How We Treat Locally Advanced HER2-Positive Breast Cancer

Pedro Exman, MD, Sonia Pernas, MD, PhD, and Sara M. Tolaney, MD, MPH

The authors are affiliated with the Department of Medical Oncology at the Dana-Farber Cancer Institute in Boston, Massachusetts. Drs Exman and Pernas are research fellows and Dr Tolaney is an assistant professor.

Overview

- Neoadjuvant therapy should be the first choice in patients with HER2-positive locally advanced breast cancer.
- Pertuzumab should be added to trastuzumab and a taxane as first-line treatment in patients with HER2-positive metastatic breast cancer.
- Ado-trastuzumab (T-DM1) is the new standard of treatment for patients with HER2-positive breast cancer and residual disease after neoadjuvant treatment.
- Neratinib may be considered in selected cases in the adjuvant setting after trastuzumab-based therapy. However, no data are available on the use of neratinib in those patients who received prior pertuzumab or prior T-DM1.
- Anthracycline- and non–anthracycline-based chemotherapy are similar in efficacy but have different toxicity profiles.

Introduction

Breast cancer is a heterogeneous disease comprising several biological subtypes that are distinct in behavior, aggressiveness, and prognosis.[1,2] Locally advanced breast cancer (LABC), which accounts for 6% to 10% of new cases of breast cancer, generally is associated with a poor prognosis and may be inoperable at presentation or require mastectomy.[3-5]

The approach to LABC has evolved considerably over the years, and preoperative therapy is now the cornerstone of treatment. The goals of preoperative systemic therapy are to treat subclinical micrometastatic disease and increase the rate of downstaging, therefore increasing the likelihood of successful surgical resection. Additionally, this approach provides information regarding the responsiveness of the tumor to systemic therapy.

Amplification or overexpression of human epidermal growth factor receptor 2 (HER2) is present in approximately 20% of early breast cancers and 35% of LABCs,[6] and historically it has been associated with a poor prognosis.[2] However, the introduction of anti-HER2 agents has changed the paradigm of HER2-positive breast cancer in the last 2 decades, leading to unprecedented survival outcomes[7-10] and modifying the natural history of the disease.

Historically, the introduction of trastuzumab to neoadjuvant chemotherapy remarkably improved the probability of achieving a pathologic complete response (pCR)[9,10] with a favorable toxicity profile, which has been even further improved with the addition of pertuzumab to trastuzumab as dual HER2 blockade. Therefore, current National Comprehensive Cancer Network (NCCN) guidelines and the St. Gallen International Expert Consensus support neoadjuvant systemic therapy for locally advanced HER2-positive breast cancer, along with surgery, radiation therapy, and (when appropriate) endocrine therapy.[11,12]

In this article, we review the best approaches to the treatment of locally advanced HER2-positive breast cancer (see Figure for an initial approach), considering the clinical trial data that are currently available (see Table).[6,13-35]

Anti-HER2 Drugs

Trastuzumab

The addition of trastuzumab to standard therapy dramatically improves disease-free survival (DFS) and overall survival (OS) in both the early and advanced settings. In the neoadjuvant setting, the addition of trastuzumab to standard chemotherapy was a landmark in the treatment of HER2-positive breast cancer, doubling the probability of achieving a pCR.[6,36,37] The NOAH (Neoadjuvant Herceptin)[6] trial was the first randomized phase 3 trial to evaluate the addition of 1 year of

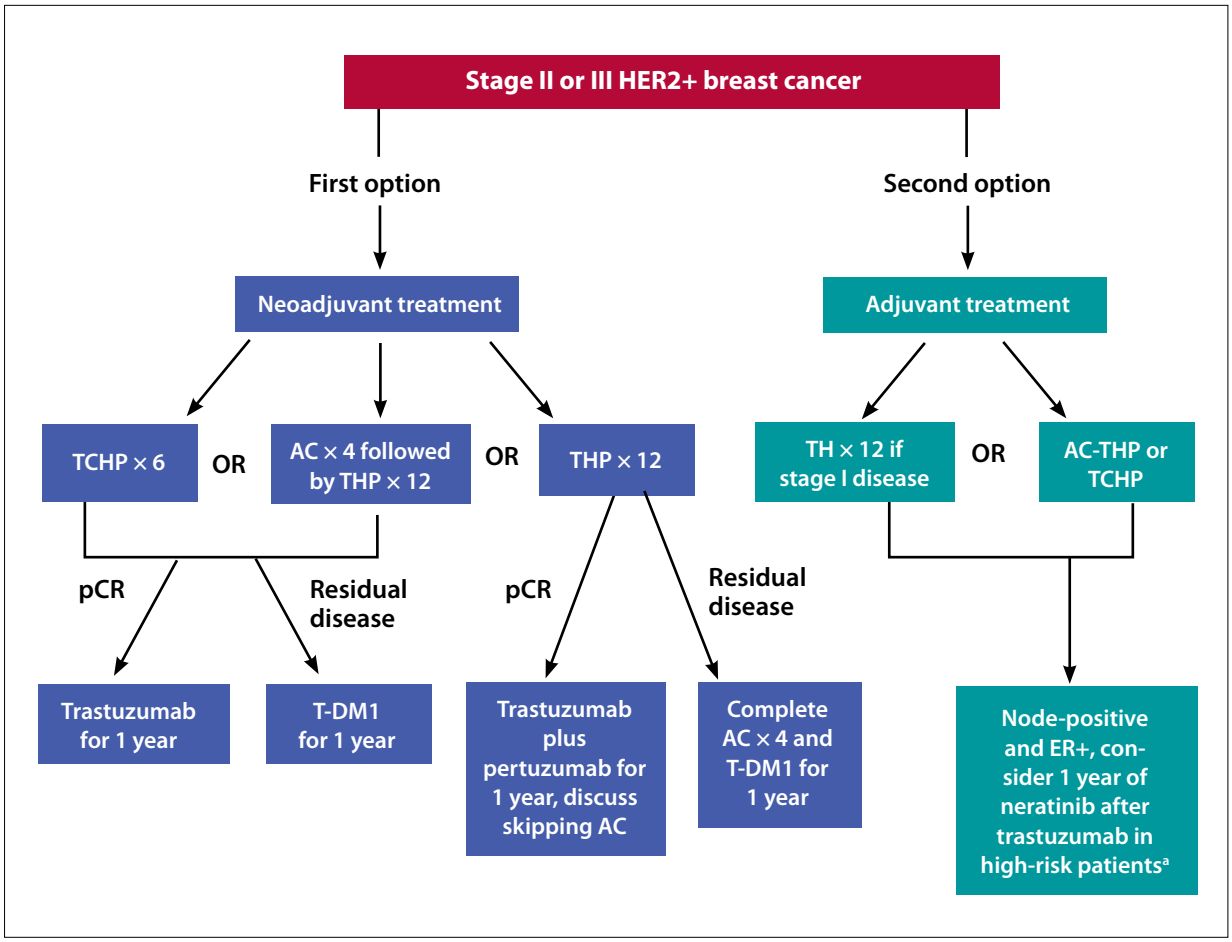

Figure. Recommended treatment for patients with locally advanced HER2-positive breast cancers.

[a] No data are available on the use of neratinib for 1 year in those patients who received prior pertuzumab.

AC, doxorubicin and cyclophosphamide; AC-THP, doxorubicin and cyclophosphamide followed by paclitaxel, pertuzumab, and trastuzumab; ER+, estrogen receptor–positive; HER2+, human epidermal growth factor receptor 2–positive; pCR, pathologic complete response; TCHP, docetaxel, carboplatin, and trastuzumab plus pertuzumab; T-DM1, ado-trastuzumab emtansine; TH, paclitaxel and trastuzumab; THP, docetaxel, trastuzumab, and pertuzumab.

trastuzumab (started as neoadjuvant and continued as adjuvant therapy) to neoadjuvant chemotherapy in HER2-positive LABC. The primary endpoint of event-free survival (EFS) was met, demonstrating an absolute improvement of 15% in events when patients who received trastuzumab were compared with patients who received chemotherapy alone (hazard ratio [HR], 0.59; 95% CI, 0.38-0.90; *P*=.013).[6] Furthermore, the addition of trastuzumab significantly increased the proportion of patients with a pCR in the breast (43% vs 22%, respectively). Results after 5.4 years of follow-up showed a sustained significant benefit in EFS associated with trastuzumab-containing therapy and provided important insight into the association between pCR and EFS in patients receiving trastuzumab (HR, 0.64; 95% CI, 0.54-0.93; *P*=.016).[13] Similar findings were obtained in the TECHNO (Taxol Epirubicin Cyclophosphamide Herceptin Neoadjuvant) and GeparQuattro (Combination Chemotherapy With or Without Capecitabine and/or Trastuzumab Before Surgery in Treating Women With Stage I, Stage II, or Stage III Breast Cancer) trials, demonstrating that patients with HER2-positive disease who received trastuzumab in combination with neoadjuvant chemotherapy and achieved a pCR in breast and lymph nodes (38.7% and 34.7%, respectively) had better long-term outcomes than those of patients without a pCR.[14,15]

These results further support the use of trastuzumab as the mainstay for the treatment of HER2-positive LABC.

Table. Clinical Trials That Evaluated Neoadjuvant Treatment in HER2-Positive Breast Cancer

Trial	Phase	N	Drugs	pCR	*P* Value	Survival
Trastuzumab-based treatment						
NOAH[6,13]	3	235	Arm A: AT CMF Arm B: AT>CMF+H	22% 43%	.0007	EFS HR 0.59; *P*=.013
TECHNO[14]	2	217	EC-T>H	38.7%	Not compared	3-y DFS 88.1%
GeparQuattro[15]	3	451	EC-T>H	34.7%	Not compared	NR
ACOSOG Z1041[16,17]	3	282	Arm A: FEC>TH Arm B: TH>FEC+H	56.5% 54.2%	>.05	NR
Pertuzumab-based treatment						
NeoSphere[18,19]	2	417	Arm A: T+H Arm B: T+P Arm C: T+HP Arm D: H+P	29% 24% 46% 17%	.0141	DFS HR 0.69 95% CI 0.34-1.40
TRYPHAENA[20,21]	2	225	Arm A: FEC+HP>T+HP Arm B: FEC>T+HP Arm C: TCb+HP	61.6% 57.3% 66.2%	Not compared	NR
KRISTINE[22]	3	432	Arm A: T-DM1+P Arm B: TCHP	44.4% 55.7%	.016	NR
BERENICE[23]	2	397	Arm A: ddAC-THP Arm B: FEC-THP	61.8% 60.7%	Not compared	NR
WSG-ADAPT (in HR- , HER2+)[24]	2	134	Arm A: THP Arm B: H+P	90.5% 36.3%	Not compared	NR
Lapatinib-based treatment						
Neo ALTTO[25]	3	455	Arm A: T+L Arm B: T+H Arm C: T+H+L	24.7% 29.5% 51.3%	.0001	Nonsignificant
NSABP B-41[26]	3	529	Arm A: T+L Arm B: T+H Arm C: T+H+L	53.2% 52.5% 62%	.09	NR
CALGB-40601[27]	3	305	Arm A: T+L Arm B: T+H Arm C: T+H+L	46% 32% 56%	.11	NR
CHER-LOB[28]	2	121	Arm A: FEC+L Arm B: FEC+H Arm C: FEC+H+L	26% 25% 46%	.19	NR
PAMELA[29]	2	151	Arm A: L+H	30%	-	NR
TBCRC 006[30]	2	65	Arm A: L+H (letrozole if ER+)	27%	-	NR
T-DM1–based treatment						
I-SPY2[31]	2	127	Arm A: T-DM1+P Arm B: T+H	52% 22%	Not compared	NR
KRISTINE[22]	3	432	Arm A: T-DM1+P Arm B: TCH+P	44.4% 55.7%	.016	NR
KATHERINE[32]	3	1486	Arm A: T-DM1 Arm B: H	NR	<.001	iDFS HR 0.50; 95% CI 0.39-0.64

(Table continued on next page)

Table. *(Continued)* Clinical Trials That Evaluated Neoadjuvant Treatment in HER2-Positive Breast Cancer

Trial	Phase	N	Drugs	pCR	*P* Value	Survival
T-DM1–based treatment *(Continued)*						
WSG-ADAPT (in HR+, HER2+)[33]	2	375	Arm A: T-DM1+endocrine therapy Arm B: T-DM1 Arm C: T+endocrine therapy	41.5% 41.0% 15.1%	<.001	NR
Neratinib-based treatment						
NSABP FB-7[34]	2	140	Arm A: T+neratinib Arm B: T+H Arm C: T+H+neratinib	33% 38% 50%	Not compared	NR
I-SPY2[35]	2	127	Arm A: neratinib+AC-T Arm B: AC-TH	56% 33%	Not compared	NR

AC-T, doxorubicin and cyclophosphamide followed by paclitaxel; AC-TH, doxorubicin and cyclophosphamide followed by paclitaxel and trastuzumab; AT, doxorubicin and paclitaxel; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; ddAC, dose-dense doxorubicin plus cyclophosphamide; DFS, disease-free survival; EC-T, epirubicin and cyclophosphamide followed by docetaxel; EFS, event-free survival; ER+, estrogen receptor–positive; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; FEC+HP, 5-fluorouracil, epirubicin, and cyclophosphamide plus trastuzumab and pertuzumab; FEC-T, 5-fluorouracil, epirubicin, and cyclophosphamide followed by docetaxel; H, trastuzumab; HP, trastuzumab and pertuzumab; HR, hazard ratio; iDFS, invasive DFS; L, lapatinib; NR, not reported; P, pertuzumab; pCR, pathologic complete response; T, docetaxel or paclitaxel; T-DM1, ado-trastuzumab; TCb+HP, docetaxel and carboplatin plus trastuzumab and pertuzumab; TH, docetaxel or paclitaxel and trastuzumab; THP, docetaxel or paclitaxel, trastuzumab, and pertuzumab; TP, docetaxel or paclitaxel and pertuzumab.

Pertuzumab

The incorporation of pertuzumab (Perjeta, Genentech) was also a breakthrough in the treatment of advanced HER2-positive breast cancer. This anti-HER2 antibody binds the extracellular domain 2 of the HER2 protein and inhibits the heterodimerization of HER2 with HER3 receptors, one of the most powerful heterodimers. In the phase 3 CLEOPATRA trial (A Study to Evaluate Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-positive Metastatic Breast Cancer), the addition of pertuzumab to trastuzumab and docetaxel in the first-line treatment of HER2-positive metastatic breast cancer achieved an absolute survival gain of 15.7 months vs trastuzumab and docetaxel alone.[38]

The phase 2 NeoSphere trial (A Study of Pertuzumab in Combination With Herceptin in Patients With HER2 Positive Breast Cancer) evaluated pertuzumab in the preoperative setting.[18] Patients were randomly assigned to receive neoadjuvant docetaxel plus trastuzumab, docetaxel plus pertuzumab, docetaxel plus trastuzumab and pertuzumab, or the combination of trastuzumab and pertuzumab without chemotherapy. All patients received adjuvant 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) after surgery and 1 year of maintenance trastuzumab. With pCR as the primary endpoint, the combination of chemotherapy plus dual HER2-targeting agents achieved a pCR rate in breast (ypT0/is) of 45.8%, compared with 29% for trastuzumab and docetaxel, 24% for pertuzumab and docetaxel, and 16.8% for dual HER2 blockade without chemotherapy (*P*=.0141). In addition, in the 5-year update of NeoSphere, the addition of pertuzumab to trastuzumab and docetaxel seemed to improve DFS compared with trastuzumab plus docetaxel alone, but the trial was not powered for formal statistical hypothesis testing.[19]

Similarly, the randomized phase 2 TRYPHAENA trial (A Study of Pertuzumab in Combination With Herceptin and Chemotherapy in Participants With HER2-Positive Breast Cancer)[20] assessed overall safety and cardiac toxicity (primary objective) in patients who received dual HER2 blockade with trastuzumab and pertuzumab in combination with anthracycline- and taxane-based chemotherapy or an anthracycline-free regimen in the neoadjuvant setting. Patients with operable, locally advanced or inflammatory, HER2-positive breast cancer were randomly assigned to receive one of the following regimens: FEC plus concomitant trastuzumab and pertuzumab followed by docetaxel plus trastuzumab and pertuzumab (arm A); FEC followed by docetaxel plus trastuzumab and pertuzumab (arm B); or a non-anthracycline regimen with docetaxel and carboplatin plus trastuzumab and pertuzumab (arm C). The number of cardiac events was low in all 3 arms, and the combination of trastuzumab and pertuzumab was well tolerated regardless of whether the agents were

given sequentially or concomitantly with anthracycline-based chemotherapy or combined with carboplatin-based chemotherapy. All regimens were highly active in terms of pCR, with pCR rates in breast (ypT0/is) of 61.6% in arm A, 57.3% in arm B, and 66.2% in arm C.[20] Long-term survival outcomes were similar across treatment arms in the TRYPHAENA trial, with improved DFS in those patients with a pCR. No new safety issues were identified during long-term follow-up.[21] The results of the TRYPHAENA and NeoSphere trials led to US Food and Drug Administration (FDA) approval of pertuzumab in the preoperative setting.

More recently, the phase 2 BERENICE trial (A Study Evaluating Pertuzumab Combined With Trastuzumab and Standard Anthracycline-based Chemotherapy in Participants With Human Epidermal Growth Factor Receptor 2-Positive Locally Advanced, Inflammatory, or Early-stage Breast Cancer) demonstrated safety and efficacy in terms of pCR of dual anti-HER2 therapy combined with 2 different anthracycline-containing regimens followed by paclitaxel or docetaxel.[23] The WSG-ADAPT trial (Adjuvant Dynamic Marker-Adjusted Personalized Therapy Trial Optimizing Risk Assessment and Therapy Response Prediction in Early Breast Cancer) from the West German Study Group evaluated the efficacy of 12 weeks of neoadjuvant dual blockade with trastuzumab and pertuzumab with or without weekly paclitaxel in an estrogen receptor (ER)-negative/HER2-positive subgroup.[24] The impressive pCR of 90.5% achieved in the chemotherapy arm compared with 36.3% in the arm that received pertuzumab plus trastuzumab without chemotherapy confirmed the favorable approach of associating chemotherapy with anti-HER antibodies.[24] Yet, although the inclusion of chemotherapy should be considered the standard treatment owing to significantly better outcomes, isolated dual HER2-antibody blockade remarkedly eradicated HER2-positive disease in a considerable proportion of patients, with a favorable toxicity profile. This finding points to the need to identify a subset of patients who can be treated exclusively with HER2-directed therapy.

The phase 3 APHINITY trial (A Study of Pertuzumab in Addition to Chemotherapy and Trastuzumab as Adjuvant Therapy in Participants With Human Epidermal Growth Receptor 2-Positive Primary Breast Cancer) evaluated the addition of pertuzumab or placebo to chemotherapy plus trastuzumab as adjuvant treatment for patients with HER2-positive early breast cancer.[39] After a median follow-up of 45.4 months, an increased benefit from 1 year of pertuzumab plus trastuzumab was mainly observed in the patients who had positive nodes at initial presentation (62.6%), with an absolute gain in 3-year invasive DFS (iDFS) of 1.8% and a 23% reduction in death due to invasive disease. In contrast, no increase in 3-year iDFS (HR, 1.13; 95% CI, 0.68-1.86; *P*=.64) was observed in patients with node-negative disease. Additionally, a trend toward an increased benefit with pertuzumab was observed in ER-negative patients (iDFS of 91.0% in the pertuzumab arm and 88.7% in the placebo arm; *P*=.085). Grade 3 or 4 diarrhea was more frequent in patients in the pertuzumab arm than in patients in the control arm (9.8% vs 3.7%, respectively), but no difference was observed between the rates of cardiac toxicities in the 2 arms.[39] The results led to FDA approval of pertuzumab in the adjuvant setting.

Lapatinib

Lapatinib (Tykerb, Novartis), a reversible inhibitor of the tyrosine kinase domains of both endothelial growth factor receptor (EGFR) and HER2, has demonstrated activity in the metastatic setting.[40] However, data to support its use for curative intent (neoadjuvant or adjuvant setting) are still lacking.[41] When compared with trastuzumab as the sole anti-HER2 therapy administered with standard neoadjuvant chemotherapy, lapatinib achieved lower pCR rates (22.7% vs 30.3%; odds ratio, 0.68; 95% CI, 0.47-0.97; *P*=.04) with a significant increase in adverse events, such as grade 3/4 diarrhea (11.7% vs 2.6%; *P*<.0001) and grade 3 skin rashes (7.1% vs 0.7%, *P*<.0001); one-third of the patients in the lapatinib group discontinued treatment owing to side effects.[26,42]

The largest trial that evaluated the addition of lapatinib to standard neoadjuvant chemotherapy plus trastuzumab was the NSABP B-41 trial (A Study of AC Followed by a Combination of Paclitaxel Plus Trastuzumab or Lapatinib or Both Given Before Surgery to Patients With Operable HER2 Positive Invasive Breast Cancer).[26] This phase 3 trial compared 3 regimens: standard chemotherapy with lapatinib alone, standard chemotherapy plus trastuzumab, and standard chemotherapy with trastuzumab plus lapatinib. The percentage of patients with pCR was 53.2% in the lapatinib group, 52.5% in the trastuzumab group, and 62% in the combination group; however, this difference was not statistically significant (*P*=.095). Furthermore, more grade 2 and 3 toxic effects occurred in the 2 groups receiving lapatinib, with an incidence of grade 3 diarrhea of 20% to 27%.[26] These findings were supported by the phase 3 CALGB 40601 study (Paclitaxel and Trastuzumab With or Without Lapatinib in Treating Patients With Stage II or Stage III Breast Cancer That Can Be Removed by Surgery), which also demonstrated a higher pCR rate when lapatinib was combined with trastuzumab and chemotherapy, although no statistically significant difference was seen.[27]

In contrast, the Neo ALTTO trial (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation)

showed a significantly higher pCR rate for preoperative chemotherapy combined with lapatinib plus trastuzumab than for preoperative chemotherapy combined with either lapatinib or trastuzumab alone (51.3% vs 24.7% vs 29.5%, respectively; *P*=.0001).[25] However, in an updated analysis with long-term survival outcomes, no differences in EFS (HR, 0.78, CI; 95%, 0.47-1.28; *P*=.33) or OS (HR, 0.62; 95% CI, 0.30-1.25; *P*=.19) were seen when the dual anti-HER2 treatment was compared with the trastuzumab-only treatment. Likewise, in the NSABP B-41 trial, patients in both lapatinib arms experienced limiting toxicities, with a high rate of grade 3 diarrhea and an increase in abnormal liver function tests.[25]

In a meta-analysis of randomized trials evaluating dual blockade with lapatinib and trastuzumab vs single-agent trastuzumab combined with chemotherapy as neoadjuvant treatment of HER2-positive breast cancer, the dual blockade was associated with a significant absolute increase in pCR of 13%, but this gain was more evident in patients with ER-negative disease than in those with ER-positive disease (18% vs 8%), and in those who received taxane monotherapy regimens vs polychemotherapy (16% vs 10%).[43]

Owing to its higher toxicity profile, its lack of efficacy in the adjuvant setting as demonstrated in the ALTTO trial (Adjuvant Lapatinib And/Or Trastuzumab Treatment Optimisation),[41] and conflicting results regarding its use as a neoadjuvant drug, with absence of benefit in DFS or OS, lapatinib is not recommended for patients with early-stage or locally advanced HER2-positive breast cancer.

Ado-Trastuzumab Emtansine

Ado-trastuzumab emtansine (Kadcyla, Genentech), often referred to as T-DM1, is an antibody-drug conjugate in which a microtubule toxin (emtansine) is linked to trastuzumab. After binding to HER2, the conjugate is internalized and the toxin is released within the cell, resulting in cell death. On the basis of impressive results and a favorable toxicity profile in patients with metastatic disease,[44,45] T-DM1 has been evaluated in the neoadjuvant setting. One of the experimental arms of the I-SPY2 (Neoadjuvant and Personalized Adaptive Novel Agents to Treat Breast Cancer) platform randomized patients with HER2-positive LABC to receive T-DM1 plus pertuzumab or paclitaxel plus trastuzumab; patients in both arms then received doxorubicin and cyclophosphamide before surgery.[31] Although not directly compared, the pCR rate was numerically higher in the T-DM1 arm than in the arm that received paclitaxel plus trastuzumab (52% vs 22%, respectively), with fewer side effects.[31]

In the ER-positive/HER2-positive cohort of the WSG-ADAPT trial, T-DM1 with and without endocrine therapy in the neoadjuvant setting was associated with substantial pCR rates of 41.5% and 41.0%, respectively, and a low profile of adverse effects.[33]

The randomized phase 3 KRISTINE trial (A Study Evaluating Trastuzumab Emtansine Plus Pertuzumab Compared With Chemotherapy Plus Trastuzumab and Pertuzumab for Participants With Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer) assigned patients to receive either 6 cycles of neoadjuvant docetaxel, carboplatin, and trastuzumab plus pertuzumab (TCH+P) or 6 cycles of T-DM1 plus pertuzumab.[22] After surgery, patients resumed the same HER2-targeted regimen to which they had been randomly assigned in the neoadjuvant phase (T-DM1 plus pertuzumab or trastuzumab plus pertuzumab) for an additional 12 cycles. The primary endpoint was pCR, and secondary endpoints were DFS, OS, safety, rates of breast-conserving surgery, and patient-reported quality of life. A pCR was achieved in 44.4% of patients in the T-DM1 plus pertuzumab group and in 55.7% of patients in the TCH+P group (*P*=.016). However, not surprisingly, fewer patients in the T-DM1 treatment group had grade 3/4 adverse events.[22]

The KATHERINE trial (A Study of Trastuzumab Emtansine Versus Trastuzumab as Adjuvant Therapy in Patients With HER2-Positive Breast Cancer Who Have Residual Tumor in the Breast or Axillary Lymph Nodes Following Preoperative Therapy), which was presented at the San Antonio Breast Cancer Symposium in 2018 and simultaneously published in the *New England Journal of Medicine*, established a new paradigm in the treatment of patients who had HER2-positive breast cancer with residual disease after neoadjuvant treatment.[32] This phase 3, multicenter trial randomly assigned patients with residual disease after taxane-based neoadjuvant systemic therapy to receive 14 cycles of 3.6 mg of T-DM1 every 3 weeks or standard trastuzumab every 21 days for 14 cycles. A total of 1486 patients (743 in each arm) were assigned to receive T-DM1 or trastuzumab. The primary endpoint was iDFS, and secondary endpoints included distant recurrence–free survival, OS, and safety. After a follow-up of 41 months, the 3-year iDFS rate was 88.3% in the T-DM1 arm and 77.0% in the trastuzumab arm (HR, 0.50; 95% CI, 0.39-0.64; *P*<.001). In addition, an absolute improvement in the distant recurrence–free survival rate at 3 years of 6.7% (HR, 0.60; 95% CI, 0.45-0.79) and a trend toward improvement in the interim OS analysis (HR, 0.70; 95% CI, 0.47-1.05; *P*=.08) were observed. It is important to note, however, that no differences were found in terms of preventing central nervous system (CNS) recurrences.[32] Of note, 75.9% of the patients assigned to the trastuzumab group and 77.9% of patients in the T-DM1 group had previously received

anthracycline-based therapy. In the subgroup analyses, the benefit was consistent across all groups, including patients with residual disease of at least 1 cm, those with ER-positive or ER-negative disease, and those who had received neoadjuvant dual anti-HER2 therapy (18.7% of the patients had received neoadjuvant pertuzumab). A higher percentage of patients in the T-DM1 arm than in the trastuzumab arm had grade 3 or higher adverse events (25.7% vs 15.4%, respectively). Patients assigned to the T-DM1 group most commonly presented with fatigue, thrombocytopenia, and elevated liver function test values. The incidence of cardiac events was similar in the 2 groups (0.6 % in the trastuzumab group and 0.1% in the T-DM1 group). Of note, 18% of patients discontinued T-DM1 and crossed over to trastuzumab owing to adverse events, raising the question of the optimal duration of the T-DM1 treatment. As has been done with trastuzumab, more studies are needed to evaluate if a shorter duration of T-DM1 can achieve similar benefits.[32]

Although not yet FDA-approved in this setting, T-DM1 will shortly become the new standard of treatment for patients with HER2-positive breast cancer and residual disease after neoadjuvant treatment. In addition, the phase 3 KAITLIN trial (A Study of Trastuzumab Emtansine Plus Pertuzumab Following Anthracyclines in Comparison With Trastuzumab Plus Pertuzumab and a Taxane Following Anthracyclines as Adjuvant Therapy in Participants With Operable HER2-Positive Primary Breast Cancer; NCT01966471) is comparing T-DM1 plus pertuzumab with a taxane plus pertuzumab and trastuzumab after anthracycline-based treatment in the adjuvant setting.[46] This multicenter randomized trial has accrued 1846 patients, and its results may strengthen the role of T-DM1 in early-stage HER2-positive disease.[46]

Neratinib

Neratinib (Nerlynx, Puma Biotechnology), a potent irreversible tyrosine kinase inhibitor of HER1, HER2, and HER4, was approved by the FDA for the treatment of early-stage HER2-positive breast cancer after the ExteNET trial (Study Evaluating The Effects Of Neratinib After Adjuvant Trastuzumab In Women With Early Stage Breast Cancer) demonstrated an increase in iDFS in patients who received 1 year of adjuvant neratinib after trastuzumab-based standard treatment (5-year iDFS rate, 90.2% vs 87.7%; HR, 0.73; 95% CI, 0.57-0.92). Preplanned subgroup analysis demonstrated a benefit only in patients with ER-positive disease (HR, 0.60; 95% CI, 0.43-0.83) and in patients with more than 4 positive lymph nodes (HR, 0.67; 95% CI, 0.46-0.96). No benefit in iDFS was seen in patients with ER-negative disease (HR, 0.95; 95% CI, 0.66-1.35; *P*=.06).[47]

A limiting aspect of the daily use of neratinib is its toxicity, with diarrhea a significant adverse event. Among those patients receiving neratinib in the trial, the frequency of grade 3 to 4 diarrhea was 40% without diarrhea prophylaxis.[47] The CONTROL trial was designed to achieve better control of diarrhea during neratinib treatment in the adjuvant setting. This open-label phase 2 study (A Study Looking the Incidence and Severity of Diarrhea in Patients With Early-Stage HER2+ Breast Cancer Treated With Neratinib and Loperamide; NCT02400476) evaluated the addition of budesonide or colestipol to loperamide for 1 or 2 cycles to improve the prophylaxis for grade 3 diarrhea.[48] A total of 137 women were enrolled in the loperamide-alone arm, 64 women were enrolled in the loperamide plus budesonide arm, and 39 women were enrolled in the loperamide plus colestipol arm. The incidence rates of grade 3 diarrhea were 30.7%, 25%, and 7.7%, respectively; the incidence, severity, and duration of diarrhea were lower than in the ExteNET data.[48]

The I-SPY2 trial compared neratinib plus doxorubicin/cyclophosphamide followed by paclitaxel with standard doxorubicin and cyclophosphamide followed by paclitaxel plus trastuzumab. The pCR rate was higher in the neratinib arm (39% vs 23%), and this benefit was greater in patients with ER-negative disease than in patients with ER-positive disease (56% vs 33%).[35]

The NSABP-FB7 trial (Phase II Randomized Trial Evaluating Neoadjuvant Therapy With Neratinib and/or Trastuzumab Followed by Postoperative Trastuzumab in Women With Locally Advanced HER2-positive Breast Cancer), presented at the San Antonio Breast Cancer Symposium in 2015, randomly assigned 140 patients to weekly paclitaxel plus neratinib, paclitaxel plus trastuzumab, or paclitaxel plus neratinib/trastuzumab, followed by AC. The pCR rates in breast and nodes were 33%, 38% and 50%, respectively. Again, the highest pCR rate achieved with the dual anti-HER2 therapy was observed in patients with ER-negative disease, with a pCR of 73%.[34]

Because of the lack of strong data, neratinib is not indicated as standard in the neoadjuvant treatment of locally advanced HER2-positive disease. However, it may be considered in the adjuvant setting, with particular benefit in patients with ER-positive disease, as previously mentioned. The challenge, however, is that patients in the ExteNET study had not received prior pertuzumab, so it is hard to know if the benefits would persist in a pertuzumab-pretreated population. Additionally, with the recent data from KATHERINE suggesting benefits of adjuvant T-DM1 in patients with residual disease after preoperative therapy, it is also hard to know what the additional benefit would be with neratinib after T-DM1.

The Chemotherapy Backbone

Traditionally, most data for neoadjuvant therapy in HER2-positive breast cancer come from randomized trials that have used anthracycline- and taxane-based chemotherapy because locally advanced HER2-positive disease presents with an intrinsic substantial risk for recurrence. The randomized phase 3 ACOSOG-Z1041 trial (Combination Chemotherapy and Paclitaxel Plus Trastuzumab in Treating Women With Palpable Breast Cancer That Can Be Removed by Surgery) was designed to assess 2 different strategies for administering trastuzumab with neoadjuvant chemotherapy: concurrent vs sequential use of trastuzumab and anthracyclines (paclitaxel and trastuzumab followed by concurrent trastuzumab and FEC-75 vs FEC-75 followed by paclitaxel and trastuzumab).[16] The pCR rates were similar in the 2 arms (nearly 55%), and the occurrence of asymptomatic decreases in left ventricular ejection fraction (LVEF) during neoadjuvant chemotherapy was similar in the 2 groups.[16] After a median follow-up of 5 years, no differences were found in respect to DFS or OS between the 2 approaches of administering trastuzumab; thus, the concurrent administration of trastuzumab with anthracyclines offers no additional benefit.[17]

In addition, 2 other randomized studies (NSABP B-41 and GeparQuinto) evaluated the role of lapatinib in the neoadjuvant setting also demonstrated efficacy and safety profiles for the use of anthracycline-based regimens with anti-HER2 agents.[26,42]

Non–anthracycline-based regimens with carboplatin, a taxane, and trastuzumab have demonstrated similar efficacy and less long-term toxicity in the adjuvant setting.[49] In the BCIRG 006 trial (Combination Chemotherapy With or Without Trastuzumab in Treating Women With Breast Cancer), 3222 women with high-risk HER2-positive disease were randomly assigned to receive docetaxel plus carboplatin and trastuzumab (TCH) vs doxorubicin plus cyclophosphamide followed by a taxane (ACT) plus trastuzumab (AC+TH) or ACT alone.[50] Although the trial was not powered to compare the 2 different trastuzumab-based regimens, the DFS rate at 10.3 years of follow-up was 74.6% in the women who received AC+TH and 73% in the TCH arm, with only 10 events separating the 2 trastuzumab-based regimens. However, significantly lower rates of grade 3 or 4 neutropenia (66% vs 72%, respectively), lower rates of congestive heart failure (0.4% vs 2%, respectively), and lower rates of sensory neuropathy (36% vs 50%, respectively) were seen in the TCH arm than in the AC+TH arm. Both trastuzumab-containing regimens resulted in improved survival outcomes when compared with ACT.[50] In the neoadjuvant scenario, the phase 3 TRAIN-2 study (Neoadjuvant Chemotherapy in HER2 Positive Breast Cancer), presented at the American Society of Clinical Oncology (ASCO) annual meeting in 2017, assessed pCR in patients who underwent chemotherapy with FEC followed by carboplatin and paclitaxel vs pCR in patients who underwent a non-anthracycline regimen with carboplatin plus paclitaxel.[51] Both arms received dual anti-HER2 therapy with trastuzumab and pertuzumab. Although the follow-up was too short to evaluate survival outcomes, the pCR rates were similar in the 2 arms (68% and 67%, respectively; P=.75). Subgroup analyses did not demonstrate different responses in patients with ER-positive vs ER-negative disease. However, rates of febrile neutropenia and decreased LVEF were higher in the patients who received the anthracycline regimen.[51]

Data in the adjuvant and neoadjuvant settings for anthracycline- and non–anthracycline-based chemotherapy demonstrate similar efficacy but different toxicity profiles; therefore, the choice of regimen should be individualized for each patient.

Approach to Patients Treated With Up-front Surgery

In patients with HER2-positive LABC, neoadjuvant treatment with pertuzumab, trastuzumab, and chemotherapy should be strongly recommended. However, for those patients with HER2-positive LABC who have undergone surgery as initial therapy, adjuvant treatment with chemotherapy and pertuzumab and trastuzumab should be recommended based on data from APHINITY[39] trial and the high risk for relapse.

The sequential use of neratinib should be considered in those patients with ER-positive tumors who have already completed adjuvant treatment with chemotherapy and trastuzumab.[47] However, no data exist to support the benefits of adjuvant neratinib following treatment with pertuzumab and trastuzumab or after T-DM1.

Conclusions

Neoadjuvant therapy should be the first choice for patients with HER2-positive LABC. This strategy treats micrometastatic disease, allows an early evaluation of disease sensitivity to available drugs, and improves rates of breast-conserving surgery in some cases. It also allows adjuvant treatment strategies to be adapted according to response to therapy so that therapy can be escalated for those without a pCR and de-escalated for those with a pCR. TCHP or doxorubicin/cyclophosphamide followed by paclitaxel, trastuzumab, and pertuzumab (AC-THP) have similar pCR rates but different toxicity profiles, and both are reasonable choices, with selection

of the chemotherapy backbone dependent on cardiac risk factors. Another option is a treatment scheme based on the NeoSphere trial, in which patients received THP followed by surgery and then anthracycline-based treatment postoperatively.

On the basis of the outstanding results of the KATHERINE trial, patients with residual disease after neoadjuvant chemotherapy should also receive 14 cycles of adjuvant T-DM1. Adjuvant sequential neratinib may be considered in high-risk patients with ER-positive disease who have completed 1 year of trastuzumab. However, no data exist that support the benefits of adjuvant neratinib following treatment with pertuzumab and trastuzumab or after T-DM1.

Finally, better strategies to decrease the incidence of brain metastasis should also be a priority because of the intrinsic high risk for brain metastases in HER2-positive breast cancer.[52] The use of T-DM1 in the KATHERINE trial was not effective in preventing CNS recurrence (4.3% in the trastuzumab group and 5.9% in the T-DM1 arm). Conversely, although neratinib was studied in the metastatic setting, the recently announced positive NALA trial (A Study of Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in Patients With HER2+ Metastatic Breast Cancer Who Have Received Two or More Prior HER2 Directed Regimens in the Metastatic Setting) showed that it has activity in the CNS, with fewer CNS events occurring with neratinib plus capecitabine than with lapatinib plus capecitabine (P=.043).[53] Therefore, the combination of T-DM1 and neratinib in high-risk patients with residual disease may be worthy of study.

Disclosures

Dr Exman has no disclosures. Dr Pernas has received personal fees to participate in a speaker's bureau and nonfinancial support from Roche, and has served as an advisor/consultant to Polyphor (all outside the submitted work). Dr Tolaney has received institutional research funding from Novartis, Genentech, Eli Lilly, Pfizer, Merck, Exelixis, Eisai, Bristol-Myers Squibb, AstraZeneca, Cyclacel, Immunomedics, Odonate Therapeutics, and Nektar, and she has served as an advisor/consultant to Novartis, Eli Lilly, Pfizer, Merck, AstraZeneca, Eisai, Puma, Genentech, Immunomedics, Nektar, Tesaro, and NanoString.

Acknowledgements

The authors acknowledge Kaitlyn Bifolck for her editorial support.

References

1. American Cancer Society. Cancer Facts & Figures 2016. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2016.html. Accessed March 20, 2019.
2. Noone AM, Cronin KA, Altekruse SF, et al. Cancer incidence and survival trends by subtype using data from the Surveillance Epidemiology and End Results Program, 1992-2013. *Cancer Epidemiol Biomarkers Prev*. 2017;26(4):632-641.
3. Giordano SH. Update on locally advanced breast cancer. *Oncologist*. 2003;8(6):521-530.
4. Chia S, Swain SM, Byrd DR, Mankoff DA. Locally advanced and inflammatory breast cancer. *J Clin Oncol*. 2008;26(5):786-790.
5. Anderson WF, Chu KC, Chang S. Inflammatory breast carcinoma and noninflammatory locally advanced breast carcinoma: distinct clinicopathologic entities? *J Clin Oncol*. 2003;21(12):2254-2259.
6. Gianni L, Eiermann W, Semiglazov V, 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):377-384.
7. Moja L, Tagliabue L, Balduzzi S, et al. Trastuzumab containing regimens for early breast cancer. *Cochrane Database Syst Rev*. 2012;(4):CD006243.
8. Zhang B, Hurvitz S. Long-term outcomes of neoadjuvant treatment of HER2-positive breast cancer. *Clin Adv Hematol Oncol*. 2016;14(7):520-530.
9. Valachis A, Mauri D, Polyzos NP, Chlouverakis G, Mavroudis D, Georgoulias V. Trastuzumab combined to neoadjuvant chemotherapy in patients with HER2-positive breast cancer: a systematic review and meta-analysis. *Breast*. 2011;20(6):485-490.
10. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet*. 2014;384(9938):164-172.
11. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Breast Cancer. v.1.2019. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Updated March 14, 2019. Accessed March 20, 2019.
12. Coates AS, Winer EP, Goldhirsch A, et al; Panel Members. Tailoring therapies—improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol*. 2015;26(8):1533-1546.
13. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet Oncol*. 2014;15(6):640-647.
14. Untch M, Fasching PA, Konecny GE, et al. Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. *J Clin Oncol*. 2011;29(25):3351-3357.
15. Untch M, Rezai M, Loibl S, et al. Neoadjuvant treatment with trastuzumab in HER2-positive breast cancer: results from the GeparQuattro study. *J Clin Oncol*. 2010;28(12):2024-2031.
16. Buzdar AU, Suman VJ, Meric-Bernstam F, et al; American College of Surgeons Oncology Group investigators. 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):1317-1325.
17. Buzdar AU, Suman VJ, Meric-Bernstam F, 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*. 2019;5(1):45-50.
18. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012;13(1):25-32.
19. Gianni L, Pienkowski T, Im YH, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol*. 2016;17(6):791-800.
20. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol*. 2013;24(9):2278-2284.
21. Schneeweiss A, Chia S, Hickish T, et al. Long-term efficacy analysis of the

randomised, phase II TRYPHAENA cardiac safety study: evaluating pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer. *Eur J Cancer*. 2018;89:27-35.
22. Hurvitz SA, Martin M, Symmans WF, 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):115-126.
23. Swain SM, Ewer MS, Viale G, et al; BERENICE Study Group. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): a phase II, open-label, multicenter, multinational cardiac safety study. *Ann Oncol*. 2018;29(3):646-653.
24. Nitz UA, Gluz O, Christgen M, et al; West-German Study Group (WSG)-ADAPT Investigators. De-escalation strategies in HER2-positive early breast cancer (EBC): final analysis of the WSG-ADAPT HER2+/HR- phase II trial: efficacy, safety, and predictive markers for 12 weeks of neoadjuvant dual blockade with trastuzumab and pertuzumab ± weekly paclitaxel. *Ann Oncol*. 2017;28(11):2768-2772.
25. de Azambuja E, Holmes AP, Piccart-Gebhart M, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. *Lancet Oncol*. 2014;15(10):1137-1146.
26. Robidoux A, Tang G, Rastogi P, et al. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2013;14(12):1183-1192.
27. Carey LA, Berry DA, Cirrincione CT, et al. Molecular heterogeneity and response to neoadjuvant human epidermal growth factor receptor 2 targeting in CALGB 40601, a randomized phase III trial of paclitaxel plus trastuzumab with or without lapatinib. *J Clin Oncol*. 2016;34(6):542-549.
28. Guarneri V, Frassoldati A, Bottini A, et al. Preoperative chemotherapy plus trastuzumab, lapatinib, or both in human epidermal growth factor receptor 2-positive operable breast cancer: results of the randomized phase II CHER-LOB study. *J Clin Oncol*. 2012;30(16):1989-1995.
29. Llombart-Cussac A, Cortés J, Paré L, et al. HER2-enriched subtype as a predictor of pathological complete response following trastuzumab and lapatinib without chemotherapy in early-stage HER2-positive breast cancer (PAMELA): an open-label, single-group, multicentre, phase 2 trial. *Lancet Oncol*. 2017;18(4):545-554.
30. Rimawi MF, Mayer IA, Forero A, 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):1726-1731.
31. DeMichele AM, Moulder S, Buxton M, et al. Efficacy of T-DM1+pertuzumab over standard therapy for HER2+ breast cancer: results from the neoadjuvant I-SPY 2 TRIAL [AACR abstract CT042]. *Cancer Res.* 2016;76(14)(suppl).
32. von Minckwitz G, Huang CS, Mano MS, et al; KATHERINE Investigators. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med*. 2019;380(7):617-628.
33. Harbeck N, Gluz O, Christgen M, et al. De-escalation strategies in human epidermal growth factor receptor 2 (HER2)-positive early breast cancer (BC): final analysis of the West German Study Group adjuvant dynamic marker-adjusted personalized therapy trial optimizing risk assessment and therapy response prediction in early BC HER2- and hormone receptor-positive phase II randomized trial-efficacy, safety, and predictive markers for 12 weeks of neoadjuvant trastuzumab emtansine with or without endocrine therapy (ET) versus trastuzumab plus ET. *J Clin Oncol*. 2017;35(26):3046-3054.
34. Jacobs SA, Robidoux A, Garcia JMP, et al. Abstract PD5-04: NSABP FB-7: a phase II randomized trial evaluating neoadjuvant therapy with weekly paclitaxel (P) plus neratinib (N) or trastuzumab (T) or neratinib and trastuzumab (N+T) followed by doxorubicin and cyclophosphamide (AC) with postoperative T in women with locally advanced HER2-positive breast cancer [SABCS abstract PD5-04]. *Cancer Res.* 2016;76(4)(suppl).
35. Park JW, Liu MC, Yee D, et al; I-SPY 2 Investigators. Adaptive randomization of neratinib in early breast cancer. *N Engl J Med*. 2016;375(1):11-22.
36. Buzdar AU, Ibrahim NK, Francis D, 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):3676-3685.
37. Buzdar AU, Valero V, Ibrahim NK, et al. Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: an update of the initial randomized study population and data of additional patients treated with the same regimen. *Clin Cancer Res*. 2007;13(1):228-233.
38. Swain SM, Baselga J, Kim SB, et al; CLEOPATRA Study Group. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 2015;372(8):724-734.
39. von Minckwitz G, Procter M, de Azambuja E, et al; APHINITY Steering Committee and Investigators. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med*. 2017;377(2):122-131.
40. Blackwell KL, Burstein HJ, Storniolo AM, et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. *J Clin Oncol*. 2012;30(21):2585-2592.
41. Piccart-Gebhart M, Holmes E, Baselga J, et al. Adjuvant lapatinib and trastuzumab for early human epidermal growth factor receptor 2-positive breast cancer: results from the randomized phase III adjuvant lapatinib and/or trastuzumab treatment optimization trial. *J Clin Oncol*. 2016;34(10):1034-1042.
42. Untch M, Loibl S, Bischoff J, et al; German Breast Group (GBG); Arbeitsgemeinschaft Gynäkologische Onkologie-Breast (AGO-B) Study Group. Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy (GeparQuinto, GBG 44): a randomised phase 3 trial. *Lancet Oncol*. 2012;13(2):135-144.
43. Clavarezza M, Puntoni M, Gennari A, et al. Dual block with lapatinib and trastuzumab versus single-agent trastuzumab combined with chemotherapy as neoadjuvant treatment of HER2-positive breast cancer: a meta-analysis of randomized trials. *Clin Cancer Res*. 2016;22(18):4594-4603.
44. Verma S, Miles D, Gianni L, et al; EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. 2012;367(19):1783-1791.
45. Krop IE, Kim SB, Martin AG, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. *Lancet Oncol*. 2017;18(6):743-754.
46. ClinicalTrials.gov. A study of trastuzumab emtansine (Kadcyla) plus pertuzumab (Perjeta) following anthracyclines in comparison with trastuzumab (Herceptin) plus pertuzumab and a taxane following anthracyclines as adjuvant therapy in participants with operable HER2-positive primary breast cancer. www.clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/record/NCT01966471. Identifier: NCT01966471. Accessed March 20, 2019.
47. Martin M, Holmes FA, Ejlertsen B, et al; ExteNET Study Group. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2017;18(12):1688-1700.
48. Delaloge S, Hurvitz S, Chan N, et al. The impact of neratinib with or without anti-diarrheal prophylaxis on health-related quality of life in HER2+ early-stage breast cancer: analyses from the ExteNET and CONTROL trials [SABCS abstract P2-13-03]. *Cancer Res.* 2019;79(4)(suppl).
49. Slamon D, Eiermann W, Robert N, et al; Breast Cancer International Research Group. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011;365(14):1273-1283.
50. Slamon DJ, Eiermann W, Robert NJ, et al. Ten year follow-up of the BCIRG-006 trial comparing doxorubicin plus cyclophosphamide followed by docetaxel (AC->T) with doxorubicin plus cyclophosphamide followed by docetaxel and trastuzumab (AC->TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2+ early breast cancer patients [SABCS abstract S5-04]. 2016;76(4)(suppl).
51. van Ramshorst MS, van Werkhoven E, Mandjes IA, et al. A phase III trial of neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2-blockade for HER2+ breast cancer: the TRAIN-2 study (BOOG 2012-03) [ASCO abstract 507]. *J Clin Oncol.* 2017;35(15)(suppl).
52. Arvold ND, Oh KS, Niemierko A, et al. Brain metastases after breast-conserving therapy and systemic therapy: incidence and characteristics by biologic subtype. *Breast Cancer Res Treat*. 2012;136(1):153-160.
53. Puma Biotechnology announces top line results of the phase III NALA trial of neratinib in patients with HER2-positive metastatic breast cancer [press release]. https://www.marketwatch.com/press-release/puma-biotechnology-announces-top-line-results-of-the-phase-iii-nala-trial-of-neratinib-in-patients-with-her2-positive-metastatic-breast-cancer-2018-12-17. Posted December 17, 2018. Accessed March 20, 2019.