Long-term Outcomes of Neoadjuvant Treatment of HER2-Positive Breast Cancer

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Abstract: Long-term outcomes for women with a diagnosis of human epidermal growth factor receptor 2 (HER2)–driven early-stage breast cancer have significantly improved since the advent of HER2-targeted therapy. Although the first studies in the early-stage setting focused on the adjuvant use of trastuzumab plus chemotherapy, clinical trials increasingly are using a neoadjuvant design to evaluate novel HER2-targeted therapies. Neoadjuvant therapy downstages locally advanced breast cancer, improves rates of breast conservation, and provides information regarding the responsiveness of a cancer to systemic therapy; in addition, studies have shown that the pathologic response to neoadjuvant therapy is correlated with event-free and overall survival. Given these advantages, multiple studies of neoadjuvant therapy, several of which have reported longer-term outcomes, have been conducted to evaluate HER2-targeted therapies. This review summarizes available data from prior and ongoing neoadjuvant trials in HER2-positive breast cancer, focusing on those studies that have reported not only pathologic response rates but also event-free, disease-free, and/or overall survival. The long-term outcomes associated with the achievement of a pathologic complete response are explored, and the comparisons of pathologic complete response rates, event-free survival, and overall survival reported for different HER2-targeted regimens are reviewed.

Introduction

Chemotherapy and endocrine therapy have significantly improved disease-free survival (DFS) and overall survival (OS) for women with nonmetastatic breast cancer.[1,2] Traditionally, systemic therapy has been given in the postoperative, or adjuvant, setting. In the past 2 decades, however, its use has been evaluated in the preoperative, or neoadjuvant, setting as well.[3,4] In addition to achieving survival benefits similar to those of adjuvant therapy,[5] systemic therapy delivered before surgery has several potential advantages. First, neoadjuvant therapy may downstage locally advanced breast cancer and improve rates of breast conservation.[4,6] Moreover, delivering cancer therapy while a breast tumor is intact provides the opportunity to observe

the in vivo responsiveness of the cancer before surgical resection and to switch therapy if an appropriate response is not detected. This *response-guided* approach has been associated with longer DFS, particularly in hormone receptor–positive (HR+) tumors.[7] For these reasons, women with early-stage breast cancer increasingly have been offered neoadjuvant treatment.

In addition to the above-mentioned advantages of neoadjuvant therapy, promising novel therapeutics are increasingly being evaluated in neoadjuvant trials. A recent meta-analysis has raised the possibility that pathologic complete response (pCR) may be a valid surrogate endpoint because it appears to be associated with improved event-free survival (EFS) and OS. This is especially true in human epidermal growth factor receptor 2–positive (HER2+)/hormone receptor–negative (HR–) tumors and in triple-negative tumors.[8] One advantage to the neoadjuvant study design is that the primary endpoint, pCR, may be achieved in a much shorter period than a more traditional endpoint, such as DFS or OS. The result is smaller, less expensive studies with faster readout. Based on these considerations, the US Food and Drug Administration (FDA) has published guidance relating to the design of neoadjuvant clinical trials, with a regulatory pathway to accelerated approval in mind.[9]

Long-term outcomes for women with a diagnosis of HER2-driven early-stage breast cancer have substantially improved since the advent and availability of the HER2-targeted monoclonal antibody trastuzumab (Herceptin, Genentech).[10-13] Whereas early studies focused on treating women with trastuzumab plus chemotherapy in the adjuvant setting, clinical trials increasingly are using a neoadjuvant design to evaluate new HER2-targeted therapies.[14-16] Although the majority of these studies have reported pCR rates, long-term outcomes are just beginning to appear. Extended follow-up of these trials will be critical in determining whether pCR will indeed be a reliable surrogate marker for long-term outcomes. This review summarizes data available from prior and ongoing neoadjuvant trials in HER2+ breast cancer. We focus on studies that have reported both short-term outcomes (pCR) and long-term outcomes (DFS, EFS, and OS). The long-term outcomes associated with the achievement of pCR are explored, and the comparisons of pCR rates, DFS, EFS, and OS reported for different HER2-targeted regimens are reviewed.

Neoadjuvant Trials of Trastuzumab

Since the FDA approval of trastuzumab in the adjuvant setting in 2006, multiple trials have studied the benefit of adding trastuzumab to chemotherapy in the neoadjuvant setting.[14,15,17-20] Because these are primarily older studies, several of them have reported long-term outcomes, such as DFS and OS (Table 1).

By design, nonrandomized, single-arm trials cannot determine whether the addition of trastuzumab to a chemotherapy regimen improves pCR rates or long-term outcomes. They can only estimate the pCR rates for a given regimen compared with historical controls. However, they are able to assess whether patients who achieve a pCR have a longer DFS or OS. The nonrandomized phase 2 TECHNO trial (Taxol Epirubicin Cyclophosphamide Herceptin Neoadjuvant) evaluated epirubicin and cyclophosphamide (EC) followed by paclitaxel plus trastuzumab in the neoadjuvant setting. Of 217 patients, 84 (38.7%) achieved a pCR, defined as lack of invasive cancer in the breast and lymph nodes (ypT0/is ypN0; 95% CI, 32.2%-45.2%). The 3-year DFS was 77.9% and the 3-year OS was 89.4%. The study also analyzed OS and DFS based on pCR status. The 3-year DFS was 88.1% in patients with a pCR and 71.4% in patients without a pCR (P=.0033). Similarly, the 3-year OS was higher in patients with a pCR than in those with residual cancer (96.3% vs 85.0%, respectively; P=.007).[19]

The first randomized trial to study neoadjuvant trastuzumab plus chemotherapy in operable HER2+ breast cancer looked at paclitaxel followed by fluorouracil, epirubicin, and cyclophosphamide (FEC) with or without trastuzumab.[14] The study was stopped early after only 42 of the intended 142 patients had been randomized (34 completed therapy) because of the substantial superiority seen in the trastuzumab arm. The pCR rate (ypT0/is ypN0) was 66.7% (95% CI, 43%-84%) in the trastuzumab-plus-chemotherapy arm (n=18) compared with 25% (95% CI, 9.1%-51.2%) in the chemotherapy-alone arm (n=16; P=.016).[14]

The updated analysis of the initial cohort, as well as an additional cohort of 22 patients treated with trastuzumab plus chemotherapy, supported the initial findings.[21] In the second cohort, the pCR rate was 54.5% (95% CI, 32.2%-75.6%), and the pCR rate among all 45 patients who received trastuzumab plus chemotherapy was 60% (27/45; 95% CI, 44.3%-74.3%). After a median follow-up of 36.1 months, recurrence developed in 3 patients in the chemotherapy-only group, and 1 patient died of progressive disease. The DFS in the chemotherapy-only group at 1 year was 94.7% (95% CI, 85.2%-100%) and at 3 years was 85.3% (95% CI, 67.6%-100%). DFS was significantly better in the trastuzumab group; no recurrence was noted in the patients, and the estimated DFS was 100% at 1 and 3 years (P=.041). Although this study was small, it was the first to highlight the dramatic improvement not only in pCR rate but also, importantly, in DFS and OS with the addition of trastuzumab to neoadjuvant chemotherapy. Although no clinical cardiac

Table 1. Summary of Major Neoadjuvant Studies in HER2+ Breast Cancer

Trial	Phase	Neoadjuvant Regimens	pCR (ypT0/is ypN0)	DFS/EFS	OS
TECHNO[19]	2	EC × 4→P (q3w, 175 mg/m^2) × 4 + T T: q3w	38.7% 95% CI 32.2%-45.2%	77.9% (3-y DFS)	89.4% (3 y)
Buzdar et al[14,21]	3	P (q3w, 225 mg/m^2) × 4→FEC75 × 4 P + T→FEC75 + T T: q1w	25% vs 66.7% (w/T) *P*=.016	100% (w/T) vs 94.7% (1-y DFS) 100% (w/T) vs 85.3% (3 y)	NA
NOAH[15,22]	3	A (60 mg/m^2)/P_1 × 3→P_2 × 4→FCM × 3 A/P × 3 + T→P × 4 + T→FCM + T T: q3-4w, P_1: q3w 150 mg/m^2, P_2: q3w 175 mg/m^2, FCM: q4w, 600/600/40 mg/m^2	19% vs 38% (w/T) *P*=.001	71% (w/T) vs 56% (3-y EFS, *P*=.013) 58% (w/T) vs 43% (5-y EFS, *P*=.016)	87% (w/T) vs 79% (3 y, *P*=.114) 74% (w/T) vs 63% (5 y, *P*=.055)
GeparQuattro[16,23]	3	1. EC × 4→D (100 mg/m^2) × 4 2. EC × 4→D (75 mg/m^2) + X (1800 mg/m^2) × 4 3. EC × 4→D (75 mg/m^2) × 4→ X × 4 If HER2+, add T: q3w	41.4% (HER2+) vs 17.8% (HER2–) By arms in HER2+ group, ypT0: 32.9% (1), 31.3% (2), 34.6% (3) No *P* value	Hazard ratio 0.89 (5.4-y DFS, HER2+ vs HER2–, *P*=.305) No difference in DFS by treatment arms, data not published	Hazard ratio 0.76 (5.4-y OS, HER2+ vs HER2–, *P*=.074) No difference by treatment arms, post-progression survival better in HER2+ (*P*=.039), data not published
Pierga[17]	2	EC (75/750 mg/m^2) 4→D (100 mg/m^2) × 4 EC × 4→D × 4 + T T: q3w	19% vs 26% (w/T) No *P* value	NA	NA
ABCSG24[18]	3	ED (75/75 mg/m^2) ± X (1000 mg/m^2) × 6 ED ± X × 6 + T T: q3w	23% vs 15.4% (EDX vs ED, *P*=.027) 38.6% vs 26.5% (EDX + T vs ED + T, *P*=.212) pCR: ypT0/is	NA	NA
GeparQuinto, GBG 44[20]	3	EC × 4 + T→D (100 mg/m^2) × 4 + T EC × 4 + L→D × 4 + L T: q3w, L: 1000-1250 mg/d	30.3% (T) vs 22.7% (L), *P*=.04 pCR: ypT0 ypN0	NA	NA
GEICAM/2006-14[24]	2	EC × 4→D (100 mg/m^2) × 4 + T EC × 4→D × 4 + L T: q3w, L: 1250 mg/d	47.9% (T) vs 23.5% (L), *P*=.011	NA	NA
TBCRC 006[34]	2	T/L × 12, + letrozole if ER+, + LHRH if premenopausal T: q1w, L: 1000 mg/d	27% (ER+ 21%, ER– 36%) pCR: ypT0/is	NA	NA
CHER-LOB[30]	2	P (q1w) × 12 + T→FEC × 4 + T P × 12 + L→FEC × 4 + L P × 12 + T/L→FEC × 4 + T/L T: q1w, L: 1500 mg/d (alone) or 1000 mg/d (combination), FEC: 600/75/600 mg/m^2	25% (T), 26.3% (L), 46.7% (T/L), *P*=.019	NA	NA
Holmes et al[31]	2	FEC75 × 4→P (q1w) × 12 + T FEC75 × 4→P × 12 + L FEC75 × 4→P × 12 + T/L T: q1w, L: 1500 mg/d reduced to 1250 mg/d (alone), 1000 mg/d reduced to 750 mg/d (combination)	54% (T), 45% (L), 74% (T/L) No *P* value	NA	NA

(Table continues on next page)

Table 1. *(Continued)* Summary of Major Neoadjuvant Studies in HER2+ Breast Cancer

Trial	Phase	Neoadjuvant Regimens	pCR (ypT0/is ypN0)	DFS/EFS	OS
CALGB 40601[35]	3	P (q1w) × 16 + T P × 16 + L P × 16 + T/L T: q1w, L: 1500 mg/d (alone) or 1000 mg reduced to 750 mg/d (combination)	46% (T), 32% (L), 56% (T + L) *P*=.13, pCR: ypT0/is	NA	NA
NeoALTTO[29,36]	3	T × 6→P (q1w) × 12 L × 6w→P × 12 T/L × 6w→P × 12 T: q1w, L: 1500 mg/d (alone) or 1000 mg reduced to 750 mg/d (combination)	27.6% (T), 20.0% (L), 46.8% (T + L), *P*=.0007 (combination vs T)	76% (T), 78% (L), 84% (T/L) (3-y EFS, *P*=.33 combination vs T)	90% (T), 93% (L), 95% (T/L) (3 y, not significant)
NeoSphere[39,40]	2	Arm (A): T + D (75-100 mg/m^2) × 4 Arm (B): Pert + T + D × 4 Arm (C): T + Pert × 4 Arm (D): Pert + D × 4 T: q3w	(A): 21.5%, (B): 39.3%, (C): 11.2%, (D): 17.7% No *P* value	(A): 81%, (B): 84%, (C): 80%, (D): 75% (5-y DFS) (A): 81%, (B): 86%, (C): 73%, (D): 73% (5-y PFS=EFS)	NA
NSABP B41[33]	3	AC × 4→P (q1w) × 4 + T AC × 4→P × 4 + L AC × 4→P × 4 + T + L T: q1w, L: 1250 mg/d (alone) or 750 mg/d (combination)	49.4% (T), 47.4% (L), 60.2% (T/L), *P*=.056 (combination vs T)	Ongoing (RFS)	Ongoing
TRYPHAENA[38]	2	1. FEC + T + Pert × 3→D (75-100 mg/m^2) + T + Pert × 3 2. FEC × 3→D + T + Pert × 3 3. D (75/ mg^2) + carboplatin (AUC 6) + T + Pert × 6 T: q3w, FEC: 500/100/600 mg/m^2	1: 56.1%, 2: 54.7%, 3: 63.6% No *P* value	Ongoing	Ongoing
ADAPT[43-45]	2/3	HER2+/HR+: Arm (A): T-DM1 (q3w, 3.6 mg/kg) × 4 Arm (B): T-DM1 + endocrine therapy Arm (C): T (q3w) + endocrine therapy HER2+/HR–: Arm (A): q3w T/Pert × 4 Arm (B): q3w T/Pert × 4 + P (q1w) × 12	HER2+/HR+: (A): 41.0%, (B): 41.5%, (C): 15.1% (*P*<.001)	Ongoing	Ongoing

AUC, area under the curve; d, day; DFS, disease-free survival; EFS, event-free survival; ER, estrogen receptor; forward arrow, followed by; HER2, human epidermal growth factor 2; HR, hormone receptor; LHRH, luteinizing hormone–releasing hormone; NA, not available; OS, overall survival; pCR, pathologic complete response; q, every; RFS, relapse-free survival; w, weeks; y, year; ypT0, absence of invasive and in situ cancer in breast only; ypT0/is, absence of invasive cancer in breast only; ypT0/is ypN0: absence of invasive cancer in breast and lymph nodes; ypT0 ypN0, absence of invasive and in situ cancer in breast and lymph nodes following completion of neoadjuvant therapy; ypT0/is ypN0, absence of invasive cancer in breast and lymph nodes following completion of neoadjuvant therapy.

Unless otherwise specified in the table, names and doses of neoadjuvant regimens are as follows: **A**, Adriamycin (doxorubicin), 60 mg/m^2; **C**, cyclophosphamide, 600 mg/m^2; **D**, docetaxel; **E**, epirubicin, 90 mg/m^2; **F**, fluorouracil, 600 mg/m^2; **FEC75**, 500/75/500 mg/m^2; **L**, lapatinib; **M**, methotrexate, 40 mg/m^2; **P**, paclitaxel, q1w dosing: 80 mg/m^2; **Pert**, pertuzumab, 840-mg loading dose, then 420 mg q3w; **T**, trastuzumab, q1w dosing: 4-mg/kg loading dose, then 2 mg/kg; q3w dosing: 8-mg/kg loading dose, then 6 mg/kg; **T-DM1**, trastuzumab emtansine, 3.6 mg/kg q3w.

dysfunction events occurred in the 45 patients treated with trastuzumab and anthracycline-based chemotherapy in this study, the short-term follow-up and small size are inadequate to allow clear conclusions to be drawn regarding the cardiac safety of this regimen.[21]

The randomized, international phase 3 NOAH trial (Neoadjuvant Herceptin in Patients With HER2-Positive Locally Advanced Breast Cancer) was the first large ran-

domized study to provide support for the addition of trastuzumab to chemotherapy in the neoadjuvant setting. In this study, 235 patients with HER2+ breast cancer were randomly assigned to treatment with trastuzumab plus anthracycline- and taxane-based chemotherapy (n=117) vs chemotherapy alone (n=118).[15] The pCR rate in the trastuzumab arm was almost double that in the chemotherapy-only arm (ypT0/is ypN0, 38% vs 19%; *P*=.001; ypT0/is, defined as absence of invasive cancer in the breast only, 43% vs 22%; *P*=.0007). The 3-year EFS also was significantly improved in patients receiving trastuzumab (71% vs 56%; hazard ratio, 0.59; 95% CI, 0.38-0.90; *P*=.013). At 3 years, there was a trend toward improvement in OS favoring trastuzumab that did not reach statistical significance (87% vs 79%; *P*=.114).[15] After a median follow-up of 5.4 years, EFS remained significantly higher in the trastuzumab-containing arm (58% vs 43%; hazard ratio, 0.64; 95% CI, 0.44-0.93; *P*=.016). Again, OS tended to be better in the trastuzumab arm but did not reach statistical significance (74% vs 63%; hazard ratio, 0.66; 95% CI, 0.43-1.01; *P*=.055). The study also noted a significant association between pCR and both EFS and OS regardless of treatment arm (*P*=.014).[22] Additionally, the incidence of symptomatic cardiac failure was low (1.7%; n=2) with the concurrent use of trastuzumab and anthracyclines, and there was no increase in noncardiac toxicities in the trastuzumab group.

The GeparQuattro study (Neoadjuvant Treatment With Trastuzumab in HER2-Positive Breast Cancer) was a large, multicenter, randomized phase 3 trial evaluating neoadjuvant capecitabine in breast cancer. Patients were treated with EC followed by docetaxel with or without capecitabine (capecitabine was given concurrently with docetaxel or sequentially). Patients who had HER2+ tumors were also treated with trastuzumab concurrently with all chemotherapy cycles. Of 1509 patients, 1064 who had HER2-negative (HER2–) tumors were treated with the same chemotherapy regimen without trastuzumab as a reference group and 445 patients who had HER2+ tumors received trastuzumab. Total pCR (ypT0/is ypN0) was observed in 41.4% of patients in the HER2+ group and 17.8% of patients in the HER2– reference group.[16] No difference in pCR was noted among the different treatment arms for HER2+ disease, indicating that the addition of capecitabine does not add to the pathologic response in the HER2+ setting. After a median follow-up of 5.4 years, no difference in DFS or OS was found between the HER2+ and HER2– cohorts. However, post hoc analysis showed that OS after progression was significantly better in the patients who had HER2+ cancer treated with trastuzumab than in the patients who had HER2– disease treated with chemotherapy alone (*P*=.039).[23] This signifies that adding HER2-directed therapy alters the natural course of HER2+ breast cancer from one of the worst prognoses to one with an outcome similar to or better than that of HER2– disease.

In reviewing the pCR rates reported for different trials, it is important to highlight that cross-trial comparison is difficult owing to the heterogeneous definition of pCR. The FDA's *Guidance for Industry* recommends that researchers use a uniform definition of pCR when conducting trials. The pCR should be defined either as the absence of invasive cancer in breast and lymph nodes following completion of neoadjuvant therapy (ypT0/is ypN0) or as the absence of invasive and in situ cancer in breast and lymph nodes following completion of neoadjuvant therapy (ypT0 ypN0).[9] However, various other definitions of pCR have been used in the trials, including absence of invasive and in situ cancer in the breast only (ypT0) and absence of invasive cancer in the breast only (ypT0/is). With that caveat in mind, the randomized neoadjuvant trials of trastuzumab overall generated pCR rates ranging from 26% to 67%, and all the trastuzumab arms outperformed the arms that received chemotherapy alone. Long-term follow-up of the randomized trials discussed above has demonstrated that the addition of trastuzumab to chemotherapy not only improves pCR rates but also improves DFS, EFS, and OS. In addition, TECHNO and NOAH both showed that regardless of treatment arm, pCR is associated with improved DFS/EFS and OS.

Lapatinib in the Neoadjuvant Setting

Lapatinib (Tykerb, Novartis), a small-molecule dual tyrosine kinase inhibitor targeting epidermal growth factor receptor (EGFR) and HER2, was approved by the FDA in 2007 for the treatment of HER2+, trastuzumab-resistant metastatic breast cancer. Lapatinib subsequently was compared with trastuzumab in the neoadjuvant setting in 2 trials,[20,24] both of which reported higher pCR rates in the trastuzumab arms. DFS or OS data are not available for either trial. Based on preclinical studies that demonstrated synergy between lapatinib and trastuzumab,[25,26] as well as phase 3 data in the metastatic setting showing survival benefit for the combination of lapatinib plus trastuzumab compared with lapatinib alone,[27,28] multiple neoadjuvant trials[29-35] have been conducted to assess this combination, some showing a significantly improved pCR with dual inhibition[29,30] and others showing no difference.[32,33] However, the only study to report longer-term data thus far is NeoALTTO (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation).

NeoALTTO is an international, randomized phase 3 trial evaluating neoadjuvant lapatinib and trastuzumab combination therapy in HER2+ operable breast cancer. A total of 455 patients were randomly assigned to receive

trastuzumab, lapatinib, or a combination of the 2 agents in addition to paclitaxel. The rate of the primary endpoint of in-breast pCR (ypT0/is) was significantly higher in the combination group than in the trastuzumab-only group (51.3% vs 29.5%; *P*=.0001). The rate of total pCR (ypT0/is ypN0) was accordingly higher in the combination group than in the trastuzumab group (46.8% vs 27.6%; *P*=.0007). Both the in-breast pCR rate and the total pCR rate were numerically higher in the trastuzumab arm than in the lapatinib arm, although this difference did not reach statistical significance. In all groups, in-breast pCR rates were higher in patients with HR– tumors than in patients with HR+ tumors. Of note, toxicity was higher in the lapatinib group, especially with regard to excessive diarrhea. Based on this toxicity, the protocol was amended to reduce the lapatinib dose midway through the study. Hepatic adverse events also caused treatment discontinuation in 30 patients who received lapatinib.[29]

The recently published survival outcomes of NeoALTTO showed no significant difference in 3-year EFS among all groups (trastuzumab, 76%; lapatinib, 78%; combination, 84%; *P*=.33), and similarly no difference in 3-year OS (90%, 93%, 95%).[36] There was no significant difference between treatment groups when EFS and OS were analyzed by HR status. Given that pCR was significantly higher in the combination group, it was surprising that the 3-year EFS and OS were not different among groups. The authors suggested that the study was not powered to detect a significant difference in survival outcomes. The underlying heterogeneity of HER2+ tumors also may be a contributing factor, given that previous studies suggested that HER2+/HR– tumors and HER2+/HR+ tumors behave very differently. It should be kept in mind that all patients received further systemic chemotherapy after surgery (and patients with HR+ tumors received endocrine therapy). Therefore, the pCR rates in each of the arms do not reflect response to all the therapy that these patients ultimately received for their disease. This may also explain the discordant outcomes reported from another large randomized study, National Surgical Adjuvant Breast and Bowel Project Protocol B-41 (NSABP B-41: A Randomized Phase III Trial of Neoadjuvant Therapy for Patients With Palpable and Operable Breast Cancer), in which the combination of lapatinib and trastuzumab did not yield a significantly improved pCR. In that study, patients received all their systemic chemotherapy before surgery.[33] Like other studies, NeoALTTO demonstrated that women who achieved a pCR had significantly better 3-year EFS (hazard ratio, 0.38; *P*=.0003) and OS (hazard ratio, 0.35; *P*=.005) than those who did not achieve a pCR. However, pCR was significantly associated with EFS and OS only in patients with HR– tumors. Therefore, in this study, pCR does not appear to be predictive of long-term outcome in patients with HER2/HR coexpression.

Pertuzumab Plus Trastuzumab in the Neoadjuvant Setting

Pertuzumab (Perjeta, Genentech) is a monoclonal antibody that targets the extracellular dimerization domain of HER2 and inhibits the ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3, and HER4. In the metastatic setting, CLEOPATRA (A Study to Evaluate Pertuzumab + Trastuzumab + Docetaxel vs Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-positive Metastatic Breast Cancer) demonstrated significantly improved progression-free survival (PFS) and OS with the addition of pertuzumab to trastuzumab and docetaxel.[37] In the neoadjuvant setting, two phase 2 trials, TRYPHAENA (A Study of Pertuzumab in Combination With Herceptin and Chemotherapy in Patients With HER2-Positive Breast Cancer) and NeoSphere (A Study of Pertuzumab in Combination With Herceptin in Patients With HER2 Positive Breast Cancer), studied the combination of trastuzumab and pertuzumab plus chemotherapy.[38,39] Based on the promising safety and efficacy results of these 2 trials, as well as the significant survival benefit seen in the metastatic setting, the FDA granted accelerated approval to pertuzumab and trastuzumab for the neoadjuvant treatment of HER2+ breast cancer. Of these studies, only NeoSphere has reported on DFS to date.

NeoSphere was a multicenter, randomized phase 2 trial studying the efficacy and safety of neoadjuvant pertuzumab and trastuzumab with docetaxel in early-stage HER2+ breast cancer.[39] A total of 417 patients were randomly assigned to 1 of 4 groups and received 4 cycles of the following therapy before surgery: (A) trastuzumab plus docetaxel; (B) trastuzumab plus pertuzumab plus docetaxel; (C) trastuzumab plus pertuzumab; or (D) pertuzumab plus docetaxel. After surgery, patients in all groups received 3 cycles of identical chemotherapy (FEC) followed by completion of a full year of trastuzumab, with the exception of those in group C, in whom 4 cycles of docetaxel were added before FEC. The primary endpoint, in-breast pCR (ypT0/is), was significantly higher in group B than in group A (45.8% vs 29%, *P*=.014), followed by group D (29%) and group C (16.8%). The total pCR rate (ypT0/is ypN0) was reported as well (see Table 1). Consistent with previous studies, the pCR rate was higher in patients with HR– tumors than in those with HR+ tumors, and the ranking among groups was conserved (HR+ tumors, groups B, A, D, and C: 26.0%, 20.0%, 17.4%, and 5.9%, respectively; HR– tumors, groups B, A, D, and C: 63.2%, 36.8%, 30.0%, and 27.3%, respectively).[39]

The 5-year follow-up data of NeoSphere were recently presented at the 2015 American Society of Clinical Oncology (ASCO) annual meeting.[40] Although the study was not statistically powered to reach significance, the 5-year PFS—defined as time from randomization to time of first documentation of progressive disease, disease recurrence, or death—was highest in patients in group B, who received both trastuzumab and pertuzumab in addition to docetaxel (86%), and second-highest in group A (81%). This trend continued despite pCR status and/or HR status. Similarly, 5-year DFS was the highest in group B (84%) and second-highest in group A (81%). The outcome analyses in regard to pCR showed that 5-year PFS was higher in patients who achieved total pCR in the breast and axilla (ypT0/is ypN0) than in those who did not achieve total pCR (85% vs 76%; hazard ratio, 0.54; 95% CI, 0.29-1.00). Interestingly, total pCR was more predictive of PFS in patients with HR– breast cancer (PFS, 84% total pCR vs 72% no total pCR; hazard ratio, 0.65; 95% CI, 0.32-1.30) than in those with HR+ breast cancer (PFS, 90% total pCR vs 80% no total pCR; hazard ratio, 0.66; 95% CI, 0.15-2.79).

Ongoing Trials of Novel Agents (Table 2)

Trastuzumab emtansine (T-DM1; Kadcyla, Genentech) is a novel antibody–drug conjugate that links trastuzumab with the cytotoxic antimicrotubule agent DM1, a maytansine derivative. In the metastatic setting, T-DM1 was compared with lapatinib plus capecitabine in the large, randomized phase 3 EMILIA trial (An Open-label Study of Trastuzumab Emtansine [T-DM1] vs Capecitabine + Lapatinib in Patients With HER2-positive Locally Advanced or Metastatic Breast Cancer) trial. Both PFS and OS were significantly improved in the patients treated with T-DM1, and T-DM1 was associated with less toxicity.[41] This study established T-DM1 as the treatment of choice in the second-line HER2+ metastatic setting. The recently reported phase 3 MARIANNE study (A Study of Trastuzumab Emtansine [T-DM1] Plus Pertuzumab/Pertuzumab Placebo Versus Trastuzumab [Herceptin] Plus a Taxane in Patients With Metastatic Breast Cancer) evaluated T-DM1 with or without pertuzumab vs trastuzumab plus taxane (HT) as first-line therapy for advanced HER2+ breast cancer. In this study, the T-DM1 arms were shown to be noninferior (but not superior) to the trastuzumab arm.[42] Given the promising results of T-DM1 in the metastatic setting, neoadjuvant T-DM1 is undergoing active evaluation. The large, multicenter, randomized phase 2/3 "umbrella" trial ADAPT (Adjuvant Dynamic Marker-Adjusted Personalized Therapy Trial Optimizing Risk Assessment and Therapy Response Prediction in Early Breast Cancer) was designed to enroll approximately 5000 patients into 4 distinct subtrials based on their breast cancer subtype.[43] A total of 376 patients with HER2+/HR+ breast cancer were randomly assigned to receive 4 cycles (12 weeks) of 1 of 3 neoadjuvant therapies: T-DM1 (arm A), T-DM1 plus endocrine therapy (arm B), or trastuzumab plus endocrine therapy (arm C). The primary endpoint was pCR (ypT0/is ypN0). The study was closed early (376 of the planned 380 patients were enrolled) after the first interim analysis (n=130) showed that the efficacy endpoint had been reached. The pCR rate was substantially higher in the T-DM1–containing arms, with 40.5% in arm A and 45.8% in arm B vs 6.7% in arm C ($P<.001$).[44] The final analysis of 359 patients was presented at the 2015 San Antonio Breast Cancer Symposium, and pCR rates were again comparable in arm A and arm B (41.0% in arm A vs 41.5% in arm B; $P<.001$) but significantly higher than those in arm C (15.1%; $P<.001$) (Table 1).[45] Adding endocrine therapy to T-DM1 did not increase pCR, independently of menopausal status. Interestingly, early response biomarkers (low cellularity or Ki67 decrease ≥30%) were significantly associated with increased pCR rates (odds ratio, 2.2). The overall toxicity was low. Evaluation of prognostic biomarkers and mutational analyses are ongoing, and 5-year EFS and OS are included as secondary endpoints. The promising results from ADAPT support further evaluation of T-DM1 in the neoadjuvant setting and again highlight the need to investigate therapeutic regimens for HER2+/HR+ and HER2+/HR– tumors separately.

Several other neoadjuvant trials of T-DM1 with DFS and/or OS built in as an endpoint are ongoing. KRISTINE, or TRIO-021 (A Study Comparing Kadcyla Plus Perjeta Treatment to Chemotherapy Combined With Herceptin Plus Perjeta in Patients With HER2-Positive Breast Cancer; NCT02131064) is a large, randomized phase 3 trial comparing docetaxel and carboplatin plus dual inhibition with trastuzumab/pertuzumab (arm A) vs T-DM1 plus pertuzumab (arm B). A unique aspect of this trial is that after surgery, both arms will continue to receive their respective dual HER2-targeted therapy to complete a full year. The primary endpoint is pCR; secondary endpoints include EFS and DFS.

I-SPY 2 (Neoadjuvant and Personalized Adaptive Novel Agents to Treat Breast Cancer) is a phase 2 trial with 8 treatment arms that is using experimental drugs, including T-DM1/pertuzumab, pertuzumab/trastuzumab, neratinib, and ganitumab/metformin, in combination with standard chemotherapy in the neoadjuvant setting. One of the arms is comparing T-DM1 plus pertuzumab vs trastuzumab plus paclitaxel with doxorubicin and cyclophosphamide chemotherapy in HER2+ breast cancer. The trial uses an innovative adaptive design so that agents showing high or low Bayesian predictive probabilities of

Table 2. Ongoing Neoadjuvant Studies in HER2+ Breast Cancer That Are Collecting Long-term Outcome Data

Trial	Phase	**Neoadjuvant Regimen**	**Primary Endpoints**	**Selected Secondary Endpoints**
NSABP B41[33] (NCT00486668)	3	AC × 4→P (q1w) × 4 + T AC × 4→P × 4 + L AC × 4→P × 4 + T + L T: q1w, L: 1250 mg/d (alone) or 750 mg/d (combination)	pCR: ypT0/is	pCR: ypT0/is ypN0 Toxicity 5-y OS and RFS
TRYPHAENA[38] (NCT00976989)	2	1: FEC + T + Pert × 3→D (75-100 mg/m^2) + T + Pert × 3 2: FEC × 3→D + T + Pert × 3 3: D (75 mg/m^2) + carboplatin (AUC 6) + T + Pert × 6 T: q3w, FEC: 500/100/600 mg/m^2	Tolerability of neoadjuvant treatment: cardiac events, LVEF	pCR Safety/toxicity Clinical response rate, time to response DFS, PFS, OS
ADAPT[43-45] (NCT01779206)	2/3	HER2+/HR+: Arm (A): T-DM1 (q3w, 3.6 mg/kg) × 4 Arm (B): T-DM1 + endocrine therapy Arm (C): T (q3w) + endocrine therapy HER2+/HR–: Arm (A): 4c q3w T/Pert Arm (B): 4c q3w T/Pert + P (q1w) × 12	pCR rates Identify responder subpopulation within intermediate- and high-risk groups in any BC subtypes (HER2+/HR+, HER2+/HR–, HER2–/HR+, HER2–/HR–)	EFS, OS (up to 5y) Toxicity Cost-effectiveness Distant DFS Local and regional RFS
KRISTINE (NCT02131064)	3	Arm (A): D (75 mg/m^2)/carboplatin (AUC 6) + T/Pert × 6 Arm (B): T-DM1 (3.6 mg/kg) + Pert × 6 T: q3w	pCR	3-y EFS, invasive DFS, OS Breast-conserving surgery rate Adverse events Antitherapeutic antibodies
I-SPY 2 (NCT01042379)	2	Various drugs, including T-DM1, pertuzumab, neratinib ("graduated")	pCR	Establish predictive and prognostic indices for pCR and residual cancer burden 3-y and 5-y RFS and OS Adverse events
NSABP FB-7 (NCT01008150)	2	P + T→AC P + neratinib→AC P + T + neratinib→AC	pCR (ypT0/is ypN0)	pCR (ypT0/is) Clinical complete response RFS OS Toxicity

AUC, area under the curve; BC, breast cancer; DFS, disease-free survival; EFS, event-free survival; forward arrow, followed by; HER2, human epidermal growth factor 2; HR, hormone receptor; LVEF, left ventricular ejection fraction; OS, overall survival; pCR, pathologic complete response; q, every; RFS, relapse-free survival; w, weeks; y, year; ypT0, absence of invasive and in situ cancer in breast only; ypT0/is, absence of invasive cancer in breast only; ypT0 ypN0, absence of invasive and in situ cancer in breast and lymph nodes following completion of neoadjuvant therapy; ypT0/is ypN0: absence of invasive cancer in breast and lymph nodes; ypT0/is ypN0, absence of invasive cancer in breast and lymph nodes following completion of neoadjuvant therapy.

Unless otherwise specified in the table, names and doses of neoadjuvant regimens are as follows: **A**, Adriamycin (doxorubicin), 60 mg/m^2; **C**, cyclophosphamide, 600 mg/m^2; **D**, docetaxel; **E**, epirubicin, 90 mg/m^2; **F**, fluorouracil, 600 mg/m^2; **L**, lapatinib; **P**, paclitaxel, q1w dosing: 80 mg/m^2; **Pert**, pertuzumab, 840 mg loading dose, then 420 mg q3w; **T**, trastuzumab, q1w dosing: 4 mg/kg loading dose, then 2 mg/kg; q3w dosing: 8 mg/kg loading dose, then 6 mg/kg; **T-DM1**, trastuzumab emtansine, 3.6 mg/kg q3w.

success will be either "graduated" or "dropped" from the trial arms, and new drugs may enter. The primary endpoint is pCR rate, and secondary outcomes include biomarkers, safety data, and long-term relapse-free survival (RFS) and OS.

In addition to studies evaluating T-DM1, several ongoing trials are evaluating novel therapeutic targets in HER2+ breast cancer, such as neratinib, a pan-HER tyrosine kinase inhibitor. In I-SPY 2, a neoadjuvant regimen of neratinib and standard chemotherapy (paclitaxel + Adriamycin (doxorubicin) + cyclophosphamide) vs trastuzumab + standard chemotherapy) was found particularly beneficial for a subset of patients with HER2+/HR– stage 2/3 breast cancer (pCR rates of 56% vs 33%), with a predictive probability of success of 78% in the phase 3 trial. As a result, the drug was "graduated" from the trial and will be evaluated in I-SPY 3, the phase 3 study.[46] Additionally, an ongoing randomized phase 2 clinical trial, NSABP FB-7, is evaluating neoadjuvant neratinib and/or trastuzumab with paclitaxel followed by doxorubicin and cyclophosphamide as the chemotherapy backbone (NCT01008150). The preliminary data from

this 126-patient study were presented at the 2015 San Antonio Breast Cancer Symposium and showed a pCR rate of 38.1% in the trastuzumab group, 33% in the neratinib group, and 50% in the trastuzumab/neratinib combination group. As in previous studies, patients with HR– disease achieved a higher pCR rate than did those with HR+ disease.[47] Those studies included long-term RFS and OS as secondary endpoints.

Discussion

Follow-up data emerging from the first neoadjuvant trials in HER2+ disease have demonstrated that the addition of trastuzumab to chemotherapy improves not only pCR rates but also DFS/EFS and OS regardless of the chemotherapy backbone used.[16,19,21,22] These data support the standard use of trastuzumab for patients with HER2+ breast cancer who are receiving neoadjuvant systemic chemotherapy.

Although the addition of lapatinib to trastuzumab-based chemotherapy led to a statistically significant increase in pCR rates in several studies,[29,30,36] longer-term follow-up from NeoALTTO did not demonstrate a similar benefit in DFS or OS. Moreover, the addition of lapatinib to trastuzumab-based therapy significantly increased toxicity, thus limiting the delivery of standard doses of treatment to patients in the curative setting. Based on these findings, lapatinib is not considered a standard treatment in the neoadjuvant setting. In contrast, the addition of pertuzumab to trastuzumab and chemotherapy did improve pCR rates without a clinically significant increase in toxicity. In addition, the 3-year follow-up data from NeoSphere, a study that was not powered to address long-term outcomes, show a promising trend toward improved PFS with the docetaxel/trastuzumab/pertuzumab regimen.

The data are insufficient at this time to conclude that pCR is a reliable surrogate marker for EFS or OS in all breast cancer types. One issue that complicates the interpretability of data from the neoadjuvant studies in HER2+ breast cancer reported to date has been the inclusion of HR+ and HR– disease. Neoadjuvant studies using chemotherapy plus HER2-targeted therapy consistently demonstrate higher pCR rates in the HR– subgroup than in the HR+ subgroup.[15,19,36,47] Moreover, the strength of the association between pCR and EFS seems to be strongest in the HR– subtype.[8,40] It is important to note that with very few exceptions,[34,45] patients who have HR and HER2 coexpression have been treated without endocrine therapy in the neoadjuvant setting, which may impact pCR results in these patients. The fact that these patients receive many years of endocrine therapy after surgery (which positively affects their long-term outcome) may be leading to a lack of observed association between pCR and EFS in this subset of patients. It is hoped that newer studies—such as ADAPT—that include hormonally targeted therapy in combination with HER2-targeted regimens will provide additional insight into the short- and long-term benefits of dual inhibition of the hormone and HER2 pathways.

Although it is critical to define further the associations between pCR, EFS, and OS in HER2+ breast cancer, it is important to point out that the neoadjuvant trial design also provides a perfect setting to explore and validate additional novel biomarkers that may ultimately predict response to therapy and, it is hoped, long-term outcome. It may be that for certain subtypes of HER2+ breast cancer, pCR is not the optimal short-term endpoint. Instead, molecular changes in the tumor or tumor microenvironment may be more reliable predictors of long-term outcome. In fact, biomarkers such as tumor-infiltrating lymphocytes (TILs),[48-50] programmed death ligand 1 (PD-L1) expression, and activation of the phosphoinositide 3-kinase (PI3K) pathway[51] are being actively evaluated for their potential to predict long-term outcomes. Validating pCR and other markers as surrogate endpoints of long-term outcome will require that studies be thoughtfully designed to evaluate specific molecular subtypes within HER2+ breast cancer.

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