% for DFS (HR: 0.60, 95% CI: 0.28 to 1.27), and 86% and 90% for PFS (HR: 0.69, 95% CI: 0.34 to 1.40). Importantly, the addition of pertuzumab did not produce any significant drop in the cardiac function 4% to 5% EF drop across all groups). An additional neoadjuvant phase II trial (TRYPHAENA) was conducted in 225 patients with HER2-positive, locally advanced, operable, or inflammatory breast cancer and was designed primarily to assess the cardiac safety of pertuzumab in different neoadjuvant regimens [54]. Patients were randomly allocated to receive one of three neoadjuvant regimens prior to surgery as follows: three cycles of FEC followed by three cycles of docetaxel, all in combination with pertuzumab and trastuzumab; three cycles of FEC alone followed by three cycles of docetaxel and trastuzumab in combination with pertuzumab; or six cycles of docetaxel, carboplatin, and Trastuzumab (TCH) in combination with pertuzumab. Based on the assessment of pCR, all three regimens seemed active. The reported pCR ranged from 57.3% to 66.2%. The highest pCR (66.2%) was observed in patients who received pertuzumab, trastuzumab, docetaxel, and carboplatin chemotherapy.

In metastatic breast cancer, nab-paclitaxel has been shown to significantly increase PFS compared with solvent-based paclitaxel. The GeparSepto (GBG 69) trial assessed whether weekly nab-paclitaxel could increase the proportion of patients achieving PCR compared with weekly solvent-based paclitaxel, both followed by epirubicin plus cyclophosphamide as neoadjuvant treatment [55]. PCR rate was higher in the nab-paclitaxel group [38%, 95% CI: 35 to 42] than in the solvent-based paclitaxel group [29%, 25 to 33]; $p = 0.00065$). Interestingly, subgroup analysis showed different sensitivity to nab-paclitaxel across the breast cancer subgroups. In patients with HER2-positive tumors, 123 (62%) of 199 achieved a PCR with nab-paclitaxel compared with 106 (54%) of 197 with solvent-based paclitaxel ($p = 0.13$). Patients with the biological subtype of HER2-negative/ER-positive disease had a pCR in 43 (16%) of 268 cases for nab-paclitaxel versus 32 (12%) of 266 for solvent-based

paclitaxel ($p=0.23$); in HER2-positive/ER-positive disease in 79(56%) of 140 cases versus 74(50%) of 149 cases ($p=0.30$); and with HER2-positive/ER-negative in 44(75%) of 59 cases versus 32(67%) of 48 cases, respectively ($p=0.49$) (Table 2).

- Based on the recent updates in the management of HER2-positive early-stage breast cancer, we propose the treatment algorithm below: HER-2 positive disease optimal duration of adjuvant anti-HER-2 therapy is one year.
- All anti-HER2 regimens include trastuzumab every 3 weeks following chemotherapy to complete a full year of trastuzumab including what was given with chemotherapy.
- Preferred regimens.
- Doxorubicin and Cyclophosphamide (AC) followed by paclitaxel plus trastuzumab, AC given every 2 weeks or 3 weeks times 4 cycles and paclitaxel given as dose-dense every 2 weeks times 4 cycles or weekly for 12 cycles.
- Docetaxel, carboplatin, Trastuzumab (TCH).
- For stage II or higher, consider addition of pertuzumab with chemotherapy portion of regimen or for the entire year with the trastuzumab.
- Other regimens (may also consider other regimens listed in NCCN guidelines).
- Weekly paclitaxel plus trastuzumab (for low-risk disease, such as stage I).
- Consider neratinib extended adjuvant treatment for higher risk (Stage II or higher), given within 1 year following completion of trastuzumab plus or minus pertuzumab maintenance.
- Consider substituting 1 year of T-DM1 therapy for adjuvant trastuzumab in patients with residual disease after receiving neoadjuvant chemotherapy.

Optimizing therapy for hormone receptor coexpressing disease: At least half of HER2-positive breast cancer coexpresses one or both hormone receptors, and this coexpression may serve as a pathway for resistance to HER2-targeted therapy. This does not mean that HER2-targeted therapy is inactive in hormone receptor-positive breast cancer. In fact, analyses from the AC/trastuzumab and AC/T arms of the BCIRG-00651 and B-3153 trials show that the HRs for DFS are very similar for hormone receptor-positive (HR, 0.65 and 0.61 for BCIRG-006 and B-31, respectively) and hormone receptor-negative (HR, 0.64 and 0.62 for BCIRG-006 and B-31, respectively) disease. This also holds true for OS. Moreover, subset analysis of the HERA study at 11 years of follow-up also demonstrated that the presence of ER may indicate more indolent, luminal-like tumor behavior as patients with hormone receptor-negative disease had earlier recurrences [28].

Further evidence supporting the notion that disease behavior differs based on hormone receptor expression comes from neoadjuvant clinical trials, which have consistently shown that PCR rates are lower for hormone receptor-positive, HER2-positive breast cancer than for hormone receptor-negative disease [48,49,56,57]. That said, the longer follow-up of the NeoSphere trial indicates that patients with hormone receptor coexpression have numerically higher PFS compared with tumors lacking hormone receptors (5-year PFS for patients who achieved PCR: 90% if hormone receptor positive,

84% if hormone receptor negative; 5-year PFS for patients who did not achieve PCR: 80% if hormone receptor positive, 72% if hormone receptor negative) [58]. Thus, patients with hormone receptor-positive tumors may do better in the long run. Intriguing biomarker analyses from HERA suggest that although ER-positive tumors with a high level of HER2 amplification (by FISH ratio) derive clear benefit from trastuzumab, those with a low level of HER2 amplification may not receive benefit from trastuzumab-based therapy [59].

Several clinical trials aimed to evaluate co-targeting hormone receptor and HER2. The first of these, TBCRC-006, evaluated 12 weeks of neoadjuvant lapatinib plus trastuzumab (with letrozole for ER-positive tumors) [60]. The pCR (breast) in HER2-positive/hormone receptor-positive tumors were 21% in this proof of concept study, indicating that a relatively well-tolerated chemotherapy-free regimen might be highly effective for patients if accurate biomarkers could be identified.

Trastuzumab emtansine has also been evaluated in the neoadjuvant setting. The WGS-ADAPT study compared four cycles of T-DM1, either alone or in combination with endocrine therapy, to trastuzumab plus endocrine therapy for patients with hormone receptor-positive, HER2-positive patients [61]. This relatively short course of T-DM1 was associated with an impressive pCR rate (breast and lymph nodes) of 41%, which was considerably higher than that achieved with trastuzumab plus endocrine therapy. The KRISTINE trial found an inferior pCR rate to T-DM1 plus pertuzumab compared with TCHP, which suggests that T-DM1 is inferior to a free cytotoxic plus trastuzumab [62]. A pCR was achieved by 44% of patients in the T-DM1 plus pertuzumab group and 56% of patients in the TCHP group ($p=0.016$). Although neither of these studies has changed the standard of care, these results should encourage the investigation of less toxic regimens for selected patient populations.

In December 2016, the results of the NSABP B-52 trial were presented. This study was designed to evaluate whether the addition of an aromatase inhibitor to standard chemotherapy plus HER2-targeted therapy (TCHP) would improve pCR rates for hormone receptor-positive/HER2-positive breast cancer, and to also test whether endocrine therapy would be antagonistic in combination with chemotherapy [63]. Although the addition of endocrine therapy to TCHP did not lead to a statistically notable improvement in pCR (41% for TCHP vs. 46% for TCHP plus endocrine therapy), it did not appear to be antagonistic, leaving room for future studies to test less toxic chemotherapy regimens concurrently with hormone therapy approaches. Several ongoing adjuvant and neoadjuvant clinical trials are listed in Table 3.

Resistance to trastuzumab and lapatinib: Although HER2-targeted therapies have had a significant impact on patient outcomes, resistance to these agents is common. In clinical trials, 74% of patients with HER2+ metastatic breast cancer did not have a tumor response to first-line trastuzumab monotherapy and 50% did not respond to trastuzumab in combination with chemotherapy [6,64]. These examples illustrate the problem that inherent (de novo) resistance to HER2-targeted agents poses for effective treatment of HER2+ BC. Moreover, only approximately one-quarter of patients with HER2+ metastatic breast cancer who were previously treated with trastuzumab achieved a response with lapatinib plus capecitabine [8]. These limitations have led to efforts to better understand the molecular determinants of resistance to these agents in order to better select patients who are most likely to benefit from specific

therapies, and to develop new agents that can overcome resistance. Herein, we discuss some of the new strategies that are currently being investigated in metastatic breast cancer which will likely appear in some adjuvant and neoadjuvant clinical trials.

Afinib: Afatinib is an oral small molecule that irreversibly inhibits HER-1, 2 and 4 [65]. In the phase II study, 4 of 35 patients with trastuzumab-resistant metastatic breast cancer showed partial responses [65]. Adverse events included diarrhea and rash. However, the recently published LUX-Breast 1 trial was a negative trial for afatinib [66]. This was a phase III study comparing vinorelbine plus trastuzumab or afatinib plus vinorelbine for metastatic patients who progressed to one chemotherapy regimen containing trastuzumab. Recruitment was stopped on April 26, 2013, after a benefit-risk assessment by the independent data monitoring committee was unfavorable for the afatinib group. Patients on afatinib plus vinorelbine had to switch to trastuzumab plus vinorelbine.

MM-111: MM-11 is a bi-specific monoclonal antibody that reversibly targets the HER-2 and -3 heterodimer. A phase I to II study is currently evaluating its efficacy as a single agent in HER-2 positive advanced breast cancer patients who have received prior trastuzumab or lapatinib therapy (clinical trials.gov, NCT00911898). Another phase I trial is studying MM-111 plus trastuzumab in HER2-positive, heregulin-positive, advanced and refractory breast cancer (clinical trials.gov, NCT01097460).

Trastuzumab deruxtecan: Trastuzumab deruxtecan (ds-8201a), a HER2-targeting antibody-drug conjugate, demonstrated significant clinical activity in heavily pretreated patients with HER2-expressing metastatic breast cancers who previously received a do-trastuzumab emtansine (T-DM1). Whereas T-DM1 is a tubulin-targeting chemotherapy, trastuzumab deruxtecan is a topoisomerase 1 inhibitor. It is highly potent, with a drug-to-antibody ratio of 7.8, compared with 3.5 for T-DM1.

In an ongoing 2-part phase I study, the ORR to trastuzumab deruxtecan in 57 evaluable patients with HER2-positive tumors was 61.4%. In the HER2-positive cohort, the ORR was 56.4% (22 of 39) among those with ER-positive disease and 75.0% (12 of 16) in those with ER-negative disease. Notably, the ORR was 62.5% among the 50 patients in this cohort with prior pertuzumab treatment.

The Disease Control Rate (DCR) was 94.7% overall in the HER2-positive subset: 92.3% in the ER-positive group, 100.0% in the ER-negative group, and 94.0% among those who had received prior pertuzumab. Median PFS was not yet reached in the ER-positive group and was 10.3 months in the ER-negative group. Median PFS was 10.3 months in the HER2-positive cohort who had received prior pertuzumab, reported Shanu Modi, MD, at the 2017 San Antonio Breast Cancer Symposium. The main toxicity was grade 1/2 gastrointestinal toxicity. Grade 1/2 nausea was reported by 67.9%. Grade 3 and 4 events were hematologic in nature. The rates of grade 3/4 anemia were 8.7% in the HER2-positive group and 0.9% in the HER2-low group. The rates of grade 3 decreases in neutrophil count and white blood cell count were each 10.4%. Across the study, 5 patients (4.3%) had a grade 4 decrease in neutrophil count.

In August 2017, trastuzumab deruxtecan received an FDA breakthrough therapy designation for the treatment of patients with HER2-positive, locally advanced, or metastatic breast cancer who have been treated with trastuzumab and pertuzumab and have disease progression after T-DM1. An ongoing pivotal phase II trial

called DESTINY-Breast 01 is examining the efficacy and safety of trastuzumab deruxtecan in patients with HER2-positive unresectable and/or metastatic breast cancer who are resistant or refractory to T-DM1.

HER2-targeted vaccines: Cancer vaccines designed to induce specific anti-HER-2 immunity are being investigated. Different strategies include protein-based vaccines, plasmid DNA-based vaccines, and vaccines that deliver HER-2 in a viral vector. HER-2 peptide-based vaccines have been tested in patients with metastatic HER-2 positive breast cancer [67]. Patients immunized developed delayed-type hypersensitivity reactions and strong CD8+ cell responses specific for HER-2 [68]. A dendritic cell based vaccine was also tested in a small group of patients with stage IV breast cancer [69]. One patient showed a partial response and three had stable disease for ≥ 12 months. Using a different strategy, cell-based GM-CSF secreting vaccines were tested in combination with trastuzumab [70].

Other exploratory anti-HER-2 blocking strategies: Ongoing trials combining anti-HER-2 agents with drugs blocking other signaling pathways hold promise of further improvement. An auspicious approach seems to be the combination of anti-HER-2 therapy with Insulin Growth Factor Receptor (IGFR-1) blocking agents. IGFR-1 inhibition has been shown to restore sensitivity to trastuzumab in animal models [71]. Another potential combination is the dual blockade of HER-2 and SRC which was recently shown to work as a central node downstream of multiple trastuzumab-resistance mechanisms [72]. Finally, HER-3 is another strong activator of PI3K/Akt signaling pathway that has been demonstrated to be up-regulated after HER-2 blockade [73]. Although still in early phases of development, Rb disruption strategies and the use of CDK-4/6 inhibitors may be clinically useful [74]. Future studies of HER2-positive patients will be challenging because of the small window to improve outcome beyond what is achievable today [75].

Conclusion

In summary, in just over a decade, the management of early-stage HER2-positive breast cancer has changed drastically because of the development of highly effective biologically targeted therapy. Previously much feared HER2-positive breast cancer became the most treatable and patients' prospects are much more promising than they used to be. The therapeutic options available to the patient in both the neoadjuvant and adjuvant settings are now nearly countless, making the choice of optimal therapy somewhat difficult at times. Our pursuit to provide patients with the safest and most effective therapies for their particular disease requires us to design carefully selected clinical trials with attention toward the discovery of molecular drivers of disease biology and markers of response to therapy.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87-108.
2. Perou CM, Sørli T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. *Nature*. 2000;406(6797):747-52.
3. Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci U S A*. 2001;98(19):10869-74.
4. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification

- of the HER-2/neu oncogene. *Science*. 1987;235(4785):177-82.
5. Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. *Nat Rev Mol Cell Biol*. 2001;2(2):127-37.
 6. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001;344(11):783-92.
 7. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005;353(16):1673-84.
 8. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med*. 2006;355(26):2733-43.
 9. Ryan Q, Ibrahim A, Cohen MH, Johnson J, Ko CW, Sridhara R, et al. FDA drug approval summary: lapatinib in combination with capecitabine for previously treated metastatic breast cancer that overexpresses HER-2. *Oncologist*. 2008;13(10):1114-9.
 10. Blumenthal GM, Scher NS, Cortazar P, Chattopadhyay S, Tang S, Song P, et al. First FDA approval of dual anti-HER2 regimen: pertuzumab in combination with trastuzumab and docetaxel for HER2-positive metastatic breast cancer. *Clin Cancer Res*. 2013;19(18):4911-6.
 11. Chan A, Delaloge S, Holmes FA, Moy B, Iwata H, Harvey VJ, et al. Neratinib after adjuvant chemotherapy and trastuzumab in HER2-positive early breast cancer: Primary analysis at 2 years of a phase 3, randomized, placebo-controlled trial (ExteNET). *J Clin Oncol*. 2015;33(15):508.
 12. Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol*. 2013;31(31):3997-4013.
 13. Perez EA, Romond EH, Suman VJ, Jeong JH, Davidson NE, Geyer CE Jr, 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(25):3366-73.
 14. Buzdar AU, Suman VJ, Meric-Bernstam F, Leitch AM, Ellis MJ, Boughey JC, et al. Disease-Free and Overall Survival Among Patients With Operable HER2-Positive Breast Cancer Treated With Sequential vs Concurrent Chemotherapy: The ACOSOG Z1041 (Alliance) Randomized Clinical Trial. *JAMA Oncol*. 2018.
 15. Castrellon AB, Gluck S. Adjuvant therapy for HER2 positive breast cancer: are anthracyclines still necessary?. *Clin Adv Hematol Oncol*. 2008;6(9):666-72.
 16. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011;365(14):1273-83.
 17. Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas ES, Theriault RL, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. *J Clin Oncol*. 2005;23(16):3676-85.
 18. Gianni L, Eiermann W, Semiglazov V, Manikhas A, Lluch A, Tjulandini S, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet*. 2010;375(9712):377-84.
 19. Untch M, Rezai M, Loibl S, Fasching PA, Huober J, Tesch H, et al. Neoadjuvant treatment with trastuzumab in HER2-positive breast cancer: results from the GeparQuattro study. *J Clin Oncol*. 2010;28(12):2024-31.
 20. Chumsri S, Jeter S, Jacobs LK, Nassar H, Armstrong DK, Emens LA, et al. Pathologic complete response to preoperative sequential doxorubicin/cyclophosphamide and single-agent taxane with or without trastuzumab in stage II/III HER2-positive breast cancer. *Clin Breast Cancer*. 2010;10(1):40-5.
 21. Robert N, Leyland-Jones B, Asmar L, Belt R, Ilegbodu D, Loesch D, 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(18):2786-92.
 22. Perez EA. First results from the phase III ALTTO trial (BIG 2-06; NCCTG [Alliance] N063D) comparing one year of anti-HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T?L), or their combination (T+L) in the adjuvant treatment of HER2-positive early breast cancer (EBC). *J Clin Oncol*. 2014;32(18):5.
 23. Perez EA, Suman VJ, Davidson NE, Sledge GW, Kaufman PA, Hudis CA, 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(8):1231-8.
 24. Bayraktar S, Gonzalez-Angulo AM, Lei X, Buzdar AU, Valero V, Melhem-Bertrandt A, et al. Efficacy of neoadjuvant therapy with trastuzumab concurrent with anthracycline- and nonanthracycline-based regimens for HER2-positive breast cancer. *Cancer*. 2012;118(9):2385-93.
 25. Pinto AC, Ades F, de Azambuja E, Piccart-Gebhart M. Trastuzumab for patients with HER2 positive breast cancer: delivery, duration and combination therapies. *Breast*. 2013;22(2):S152-5.
 26. Pivot X, Romieu G, Debled M, Pierga JY, Kerbrat P, Bachelot T, 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(8):741-8.
 27. Mavroudis D, Saloustros E, Malamos N, Kakolyris S, Boukovinas I, Papakotoulas P, 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(7):1333-40.
 28. Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, 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(10075):1195-205.
 29. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, de Azambuja E, Procter M, Suter TM, 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(9897):1021-8.
 30. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, Alanko T, Kataja V, Asola R, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N Engl J Med*. 2006;354(8):809-20.
 31. Joensuu H, Fraser J, Wildiers H, Huovinen R, Auvinen P, Utriainen M, et al. Effect of Adjuvant Trastuzumab for a Duration of 9 Weeks vs 1 Year With Concomitant Chemotherapy for Early Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: The SOLD Randomized Clinical Trial. *JAMA Oncol*. 2018;4(9):1199-206.
 32. Contel PF, Guarneri V, Bisagni G, Piacentini F, Brandes AA, Cavanna L, et al. 9 weeks versus 1 year adjuvant trastuzumab for HER2+ early breast cancer: whom a shorter trastuzumab administration may have a favourable risk/benefit ratio. *Ann Oncol*. 2018;29(8).
 33. Gonzalez-Angulo AM, Litton JK, Broglio KR, Meric-Bernstam F, Rakhit R, Cardoso F, 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(34):5700-6.

34. Curigliano G, Viale G, Bagnardi V, Fumagalli L, Locatelli M, Rotmensz N, et al. Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node-negative breast cancer. *J Clin Oncol.* 2009;27(34):5693-9.
35. Banerjee S, Smith IE. Management of small HER2-positive breast cancers. *Lancet Oncol.* 2010;11(12):1193-9.
36. Rodrigues MJ, Peron J, Frenel JS, Vano YA, Wassermann J, Debled M, et al. Benefit of adjuvant trastuzumab-based chemotherapy in T1ab node-negative HER2-overexpressing breast carcinomas: a multicenter retrospective series. *Ann Oncol.* 2013;24(4):916-24.
37. Tolaney SM, Barry WT, Dang CT, Yardley DA, Moy B, Marcom PK, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *N Engl J Med.* 2015;372(2):134-41.
38. Baselga J, Cortés J, Kim SB, Im SA, Hegg R, Im YH, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med.* 2012;366(2):109-19.
39. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med.* 2012;367(19):1783-91.
40. von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. *N Engl J Med.* 2019;380(7):617-28.
41. Gluck S, Castrellon A. Lapatinib plus capecitabine resolved human epidermal growth factor receptor 2-positive brain metastases. *Am J Ther.* 2009;16(6):585-90.
42. Tinoco G, Warsch S, Glück S, Avancha K, Montero AJ. Treating breast cancer in the 21st century: emerging biological therapies. *J Cancer.* 2013;4(2):117-32.
43. Ahn ER, Wang E, Gluck S. Is the Improved Efficacy of Trastuzumab and Lapatinib Combination Worth the Added Toxicity? A Discussion of Current Evidence, Recommendations, and Ethical Issues Regarding Dual HER2-Targeted Therapy. *Breast Cancer (Auckl).* 2012;6:191-207.
44. Untch M, Loibl S, Bischoff J, Eidtmann H, Kaufmann M, Blohmer JU, et al. Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy (GeparQuinto, GBG 44): a randomised phase 3 trial. *Lancet Oncol.* 2012;13(2):135-44.
45. Alba E, Albanell J, de la Haba J, Barnadas A, Calvo L, Sánchez-Rovira P, et al. Trastuzumab or lapatinib with standard chemotherapy for HER2-positive breast cancer: results from the GEICAM/2006-14 trial. *Br J Cancer.* 2014;110(5):1139-47.
46. Baselga J, Bradbury I, Eidtmann H, Di Cosimo S, de Azambuja E, Aura C, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. *Lancet.* 2012;379(9816):633-40.
47. Robidoux A, Tang G, Rastogi P, Geyer CE Jr, Azar CA, Atkins JN, 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(12):1183-92.
48. Carey LA, Berry DA, Cirincione CT, Barry WT, Pitcher BN, Harris LN, 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(6):542-9.
49. Guarneri V, Frassoldati A, Bottini A, Cagossi K, Bisagni G, Sarti S, 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(16):1989-95.
50. Jimenez MM, Holmes FA, Ejlersen B, Delaloge S, Moy B, Iwata H, et al. Neratinib after trastuzumab (T)-based adjuvant therapy in early-stage HER2+ breast cancer (BC): 5-year analysis of the phase III ExteNET trial. *Ann Oncol.* 2017;28(5):v43-67.
51. Gianni L, Pienkowski T, Im YH, Tseng LM, Liu MC, Lluch A, et al. Five-year analysis of the phase II NeoSphere trial evaluating four cycles of neoadjuvant docetaxel (D) and/or trastuzumab (T) and/or pertuzumab (P). *J Clin Oncol.* 2015;33(15):505.
52. Tiwari SK, Calhoun B, Abraham J, Thomas Budd G, Moore HCF, Valente AFS, et al. Efficacy and safety of neoadjuvant docetaxel, carboplatin, trastuzumab/pertuzumab [TCH-P] in non-metastatic HER2+ breast cancer: The Cleveland Clinic experience. *J Clin Oncol.* 2015;33(15):531.
53. Untch M, Jackisch C, Schneeweiss A, Conrad B, Aktas B, Denkert C, 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(3):345-56.
54. Schneeweiss A, Chia S, Hickish T, Harvey V, Eniu A, Hegg R, 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(9):2278-84.
55. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet.* 2014;384(9938):164-72.
56. Gianni L, Pienkowski T, Im YH, Tseng LM, Liu MC, Lluch A, 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(6):791-800.
57. Loi S, Dafni U, Karlis D, Polydoropoulou V, Young BM, Willis S, et al. Effects of Estrogen Receptor and Human Epidermal Growth Factor Receptor-2 Levels on the Efficacy of Trastuzumab: A Secondary Analysis of the HERA Trial. *JAMA Oncol.* 2016;2(8):1040-7.
58. Rimawi MF, Mayer IA, Forero A, Nanda R, Goetz MP, Rodriguez AA, et al. Multicenter phase II study of neoadjuvant lapatinib and trastuzumab with hormonal therapy and without chemotherapy in patients with human epidermal growth factor receptor 2-overexpressing breast cancer: TBCRC 006. *J Clin Oncol.* 2013;31(14):1726-31.
59. Harbeck N, Gluz O, Christgen M, Braun MW, Kummel S, Aktas JPB, et al. Efficacy of 12-weeks of neoadjuvant TDM1 with or without endocrine therapy in HER2- positive hormone-receptor-positive early breast cancer: WSG-ADAPT HER2+/HR+ phase II trial. *J Clin Oncol.* 2015;33(15):S506.
60. Hurvitz SA, Martin M, Symmans WF, Jung KH, Huang CS, Thompson AM, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol.* 2018;19(1):115-26.
61. MF Rimawi, Cecchini RS, Rastogi P, Geyer CE Jr, Fehrenbacher L, Stella PJ, et al. A phase III trial evaluating pCR in patients with HR+, HER2-positive breast cancer treated with neoadjuvant docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) +/- estrogen deprivation: NRG Oncology/NSABP B-52. *Cancer Res.* 2017;77(4):S3-06.
62. Vogel CL, Cobleigh MA, Tripathy D, Gutheil JC, Harris LN, Fehrenbacher L, 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(3):719-26.
63. Lin NU, Winer EP, Wheatley D, Carey LA, Houston S, Mendelson D, et al. A phase II study of afatinib (BIBW 2992), an irreversible ErbB family blocker, in patients with HER2-positive metastatic breast cancer progressing after trastuzumab. *Breast Cancer Res Treat.* 2012;133(3):1057-65.
64. Harbeck N, Huang CS, Hurvitz S, Yeh DC, Shao Z, Im SA, et al. Afatinib plus vinorelbine versus trastuzumab plus vinorelbine in patients with

- HER2-overexpressing metastatic breast cancer who had progressed on one previous trastuzumab treatment (LUX-Breast 1): an open-label, randomised, phase 3 trial. *Lancet Oncol.* 2016;17(3):357-66.
65. Disis ML, Gooley TA, Rinn K, Davis D, Piepkorn M, Cheever MA, et al. Generation of T-cell immunity to the HER-2/neu protein after active immunization with HER-2/neu peptide-based vaccines. *J Clin Oncol.* 2002;20(11):2624-32.
 66. Knutson KL, Schiffman K, Cheever MA, Disis ML. Immunization of cancer patients with a HER-2/neu, HLA-A2 peptide, p369-377, results in short-lived peptide-specific immunity. *Clin Cancer Res.* 2002;8(5):1014-8.
 67. Park JW, Melisko ME, Esserman LJ, Jones LA, Wollan JB, Sims R. Treatment with autologous antigen-presenting cells activated with the HER-2 based antigen Lapuleucel-T: results of a phase I study in immunologic and clinical activity in HER-2 overexpressing breast cancer. *J Clin Oncol.* 2007;25(24):3680-7.
 68. Hamilton E, Blackwell K, Hobeika AC, Clay TM, Broadwater G, Ren XR, et al. Phase 1 clinical trial of HER2-specific immunotherapy with concomitant HER2 kinase inhibition [corrected]. *J Transl Med.* 2012;10:28.
 69. Nahta R, Yuan LX, Zhang B, Kobayashi R, Esteva FJ. 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(23):11118-28.
 70. Zhang S, Huang WC, Li P, Guo H, Poh SB, Brady SW, et al. Combating trastuzumab resistance by targeting SRC, a common node downstream of multiple resistance pathways. *Nat Med.* 2011;17(4):461-9.
 71. Garrett JT, Olivares MG, Rinehart C, Granja-Ingram ND, Sánchez V, Chakrabarty A, et al. Transcriptional and posttranslational up-regulation of HER3 (ErbB3) compensates for inhibition of the HER2 tyrosine kinase. *Proc Natl Acad Sci U S A.* 2011;108(12):5021-6.
 72. Witkiewicz AK, Ertel A, McFalls J, Valsecchi ME, Schwartz G, Knudsen ES. RB-pathway disruption is associated with improved response to neoadjuvant chemotherapy in breast cancer. *Clin Cancer Res.* 2012;18(18):5110-22.
 73. Spielmann M, Roché H, Delozier T, Canon JL, Romieu G, Bourgeois H, et al. Trastuzumab for patients with axillary-node-positive breast cancer: results of the FNCLCC-PACS 04 trial. *J Clin Oncol.* 2009;27(36):6129-34.
 74. Buzdar AU, Suman VJ, Meric-Bernstam F, Leitch AM, Ellis MJ, Boughey JC, et al. Fluorouracil, epirubicin, and cyclophosphamide (FEC-75) followed by paclitaxel plus trastuzumab versus paclitaxel plus trastuzumab followed by FEC-75 plus trastuzumab as neoadjuvant treatment for patients with HER2-positive breast cancer (Z1041): a randomised, controlled, phase 3 trial. *Lancet Oncol.* 2013;14(13):1317-25.
 75. Jackisch C, Kim SB, Semiglazov V, Melichar B, Pivrot X, Hillenbach C, et al. Subcutaneous versus intravenous formulation of trastuzumab for HER2-positive early breast cancer: updated results from the phase III HannaH study. *Ann Oncol.* 2015;26(2):320-5.