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Recent advances and optimal management of human epidermal growth factor receptor-2-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 bioavailable small molecule dual HER2- and EGFR/HER1-specific tyrosine kinase inhibitor, received Food and Drug Administration (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 nonanthracycline-based adjuvant chemotherapy regimens combined with trastuzumab, and optimum chemotherapy regimens in small HER2-positive tumors.

Keywords:

Breast cancer, neratinib, pertuzumab, TDM1, trastuzumab

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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. With the technological advances, we are able to characterize molecular subtypes[2,3] of breast cancer which has facilitated the development of molecularly targeted therapeutics. One type of breast cancer is identified by the human epidermal growth factor receptor 2 (HER2) gene amplification. This subtype accounts for approximately 20%–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] Up until 2005, the prognosis for HER2-positive breast cancer patients was dismal; but with the discovery of trastuzumab, it has changed significantly.

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HER2 is a member of the cErbB family of receptor tyrosine kinases, and is responsible for HER2-mediated signal transduction in the cytoplasm.[5] Trastuzumab is a humanized monoclonal antibody targeted against the extracellular portion of HER2. Trastuzumab is the first HER2-targeted agent approved by the United States Food and Drug Administration (FDA) for the treatment of both early stage or metastatic HER2-positive breast cancer.[6,7] Later on, lapatinib, an orally bioavailable dual HER2- and EGFR/HER1-specific tyrosine kinase inhibitor (TKI), received FDA approval in combination with capecitabine for patients with advanced stage HER2+ breast cancer.[8] Subsequently, pertuzumab and ado-trastuzumab emtansine in 2012 and 2013 respectively, were approved based on evidence showing an improvement in survival in patients with mostly trastuzumab 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 after the ExteNET trial results reported improved disease free and OS outcomes.[11] Several adjuvant and neoadjuvant trials are currently testing HER2-targeted drugs in combination with or without cytotoxic chemotherapy. In this article, we review the results from the most recent clinical trials which have helped to guide us on the therapeutic management of HER2-positive early-stage breast cancer.

Defining Human Epidermal Growth Factor Receptor-2-Positive Breast Cancer

Defining a HER2-positive breast cancer depends on the accurate determination of HER2 overexpression either by immunohistochemistry (IHC) or fluorescence *in situ* hybridization (FISH). The current American Society of Clinical Oncology (ASCO)/College of American Pathologists 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 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-human Epidermal Growth Factor Receptor-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

Two important clinical trials, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 and North Central Cancer Treatment Group (NCCTG) N9831 trials, have analyzed whether concomitant use of trastuzumab was better than its sequential use. They included women with high-risk node-negative disease defined as tumors ≥2 cm and ER-positive or tumors larger than 1 cm with negative hormone receptors (HRs). The treatment arms included four cycles of doxorubicin and cyclophosphamide (AC) followed by four cycles of paclitaxel (AC-T) every 3 weeks versus 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 week (AC-T-H vs. AC-TH). In combined analysis, the addition of trastuzumab to paclitaxel resulted in a significant improvement in DFS (HR 0.52, $P < 0.001$) and reduction of death by 39% (OS, HR 0.61, $P < 0.001$) compared to paclitaxel alone.[13] The efficacy of concurrent versus sequential administration of trastuzumab showed a trend toward improvement in DFS in the concurrent arm; however, sequential was still better than placebo ($P < 0.001$).

In American College of Surgeons Oncology Group (ACOSOG) Z1041 trial, Buzdar *et al*.[14] examined if administering trastuzumab with anthracyclines may have an impact on survival outcomes or not. With neoadjuvant chemotherapy in patients with HER2-positive breast cancer. ACOSOG Z1041 was a Phase 3 multicenter trial which enrolled women 18 years or older with invasive operable HER2-positive breast cancer who were randomized to arm 1 received FEC (500 mg/m^2 of fluorouracil, 75 mg/m^2 of epirubicin, and 500 mg/m^2 of cyclophosphamide) every 3 weeks for 12 weeks followed by the combination of weekly paclitaxel and trastuzumab for 12 weeks. Patients randomized to arm 2 received the same regimen but they also received weekly trastuzumab during FEC regimen. After a median follow-up of 5.1 years, pathologic complete response (pCR), and survival outcomes were not significantly different between the 2 arms. Therefore, in current clinical practice, concurrent administration of trastuzumab with anthracyclines is avoided due to lack of additional benefit and concerns of cardiotoxicity. Table 1 shows results from selected adjuvant trials comparing

Table 1: Initial adjuvant trastuzumab trials

Study name	Population included	Number of patients	Comparison	DFS (5 years) (%)	OS (5 years) (%)	Drop LVEF (%)
NCCTG N9831[13]	LN+ or high-risk LN(−)	1087	AC→T versus	71.8	88.4	0
		949	AC→T→H (52 w) versus	80.1	89.7	7
		954	AC→TH (H then 40 week more)	84.4	91.9	3.6
HERA[29]	LN+ or high-risk LN(−)	1552	Std QT→H (52 w) versus	75.9	86.9	7.2
		1553	Std QT→H (40 w) versus	76.5	88.7	4.1
		1697	Std QT→Observation	70.0	84.5	0.9
BCIRG006[16]	LN+ or high-risk LN(−)	1073	AC→docetaxel versus	75	87	11.2
		1074	AC→Docetaxel+H versus	84	92	18.6
		1075	TCH	81	91	9.4
PACS04[75]	LN+	260	FE100C or ED75→Obser versus	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 versus	74.1	82	10.5 (QT only)
		58	Vinorelbine→FEC versus	72	82.8	
		54	Docetaxel+H→FEC versus	92.5	94.4	6.8 (QT+H)
		61	Vinorelbine+H→FEC	75.2	88.4	
PHARE[26]	HER2+ early breast cancer	1690	Std QT→H (26 wk) versus	91.1	96.1	5.7 (both)
		1690	Std QT→H (52 wk)	93.8	94.5	1.9 (both)

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, TCH: Taxotere, carboplatin and Herceptin

anthracycline and nonanthracycline chemotherapy regimens combined with trastuzumab.

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 to minimize the cardiotoxicity risk.[15] The BCIRG 006[16] study was designed to provide information on this matter. The treatment arms were as following: AC followed by docetaxel (AC→T), AC followed by docetaxel with 1 year of trastuzumab (AC→TH), or docetaxel plus carboplatin and trastuzumab followed by trastuzumab to complete 1 year of therapy (TCH). After 65 months' follow-up, DFS was significantly better 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, $P = 0.038$). In addition, the incidence of cardiac toxicity was five times more with ACTH (2%) compared with TCH (0.4%). Reductions in left ventricular ejection fraction (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 nonanthracycline trastuzumab-based regimen, TCH, for adjuvant therapy.

Afterwards, several studies[17-19] have evaluated concurrent administration of anthracycline-based chemotherapy and trastuzumab in the neoadjuvant setting. 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[17,20] to 10.5%; and 2.0%[21] to 3.3%,[22,23] respectively.

In the MD Anderson Cancer Center (MDACC)[17] trial, patients with HER2-positive breast cancer received paclitaxel followed by FEC75, with or without concurrent trastuzumab. 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.[24] In the GeparQuattro trial[19] concurrent administration of trastuzumab with epirubicin yielded persistent decrease in LVEF to less than 50% in only one patient. 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[25] 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 (odds ratio [OR]: 1.45; 95% confidence interval [CI]: 1.06–1.98; $P = 0.02$). 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: 0.12–0.60; $P = 0.001$) and death (HR: 0.37; 95% CI: 0.12–1.13; $P = 0.08$) 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

Currently, the accepted standard of care is to administer trastuzumab for 1 year and in part concomitantly with chemotherapy. The choice of this duration was arbitrary[24] in the trials which established the current standard 1 year therapy. On the other hand, studies compared different durations showed that 6 months of adjuvant trastuzumab was noninferior compared with 1-year therapy,[26,27] and 2-year administration was not superior to 1 year administration.[28]

HERA trial[29] tested 1 or 2 years of trastuzumab after completion of various standard adjuvant chemotherapy regimens. Patients with HER2-positive breast cancer who had positive LNs or tumors larger than 1 cm were enrolled in the study. After 4 years of follow up, 1-year trastuzumab therapy decreased the recurrence risk by %24 (HR = 0.76, $P < 0.0001$). A recent update at 8 years of follow up confirmed the DFS (HR = 0.76, $P < 0.0001$) and OS benefit (HR = 0.76, $P = 0.0005$). Importantly, there was no incremental benefit from 2-years of trastuzumab therapy and patients had more cardiac events.

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 recently reported which did not confirm the FinHer[30] data for the efficacy of short duration trastuzumab therapy. FinHER investigators compared 9 weeks versus 1 year of trastuzumab plus docetaxel and FEC with the same regimen in the SOLD study.[31] The 9-week treatment was not found to be inferior for DFS (HR: 1.39; 90% CI: 1.12–1.72). DFS and OS as well as the cardiotoxicity were similar between the groups; however, the left ventricle ejection fraction was better maintained in the 9-week group.

The Short-HER, phase 3 multicentric Italian study, randomly assigned 1254 patients with HER2-positive early breast cancer to either 9 weeks or 1 year of treatment with trastuzumab plus chemotherapy. First results showed that the short course was not noninferior but was associated with a reduced risk of cardiotoxicity. In the newest analysis reported at ESMO in 2018, researchers 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 low risk patients treated with 9 weeks of trastuzumab had a similar DFS (88%) as with 1 year (89%; HR = 1.02, 95% CI: 0.78–1.33). Moreover, their risk of cardiac events was much lower (4.5% vs. 12.8%, relative risk = 2.88, 95% CI: 1.85–4.47).[32]

The PHARE trial[26] and PERSEPHONE trials are noninferiority studies designed to evaluate adjuvant treatment length with trastuzumab for 6 months compared to 1 year. 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: 1.05–1.56), 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 that 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 we should offer 1 year of trastuzumab therapy 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

We have very limited data on the role of trastuzumab in small node-negative tumors. Retrospective series from MDACC[33] and Milan[34] suggest small HER2-positive tumors have a poorer long-term outcome when compared to their HER2-negative counterparts. Subgroup analyses from several randomized trials have shown a benefit with adjuvant trastuzumab regardless of

tumor size,[35] though its actual absolute benefit in small stage 1 tumors (like those with T1a up to 0.5 cm disease) is unknown. A large, retrospective European study[36] 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%–3% improvement in recurrence-free survival on the trastuzumab arm after a multivariate analysis. HR status also proved to be noteworthy as bigger differences were seen in patients with high-risk features such as HR-negative or HR-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[37] included breast cancer patients with node-negative tumors up to 3 cm who received weekly treatment with paclitaxel and trastuzumab for 12 weeks, followed by 9 months of trastuzumab. 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, 97.6–99.8). The results suggest a low risk of cancer recurrence (<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-year DFS.[38] The 7-year DFS was 93.3% (95% CI: 90.4–96.2); 7-year DFS for ER+ pts was 94.6% (95% CI: 91.8–97.5) and for ER − pts was 90.7% (95% CI: 84.6–97.2). 7-year recurrence–free interval (RFI) was 97.5% (95% CI: 95.9–99.1); 7-year breast cancer specific survival is 98.6% (95% CI: 97.0–100); and 7-year OS was 95.0% (95% CI: 92.4–97.7). Absent randomized data, TH regimen might become an option for patients with small node-negative HER2-positive disease.

Changing landscape of human epidermal growth factor receptor-2-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 TKI neratinib.

Data from metastatic trials of pertuzumab[39] and ado-trastuzumab emtansine[40] 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. The results of the APHINITY trial were presented at ASCO 2017 annual meeting.[41] In this phase III clinical trial of 4805 women with HER2-positive breast cancer, the addition of pertuzumab to trastuzumab decreased risk of breast cancer recurrence by 19% compared to trastuzumab alone. Heart failure rates were similar in both groups, 0.7% in the pertuzumab group versus 0.3% in the placebo group with more diarrhea seen with pertuzumab, occurring in 9.8% of patients. In 2017, pertuzumab was approved by FDA for use in combination with trastuzumab and chemotherapy as adjuvant treatment of patients with HER2-positive early breast cancer.

The phase III KATHERINE[42] 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. Patients were randomized either to 14 cycles of ado-trastuzumab emtansine versus 14 cycles of trastuzumab. In the T-DM1 group, 88.3% of patients were free of disease versus 77.0% in the trastuzumab group. Invasive DFS was significantly higher in the T-DM1 group than in the trastuzumab group (HR: 0.50; 95% CI: 0.39–0.64; $P < 0.001$). 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. These results may immediately be applied to our clinical setting for patients with residual invasive breast cancer following neoadjuvant therapy.

Evidence supporting activity of the oral 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 pretreated HER2-positive (HER2+) metastatic breast cancer. ExteNET study examined sequential therapy with 1 year of trastuzumab followed by 1 year of neratinib in stage 2–3c 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 1–3c (modified to stage 2–3c 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 HR status (ER-positive vs. ER-negative), nodal status (0 vs. 1–3 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 2.1–5.3), 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: 0.57–0.92, $P = 0.0083$). The 5-year invasive DFS was 90.2% (95% CI: 88.3–91.8) in the neratinib group and 87.7% (85.7–89.4) in the placebo group. Without diarrhea prophylaxis, the most common grade 3–4 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. 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.

Neoadjuvant setting

In the last decade, researchers have modernized trial design by using 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[53] 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. 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 + D0 arms, respectively, 3-year survival rates were 85% and 92% for DFS (HR: 0.60, 95% CI: 0.28–1.27), and 86% and 90% for PFS (HR: 0.69, 95% CI: 0.34–1.40). Importantly, the addition of pertuzumab did not produce any significant drop in the cardiac function (4-5% EF drop across all groups). The phase II trial (TRYPHAENA)[54] was designed primarily to assess the cardiac safety of pertuzumab in different neoadjuvant regimens. Patients were randomized to one of three neoadjuvant regimens: FEC ×3 followed by docetaxel × 3, all in combination with pertuzumab and trastuzumab; FEC × 3 alone followed by docetaxel × 3 and trastuzumab in combination with pertuzumab; or docetaxel, carboplatin, and trastuzumab (TCH) ×6 in combination with pertuzumab. Among all three regimens, 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)[55] 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. pCR rate was higher in the nab-paclitaxel group [38%, 95% CI: 35–42] than in the solvent-based paclitaxel group [29%, 25–33]; $P = 0.00065$). 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 ($P = 0{\cdot}49$). Table 2 summarizes selected **clinical trials in the neoadjuvant setting for HER-2 positive breast cancer.**

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 1 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 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–positive Disease

At least half of HER2-positive breast cancer coexpresses one or both HRs, and this coexpression may serve as a pathway for resistance to HER2-targeted therapy. This

Table 2: Selected clinical trials in the neoadjuvant setting for human epidermal growth factor receptor 2-positive breast cancer

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

T: Paclitaxel, H: Herceptin (trastuzumab), F: 5-Fluorouracil, E: Epirubicin, C: Cyclophosphamide, A: Adriamycin, M: Methotrexate, Do: Docetaxel, TC: Docetaxel-cyclophosphamide, PCR: Pathologic complete response, TCH: Taxotere-carboplatin-herceptin

does not mean that HER2-targeted therapy is inactive in HR–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 HR–positive (HR, 0.65 and 0.61 for BCIRG-006 and B-31, respectively) and HR–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 HR–negative disease had earlier recurrences.[28]

Further evidence supporting the notion that disease behavior differs based on HR expression comes from neoadjuvant clinical trials, which have consistently shown that pCR rates are lower for HR-positive, HER2-positive breast cancer than for HR–negative disease.[48,49,56,57] That said, the longer follow-up of the NeoSphere trial[58] indicates that patients with HR coexpression have numerically higher PFS compared with tumors lacking HRs (5-year PFS for patients who achieved pCR: 90% if HR positive, 84% if HR negative; 5-year PFS for patients who did not achieve pCR: 80% if HR positive, 72% if HR negative). Thus, patients with HR–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 HR 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/HR–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 HR–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[62] 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. A pCR was achieved by 44% of patients in the T-DM1 plus pertuzumab group and 56% of patients in the TCHP group ($P = 0{\cdot}016$). Although neither of these studies have 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 HR–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.

Table 3: Ongoing adjuvant/neoadjuvant clinical trials for human epidermal growth factor receptor 2-positive breast cancer

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

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, HER2: Human epidermal growth factor receptor 2

Resistance to Trastuzumab and Lapatinib

Although HER2-targeted therapies have had a significant impact on patient outcomes, resistance to these agents are seen in 50%–74% of patients with HER2+ metastatic breast cancer.[6,64] 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] 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.

Afatinib

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[66] trial was a negative trial for afatinib. 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-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 (clinicaltrials.gov, NCT00911898). Another phase I trial is studying MM-111 plus trastuzumab in HER2-positive, heregulin-positive, advanced and refractory breast cancer (clinicaltrials.gov, NCT01097460).

Trastuzumab Deruxtecan

Trastuzumab deruxtecan (ds-8201a), a HER2-targeting antibody-drug conjugate (ADC), demonstrated significant clinical activity in heavily pretreated patients with HER2-expressing metastatic breast cancers who previously received ado-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 a 2-part phase I study, the objective response rate (ORR) to trastuzumab deruxtecan was 61.4%. In the ER-positive HER2-positive cohort, the ORR was 56.4% and in the ER-negative HER2-positive cohort, ORR was 75.0% (12 of 16). Importantly, the ORR was 62.5% among the 50 patients with prior pertuzumab treatment.

The disease control rate (DCR) was 94.7% overall: 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 were exposed to pertuzumab, reported Shanu Modi, MD, at the 2017 San Antonio Breast Cancer Symposium. The main toxicity was grade 1/2 gastrointestinal toxicity which included nausea in 67.9% of patients. Grade 3 and 4 events were more related to drug hematotoxicity.

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.

Human Epidermal Growth Factor Receptor-2-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-human Epidermal Growth Factor Receptor-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.

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. It is clearer now that HER2-positive breast cancer is both clinically and molecularly heterogeneous. The key to successful de-escalation of chemotherapy will be possible with elimination of other HER pathways like 1, 3, and 4. Trastuzumab blocks HER2 dimers and induces apoptosis; however, it creates only an incomplete pathway of all the HER receptors. However, the targeted therapies lapatinib, neratinib, and afatinib create a complete blockade of all the HER receptors. The results from the phase III NALA trial, which were presented at the 2019 ASCO Annual Meeting, showed that the HR for PFS favoring neratinib was 0.76 (95% CI: 0.63–0.93; log-rank P = 0.0059). Landmark analysis showed that the PFS curves began to separate after 6 months with 6-month PFS rates of 47% versus 38%, 1-year rates of 29% versus 15%, and 18-month rates of 16% versus 7% for the neratinib arm versus the lapatinib arm, respectively.[75] Moreover, U3-1402, an investigational ADC targeting HER3, induced objective response in more than 40% of heavily pretreated patients with HER3-expressing breast cancer, according to results presented at the San Antonio Breast Cancer Symposium. The ORR was 42.9% (18/42), and the overall DCR was 90.5% (38/42).[76] 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.

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Conflicts of interest

There are no conflicts of interest.

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