

# Advances in HER2-Positive Breast Cancer: Novel Therapies and Adverse Event Management

RESHMA MAHTANI, DO, and LISA HINEMAN, MS, AOCN®, PHN, ANP-C

From Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, Florida, and Los Angeles Cancer Network, Los Angeles, California

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Reshma Mahtani, DO, University of Miami Health System, 1192 East Newport Center Drive, Deerfield Beach, FL 33442. E-mail: rmahtani@miami.edu.

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## Abstract

Although breast cancer is a heterogeneous disease, approximately 20% to 25% of patients diagnosed with breast cancer have amplification of the *HER2* gene. The FDA approval of trastuzumab for the treatment of HER2-positive (HER2+) metastatic breast cancer in 1998 represented a major breakthrough for patients with HER2+ disease. In 2006, the FDA extended its approval for use in the adjuvant setting. In recent years, trials have been conducted to identify the appropriate duration of therapy in combination with chemotherapy. More recently, trials incorporating newer HER2-targeted therapies have been conducted. Some trials have demonstrated the importance of considering neoadjuvant HER2-directed therapies for selected patients with HER2+ disease, highlighting the fact that achieving pathologic complete response has important prognostic implications. In order to continue treatment and optimize patient safety, the effective and timely management of treatment-related adverse events (AEs) is crucial. As they are on the front lines of patient care, advanced practitioners need to be able to assess the clinical implications of recent advances and integrate them into practice. One area of unmet need in the management of metastatic HER2-positive disease is the treatment of brain metastases, with several promising therapies under investigation. Using several case studies as a foundation, this article highlights current and emerging data on HER2-directed therapies, outlines strategies for managing AEs, and reviews the key issues surrounding brain metastases and associated novel therapies under investigation.

**B**ased on data from the American Cancer Society (ACS), survival is improving for patients with breast cancer (BC), largely because of earlier detection and improved treatment modalities (ACS, 2018).

Notwithstanding these improvements, nearly 42,000 women died from metastatic breast cancer (MBC) in 2018 (ACS, 2018).

Breast cancer is a heterogeneous disease; approximately 20% to 25% of BCs have amplification

of the human epidermal growth factor receptor 2 (*HER2*) gene. This gene was discovered more than 30 years ago, and at the time, conferred a poor prognosis. *HER2+* BC is common in younger patients and is associated with poorly differentiated, high-grade tumors (Burstein, 2005); approximately 35,000 cases are diagnosed annually (Howlander et al., 2014). A growing understanding of the pathobiology of *HER2+* BC led to the development and approval of trastuzumab, which has resulted in a substantial change in the natural history of this cancer subtype (Slamon et al., 2011, 2015). The approval of trastuzumab for the treatment of *HER2+* MBC in 1998 represented a major breakthrough for patients with *HER2+* disease. In 2006, trastuzumab received US Food and Drug Administration (FDA) approval for use in the adjuvant setting.

Since then, the therapeutic landscape has continued to evolve. Trials have been conducted to identify the appropriate duration of therapy in combination with chemotherapy. More recently, results of trials incorporating newer *HER2*-targeted therapies, either given as dual blockade or sequentially following standard trastuzumab adjuvant therapy, have been reported. Several studies have demonstrated the importance of considering neoadjuvant *HER2*-directed therapies for certain patients with *HER2+* disease, with the understanding that achievement of a pathologic complete response (pCR) has important prognostic implications.

Best practices for the management of treatment-related adverse events (AEs) are evolving as well. One area of unmet need in the management of metastatic *HER2+* disease is the treatment of brain metastases, with several new and exciting therapies under investigation. To provide optimal patient-centered care, advanced practitioners (APs) need to be able to assess the clinical implications of all of these advances and appropriately integrate them into practice.

### Case 1: Adjuvant and Extended Adjuvant Therapy

The first case is that of a 45-year-old woman with no prior relevant medical history. A mass was palpated in her left breast, biopsy-proven to be estrogen receptor–negative (ER–), progesterone

receptor–negative (PR–), and *HER2+* (3+ by immunohistochemistry [IHC]). Lymph nodes were suggestive of metastases on imaging and were biopsied and determined to be positive. The patient was staged as cT1cN1M0. A lumpectomy was performed, with final pathology documenting a 1.8-cm invasive ductal carcinoma, with 3 of 7 nodes positive. The patient received docetaxel/carboplatin/trastuzumab/pertuzumab (TCHP) for 6 cycles following surgery. Following this, she completed 1 year of adjuvant trastuzumab and pertuzumab, as well as post-lumpectomy radiation.

### ADJUVANT SYSTEMIC THERAPY

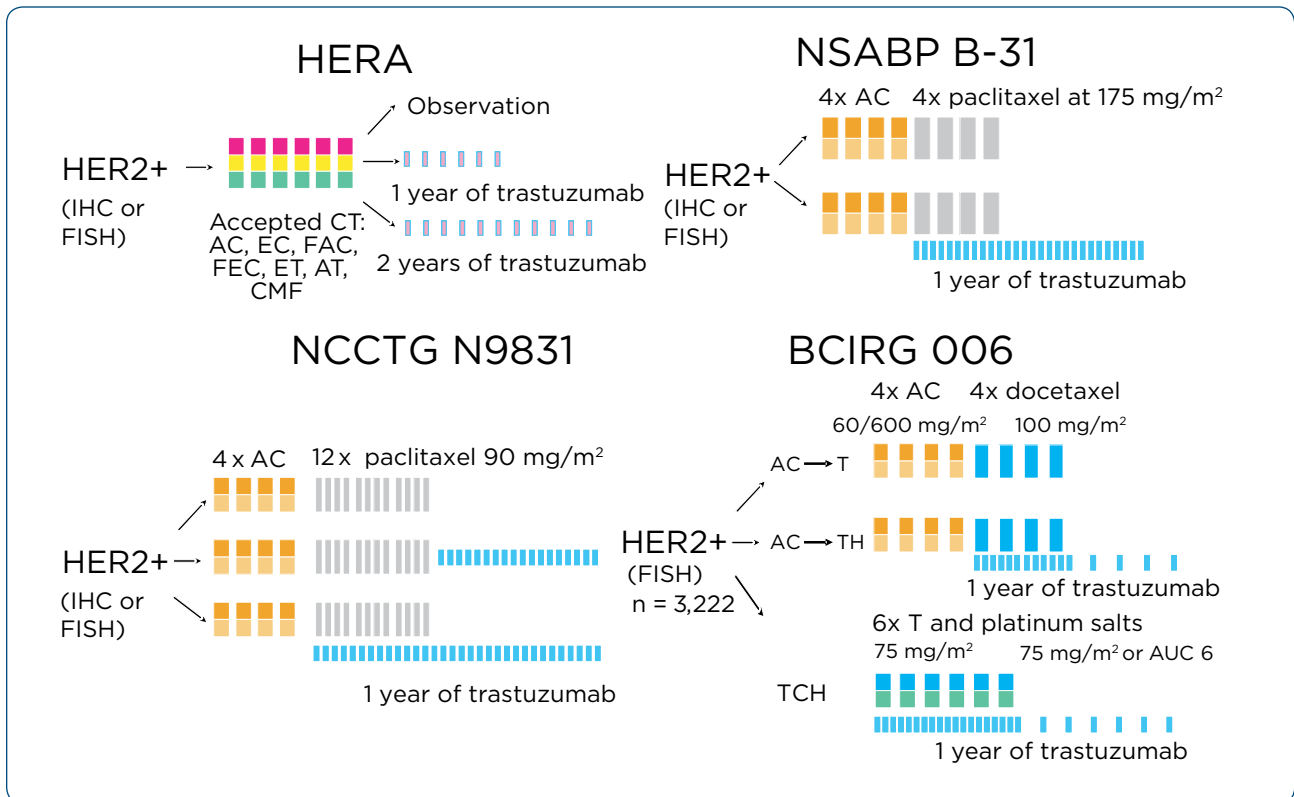
Case 1 highlights the appropriate use of adjuvant chemotherapy and *HER2*-directed therapies following surgery. While there are data to support the use of anthracycline as well as nonanthracycline regimens in the adjuvant setting, *HER2+* disease is aggressive, and therefore most patients with early-stage BC will require adjuvant chemotherapy and trastuzumab (the exception being patients with T1aNO tumors, for which the data are less clear). Four large, randomized adjuvant trastuzumab clinical trials have shown that the addition of 1 year of trastuzumab not only improves disease-free survival (DFS) but also overall survival (OS) in patients with *HER2+* BC. These four landmark trials include HERA, NSABP B-31, NCCTG N9831, and BCIRG 006. Their respective study designs are shown in Figure 1 (Goldhirsch et al., 2013; Perez et al., 2014; Romond et al., 2005; Slamon et al., 2015).

#### Dual Anti-*HER2* Adjuvant Therapy

Despite improvements in efficacy associated with the use of adjuvant trastuzumab, there is still room for improvement, as shown in Figure 2, which demonstrates long-term outcomes from BCIRG-006 and NSABP B-31/NCCTG N9831. The graphs illustrate that 1 year of adjuvant trastuzumab does not eliminate the risk of recurrence for all patients with *HER2+* BC (Perez et al., 2014; Slamon et al., 2015).

#### Improving on 1 Year of Adjuvant Trastuzumab: APHINITY

For women with *HER2+* early-stage BC who are at high risk of recurrence, additional *HER2*-targeted



**Figure 1.** Landmark adjuvant trials; 4 positive adjuvant trastuzumab trials. AC = doxorubicin/cyclophosphamide; AT = doxorubicin/docetaxel; AUC = area under the curve; CMF = cyclophosphamide/methotrexate/fluorouracil; CT = chemotherapy; EC = epirubicin/cyclophosphamide; ET = epirubicin/docetaxel; FAC = fluorouracil/doxorubicin/cyclophosphamide; FEC = fluorouracil/epirubicin/cyclophosphamide; FISH = fluorescence in situ hybridization; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; T = docetaxel; TCH = docetaxel/carboplatin/trastuzumab; TH = docetaxel/trastuzumab. Adapted from Goldhirsch et al. (2013); Perez et al. (2014); Romond et al. (2005); Slamon et al. (2011).

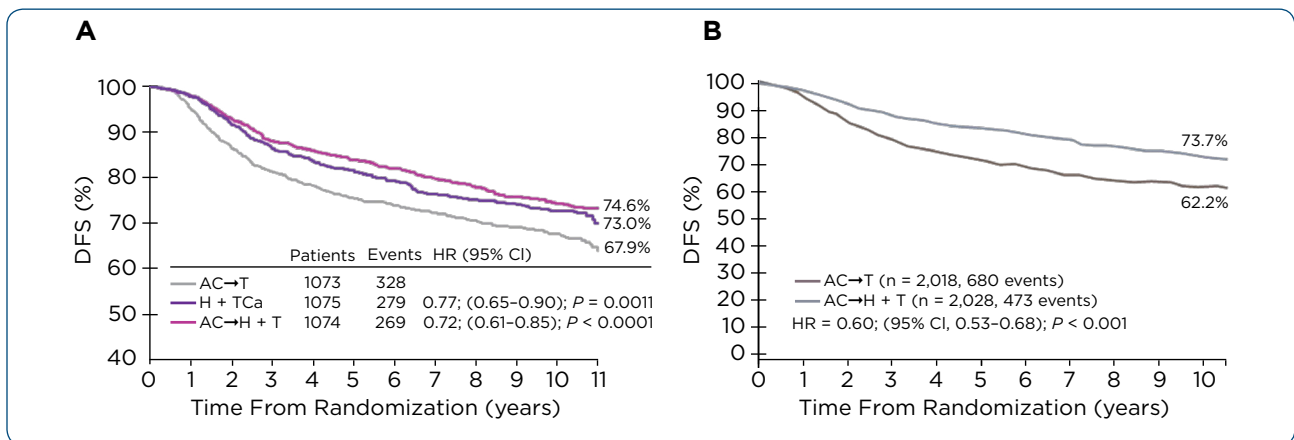
therapy may be indicated, as demonstrated by APHINITY, a phase III randomized clinical trial of 4,805 patients with operable HER2+ BC that evaluated the efficacy and safety of pertuzumab plus trastuzumab and chemotherapy compared with those of trastuzumab and chemotherapy in the adjuvant setting (von Minckwitz et al., 2017). Sixty-three percent of patients were node-positive and 36% of patients had HR-negative disease. Patients who had tumors between 0.5 and 1 cm were allowed to enroll if they had one high-risk feature (age < 35, grade 3, or ER- and PR- status). The study design is shown in Figure 3.

At the 4-year mark, a 1.7% benefit was seen for patients receiving adjuvant pertuzumab in combination with trastuzumab compared to that in patients who received trastuzumab alone, a small but significant finding (Figure 4). The magnitude

of benefit was greater in node-positive and HR-negative disease. In regard to safety with the addition of pertuzumab, there were no specific additional safety signals, including any meaningful cardiac toxicity (Table 1; von Minckwitz et al., 2017).

APHINITY demonstrated that adjuvant pertuzumab plus trastuzumab plus cytotoxic chemotherapy significantly reduced the risk of recurrence compared with that of placebo plus trastuzumab plus chemotherapy in patients with HER2+ early BC, supporting the approach to treatment for the patient in case 1, who presented with high-risk disease (node positivity and ER- status).

Another consideration for the patient in case 1 (especially if her tumor had been ER+ as opposed to ER-) is the use of extended adjuvant therapy with neratinib, an oral, irreversible tyrosine kinase inhibitor that demonstrated efficacy in patients



**Figure 2.** Long-term data in patients who were treated with adjuvant chemotherapy with or without trastuzumab for 1 year. (A) BCIRG-006 long-term follow-up: disease-free survival. (B) NSABP B-31 and NCCTG N9831 joint analysis. Despite one year of adjuvant treatment, HER2+ patients still experienced recurrence. AC = doxorubicin and cyclophosphamide; BCIRG = Breast Cancer International Research Group; Ca = carboplatin; CI = confidence interval; DFS = disease-free survival; H = trastuzumab; HR = hazard ratio; NSABP = National Surgical Adjuvant Breast and Bowel Project; NCCTG = North Central Cancer Treatment Group; T = taxane. Adapted from Perez et al. (2014); Slamon et al. (2015).

with ER+/HER2+ disease, as well as in the intention-to-treat population, at high risk for relapse in the ExteNET trial.

### Extended Adjuvant Benefit: ExteNET

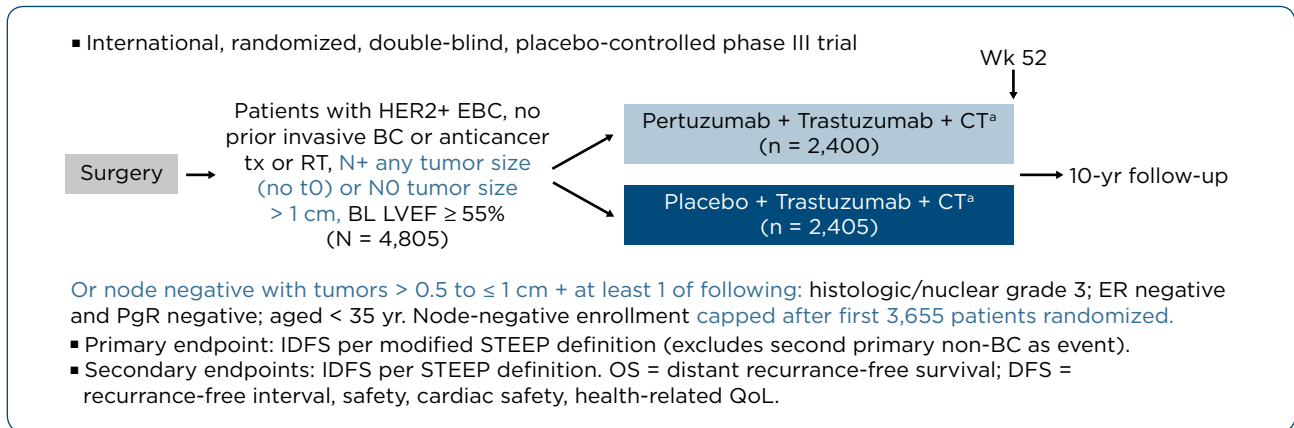
ExteNET enrolled 2,840 patients with HER2+ BC, stage I to III, who had completed adjuvant trastuzumab for 1 year into a randomized, double-blind, placebo-controlled, phase III trial. Patients were subsequently randomized to 1 additional year of neratinib or placebo (Figure 5; Chan et al., 2016; Martin et al., 2017).

Neratinib inhibits HER1, HER2, and HER4 and binds to the intercellular signaling domain of HER1, HER2, HER3, and epithelial growth factor receptor; binding inhibits phosphorylation and several HER downstream signaling pathways, which leads to decreased proliferation and increased cell death. The 3-year invasive disease-free survival (iDFS) was 92% for neratinib vs. 89.9% for placebo (Chan et al., 2016; Martin et al., 2017). Results were updated in 2017, wherein the 5-year iDFS was 90.2% with neratinib vs. 87.7% with placebo, an overall benefit of about 2.5% (Figure 6; Martin et al., 2017). When findings were analyzed by receptor status, benefit was greatest in the HR+ patients (absolute 4.4% iDFS benefit; hazard ratio of 0.60; 95%

CI = 0.43–0.83; Figure 7; Martin et al., 2017). The authors suggested that neratinib may modulate ER sensitivity to hormonal therapy, resulting in bidirectional crosstalk.

ExteNET conclusions were that neratinib provides sustained benefit for women with early-stage, HER2+ BC following adjuvant trastuzumab, with an overall benefit of 2.5% and an absolute benefit of 5.1% in HR+ patients. No indications of long-term toxicity have emerged (cardiotoxicity or secondary malignancies). The main AE was grade 3 diarrhea, which occurred in 40% of patients, most of which resolved in fewer than 30 days (1.4% of patients required hospitalization). Patients reported a transient reduction in health-related quality of life during the first month of therapy, followed by steady recovery toward baseline. The follow-up CONTROL trial (Hurvitz et al., 2017) showed the incidence of diarrhea to be further reduced as compared to the ExteNET trial with the use of prophylactic loperamide alone or in combination with budesonide, or colestipol.

The patient in case 1 was treated with dual antibody therapy and, as such, was not represented in the ExteNET trial. In addition, because this patient had ER– disease, there would be less enthusiasm to offer her extended adjuvant treat-



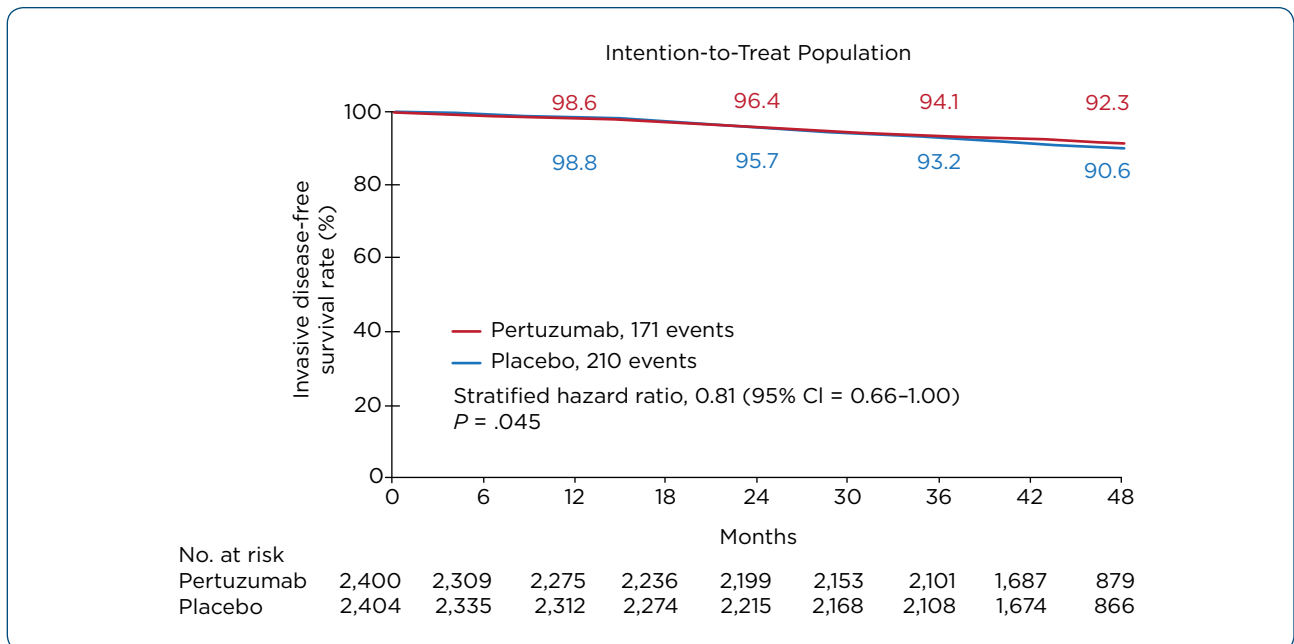
**Figure 3.** APHINITY study design. BC = breast cancer; BL = baseline; CT = chemotherapy; DFS = disease-free survival; EBC = early breast cancer; HR = hormone receptor; IDFS = invasive disease-free survival; LVEF = left ventricular ejection fraction; QoL = quality of life; RT = radiotherapy; tx = treatment. Adapted from Hudis et al. (2007); von Minckwitz et al. (2017).

<sup>a</sup>Treatment initiated ≤ 8 weeks post-surgery. Permitted CT: standard anthracycline or nonanthracycline regimens. Endocrine and/or radiotherapy could be started at end of adjuvant CT.

ment with neratinib, although there are data from an exploratory analysis that demonstrated patients with ER-/HER2+ disease who were randomized to receive neratinib within 6 months of completion of trastuzumab demonstrated a 2.8% benefit (Martin et al., 2017).

#### Key Points

- The addition of 1 year of adjuvant trastuzumab improves not only DFS but also OS in patients with early-stage disease
- Adjuvant pertuzumab plus trastuzumab plus cytotoxic chemotherapy significantly



**Figure 4.** APHINITY interim analysis of invasive disease-free survival (intention to treat). f/u = follow-up; IDFS = invasive disease-free survival; ITT = intention to treat. Data cutoff after 381 IDFS events (median f/u: 45.4 mo). Adapted from von Minckwitz et al. (2017).

**Table 1. APHINITY: Safety**

Outcome, n (%)	Pertuzumab (n = 2,364)	Placebo (n = 2,405)	Treatment difference (95% CI)
Primary cardiac endpoint	17 (0.7)	8 (0.3)	0.4% (0% to 0.8%)
Heart failure NYHA III/IV + LVEF drop <sup>a</sup>	15 (0.6)	6 (0.2)	
Cardiac death <sup>b</sup>	2 (0.1)	2 (0.1)	
Recovered according to LVEF	7 (0.3)	4 (0.2)	
Asymptomatic or mildly symptomatic LVEF drop <sup>c</sup>	64 (2.7)	67 (2.8)	-0.1% (-1.0% to 0.9%)
Grade ≥ 3 AEs			
Neutropenia	16.3	15.7	
Febrile neutropenia	12.1	11.1	
Decreased neutrophil count	9.6	9.6	
Diarrhea	9.8	3.7	
Anthracycline CT, n/N (%)	7.5	3.1	
Nonanthracycline CT, n/N (%)	18.0	6.1	
Anemia	6.9	4.7	
Fatal AE	18 (0.8)	20 (0.8)	

Note. Adapted from von Minckwitz et al. (2017).

<sup>a</sup>LVEF drop defined as ejection fraction decrease ≥ 10% from baseline to below 50%.

<sup>b</sup>Determined by Cardiac Advisory Board per prospective definition.

<sup>c</sup>Secondary cardiac endpoint.

reduces the risk of recurrence in patients with high-risk disease

- Neratinib further improves iDFS in the extended adjuvant setting after 1 year of standard adjuvant trastuzumab with no evidence of long-term toxicity

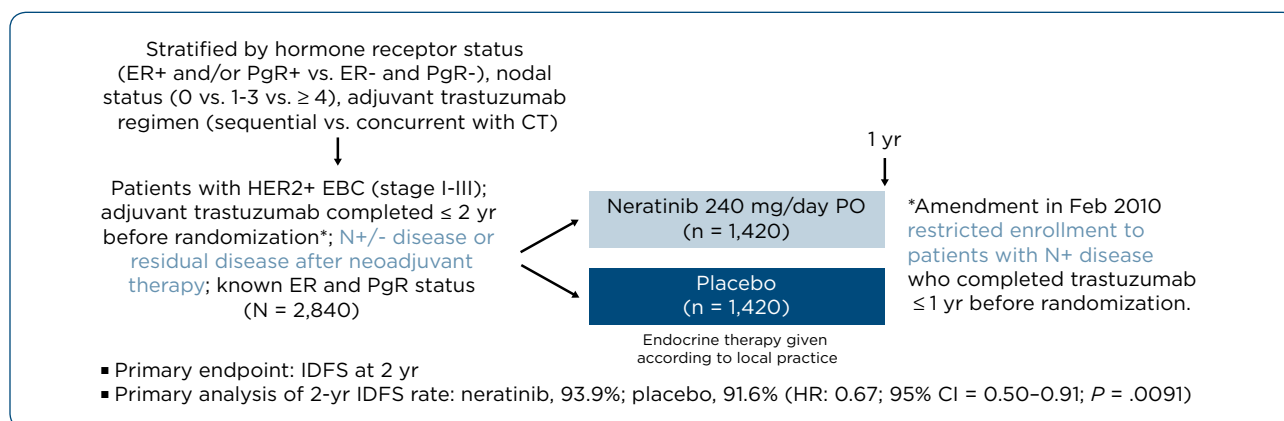
### Case 2: Treatment for Residual Disease Following Neoadjuvant Therapy

The patient is a 65-year-old woman with no prior relevant medical history. A mass palpated in her left breast was approximately 3 cm by imaging without abnormal appearing nodes, and biopsy-

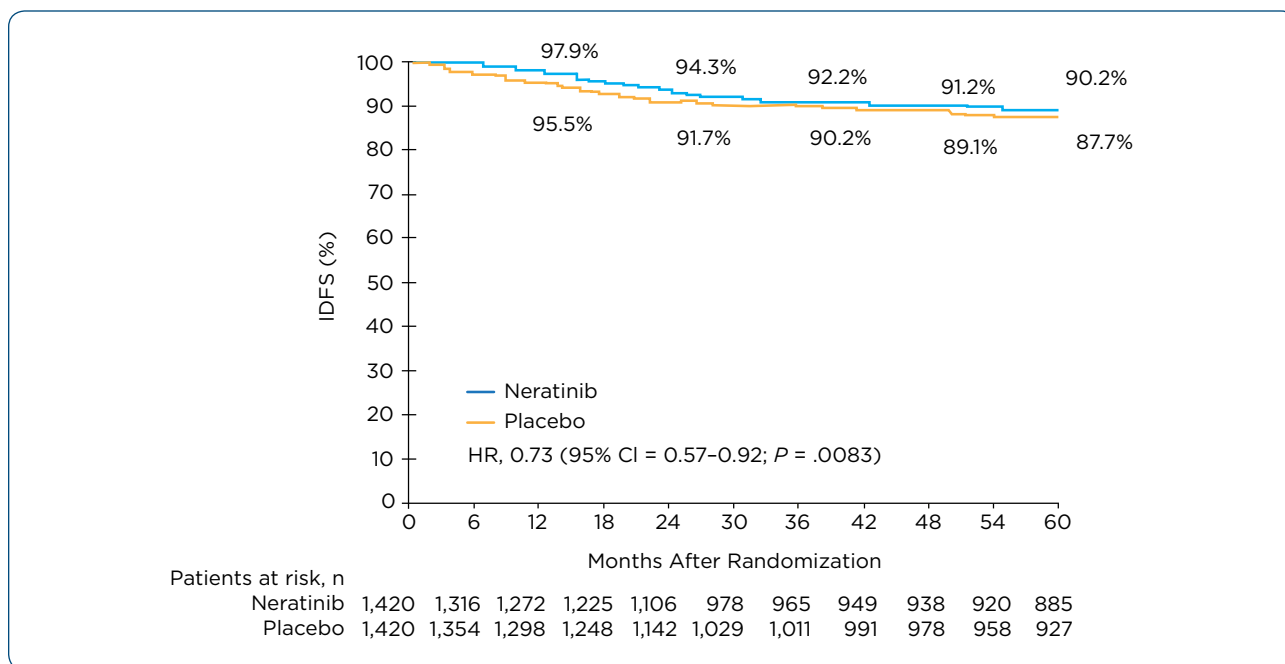
proven to be invasive ductal cancer, ER+, HER2+ (3+ by IHC), cT2N0M0. She received neoadjuvant TCHP × 6 cycles and did not achieve a pCR at the time of lumpectomy and sentinel lymph node biopsy. Residual disease was noted: 1 cm in the breast without involvement in the sentinel lymph nodes. She went on to receive post-lumpectomy radiation and receives hormonal therapy with an aromatase inhibitor in the adjuvant setting.

### NEOADJUVANT THERAPY

Patients with a high tumor-volume-to-breast ratio are not candidates for breast conservation. Pa-



**Figure 5.** ExteNET 5-year update: Neratinib vs. PBO after adjuvant trastuzumab in HER2+ EBC. CT = chemotherapy; EBC = early breast cancer; IDFS = invasive disease-free survival; PBO = placebo; pCR = pathologic CR; PgR = progesterone receptor. Adapted from Chan et al. (2016); Martin et al. (2017).



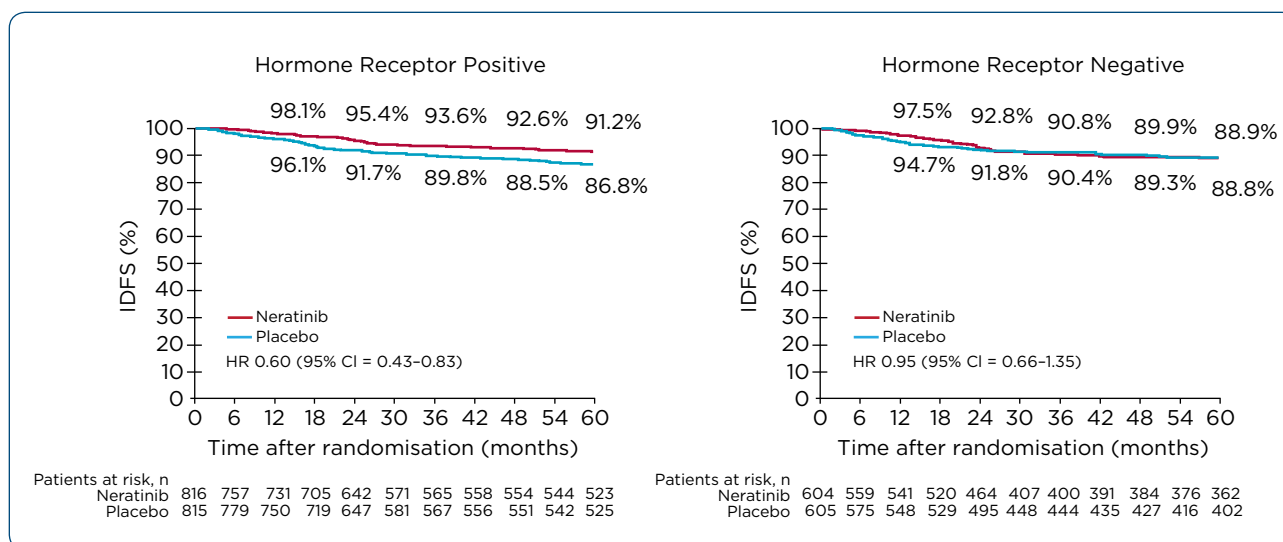
**Figure 6.** ExteNET: 5-year invasive disease-free survival analysis. Adapted from Martin et al. (2017).

tients with lymph node–positive disease, high-risk features (high grade, ER–, HER2+, or triple-negative disease), and/or younger age at diagnosis are generally considered for neoadjuvant therapy in the early-stage setting. More specifically, patients with HER2+, T2 or greater, and/or node-positive disease should be offered chemotherapy with trastuzumab/pertuzumab in the neoadjuvant setting (Burstein et al., 2016), as it has been shown to increase pCR rates. According to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Breast Cancer (NCCN, 2018a), the preferred regimens for neoadjuvant therapy for HER2+ BC are doxorubicin and cyclophosphamide followed by paclitaxel plus trastuzumab with or without pertuzumab, or docetaxel, carboplatin, and trastuzumab with or without pertuzumab. The NCCN Guidelines also list a host of other combination regimens that are appropriate neoadjuvant regimens.

Support for these recommendations is from the NeoSphere trial (Gianni et al., 2012), in which pertuzumab and trastuzumab were assessed as companion treatments for 12 weeks across four different preoperative regimens: (1) docetaxel plus trastuzumab (group A); (2) docetaxel plus pertu-

zumab plus trastuzumab (group B); (3) pertuzumab and trastuzumab without chemotherapy (group C); and (4) docetaxel plus pertuzumab (group D). Following surgery, patients received fluorouracil at 600 mg/m<sup>2</sup>, epirubicin at 90 mg/m<sup>2</sup>, and cyclophosphamide at 600 mg/m<sup>2</sup> (FEC) every 3 weeks for 3 cycles (group C received docetaxel for 4 cycles prior to FEC), and trastuzumab at 6 mg/kg every 3 weeks to complete 1 year of treatment. A significantly higher proportion of patients achieved a pCR with combined pertuzumab and trastuzumab plus docetaxel than did those treated with trastuzumab plus docetaxel (*p* = .014). The rate of pCR was higher in women with ER– tumors receiving pertuzumab and trastuzumab (27%) compared with that in women with ER+ tumors receiving pertuzumab and trastuzumab (17%).

A 5-year follow-up of NeoSphere (Gianni et al., 2016) showed that DFS and PFS were numerically higher in patients receiving docetaxel, trastuzumab, and pertuzumab for 12 weeks in the neoadjuvant setting than patients receiving docetaxel and trastuzumab. Five-year PFS rates were 81% (95% CI = 71%–87%) for docetaxel plus trastuzumab; 86% (95% CI = 77%–91%) for docetaxel plus trastuzumab plus pertuzumab;



**Figure 7.** ExteNET: 5-year invasive disease-free survival analysis by hormone receptor status. Adapted from Martin et al. (2017).

73% (95% CI = 64%–81%) for pertuzumab plus trastuzumab; and 73% (95% CI = 63%–81%) for docetaxel plus pertuzumab. Disease-free survival rates were nearly identical to PFS rates.

The TRYPHAENA trial (Schneeweiss et al., 2013) evaluated the efficacy of dual blockade of HER2 with trastuzumab and pertuzumab by combining pertuzumab with different anthracycline-containing and nonanthracycline-containing chemotherapy regimens. A total of 225 patients were randomized. The results confirmed that a high proportion of patients achieved a pCR with pertuzumab and trastuzumab as compared to trastuzumab alone (both in combination with chemotherapy).

### Case 2 Continued

As mentioned above, the patient in case 2 did not achieve a pCR at the time of surgery, with residual disease identified in the breast. The standard of care for this patient is adjuvant trastuzumab emtansine (T-DM1), the benefit of which was established in the recently reported results of the KATHERINE trial.

### RESIDUAL DISEASE AFTER NEOADJUVANT CHEMOTHERAPY PLUS HER2 THERAPY: KATHERINE

Patients with residual invasive BC after neoadjuvant chemotherapy plus HER2-targeted therapy

have a worse prognosis than patients without residual disease.

In KATHERINE, patients with HER2+ early BC with residual invasive disease in the breast or axilla following surgery after the receipt of neoadjuvant therapy containing a taxane (with or without anthracycline) and trastuzumab, with 18% of patients also receiving pertuzumab, were randomly assigned to receive adjuvant T-DM1 or trastuzumab for 14 cycles (von Minckwitz et al., 2019). T-DM1 is an antibody-drug conjugate of trastuzumab and the cytotoxic agent emtansine (DM1), a maytansine derivative and microtubule inhibitor currently approved for HER2+ MBC. At the interim analysis of 1,486 randomly assigned patients (743 in each group), invasive disease or death had occurred in 91 patients receiving T-DM1 (12.2%), and 165 patients receiving trastuzumab (22.2%). The estimated percentage of patients free of invasive disease at 3 years was 88.3% for T-DM1 and 77.0% for trastuzumab. Invasive DFS was significantly higher with T-DM1 than with trastuzumab (HR for invasive disease or death, 0.50; 95% CI = 0.39–0.64;  $p < .001$ ). Distant recurrence as the first invasive-disease event occurred in 10.5% of patients receiving T-DM1 and 15.9% receiving trastuzumab. Of note, even patients who had low volume residual disease demonstrated a benefit from receiving T-DM1 as compared to trastuzumab.



**Table 2. Summary of Adverse Events in the Safety Population<sup>a</sup>**

Event, no. of patients (%)	Trastuzumab group (N = 720)	T-DM1 group (N = 740)
Any adverse event	672 (93.3)	731 (98.8)
Grade $\geq$ 3 adverse event	111 (15.4)	190 (25.7)
Adverse event leading to death <sup>b</sup>	0	1 (0.1)
Serious adverse event	58 (8.1)	94 (12.7)
Adverse event leading to discontinuation of trial drug <sup>c</sup>	15 (2.1)	133 (18.0)
Grade $\geq$ 3 adverse event that occurred in $\geq$ 1% of patients in either group		
Decreased platelet count	2 (0.3)	42 (5.7)
Hypertension	9 (1.2)	15 (2.0)
Radiation-related skin injury	7 (1.0)	10 (1.4)
Peripheral sensory neuropathy	0	10 (1.4)
Decreased neutrophil count	5 (0.7)	9 (1.2)
Hypokalemia	1 (0.1)	9 (1.2)
Fatigue	1 (0.1)	8 (1.1)
Anemia	1 (0.1)	8 (1.1)

Note. Adapted from von Minckwitz et al. (2019).

<sup>a</sup>Listed are adverse events with an onset that occurred from the first dose of any trial treatment through 30 days after the final dose of trial treatment and adverse events with an onset in the follow-up period that were determined by the investigators to be related to the trial drug or trial procedure. Patients may have had more than one adverse event.

<sup>b</sup>One patient with a platelet count of 55,000/mm<sup>3</sup> fell at home and died of an intracranial hemorrhage.

<sup>c</sup>The most common adverse event leading to discontinuation of the trial drug in the trastuzumab group was a decreased ejection fraction in 10 of 720 patients (1.4%). The most common adverse events leading to discontinuation of the trial drug in the T-DM1 group were a decreased platelet count in 31 of 740 patients (4.2%), an increased blood bilirubin level in 19 patients (2.6%), an increased aspartate aminotransferase level in 12 patients (1.6%), an increased alanine aminotransferase level in 11 patients (1.5%), peripheral sensory neuropathy in 11 patients (1.5%), and a decreased ejection fraction in 9 patients (1.2%).

A total of 740 patients in the T-DM1 group and 720 in the trastuzumab group were included in the safety analysis, as shown in Table 2.

The most common AEs grade 3 or higher were decreased platelet counts and hypertension in the T-DM1 group and hypertension and radiation-related skin injury in the trastuzumab group. Serious AEs occurred in 12.7% of patients receiving T-DM1 and 8.1% of patients receiving trastuzumab. Adverse event-related discontinuation occurred in 18% of patients receiving T-DM1 and 2.1% receiving trastuzumab. Adverse events of any grade were slightly more common in the T-DM1 group. In addition to the safety data presented in Table 2, AEs of any grade with an incidence of at least 15% were noted (von Minckwitz et al., 2018), with fatigue presenting in about one third of patients in the trastuzumab group and nearly 50% of the patients receiving T-DM1. The authors note

that the safety profile for T-DM1 was consistent with that of previous studies and, as expected, there were more AEs in patients receiving T-DM1 than in those receiving adjuvant trastuzumab.

Although the ExteNET trial as described above did not include patients who had received adjuvant T-DM1, in this situation, it would be reasonable to consider extended adjuvant neratinib, but there are as yet no data supporting this approach.

### Key Points

- Patients with residual disease after neoadjuvant chemotherapy plus HER2 targeted therapy have a worse prognosis than do those without residual disease
- A significantly higher proportion of patients achieve a pCR with combined pertuzumab and trastuzumab plus docetaxel than do those treated with trastuzumab plus docetaxel

- DFS and PFS are higher in patients receiving docetaxel, trastuzumab, and pertuzumab for 12 weeks in the neoadjuvant setting than in patients receiving docetaxel and trastuzumab
- Even patients with very low volume residual disease demonstrate a benefit from T-DMI as compared to trastuzumab

### Case 3: Strategies for Managing AEs

The patient is a 60-year-old woman with no prior relevant medical history. A mass was palpated in her left breast, biopsy-proven to be invasive ductal carcinoma, HER2+ (3+ by IHC), ER+. The tumor was approximately 2.5 cm by imaging with suspicious axillary nodes that were biopsy-proven to be involved, cT2N1M0. She received neoadjuvant therapy with TCHP × 6 cycles and has significant side effects from therapy, including diarrhea, rash, and general intolerance. The patient was able to complete the 6 cycles of therapy but had residual disease at the time of surgery. She was offered trastuzumab emtansine (T-DMI) in the adjuvant setting yet refused. She also refused pertuzumab and/or neratinib for fear of further side effects. She did consent to complete a year of trastuzumab in the adjuvant setting, but at 6 months into the planned 1 year of treatment, she developed severe headaches and was found to have brain metastases.

### ADVERSE EVENT MANAGEMENT

To date, there is substantial experience with AE management to help patients who receive trastuzumab, pertuzumab and/or neratinib for the management of HER2+ BC. Diarrhea and rash are common side effects of pertuzumab. Both trastuzumab and pertuzumab can be associated with cardiac toxicity and infusion-related events (albeit rarely). Early identification and management of side effects is recommended.

For neratinib, diarrhea is the main side effect. It can be severe in patients who do not receive anti-diarrheal prophylaxis. Other toxicities include liver toxicity (rare) and a variety of drug interactions related to gastric-acid-reducing agents, CYP3A4 inhibitors/inducers, and P-glycoprotein substrates.

As demonstrated in the CONTROL trial, anti-diarrhea prophylaxis with the use of loperamide, budesonide, and colestipol reduces the incidence, severity, and duration of neratinib-associated di-

arrhea (Martin et al., 2017). In addition to this approach, other measures to decrease the incidence of diarrhea and prevent dehydration include instructing patients to remain hydrated by drinking 8 to 10 glasses of water daily, and having patients avoid high-fat greasy, spicy, or fried foods.

In terms of diet management, patients should eat small but frequent meals and consider foods low in fiber, high in protein and potassium, and containing live bacterial cultures (such as yogurt) or probiotics. Patients should avoid dairy, alcohol and caffeine, high-fiber foods, and foods containing grapefruit (Benson et al., 2004).

The advanced practitioner's role in managing patients on HER2 therapy overall, inclusive of addressing diarrhea, is best encapsulated as follows:

- Essential baseline assessments
  - » Extent of disease
  - » Cardiovascular history and subjective assessments (LVEF)
  - » Gastrointestinal history and subjective assessments as needed
- Patient education
  - » Disease process
  - » Treatment
  - » Self-management of potential toxicities that is proactive, not reactive
  - » Prescribing anti-diarrhea medications to have on hand with specific written instructions for when to start and what to report (i.e., loperamide 4 mg po at first episode of diarrhea and every 4–6 hours as needed; do not exceed 16 mg per day)
  - » Coordinate office personnel to contact patient on days 1, 8, 15, and 22 of first month of therapy to discuss if diarrhea is a problem or well controlled if patient is not being seen at that time for office visits
  - » Encourage patient that diarrhea usually starts to taper towards normal after first 1–2 months
  - » If diarrhea is uncontrolled with loperamide, consider adding prescription atropine/diphenoxylate 2.5-mg tablets every 4–6 hours, not to exceed 8 tablets per day
  - » May add colestipol 2 mg bid 4 hours before or 2 hours after neratinib first cycle
  - » Discuss diet restrictions: low-residue foods, bananas, rice, bread, mashed pota-

- toes, yogurt, probiotics, chicken broth, no fried/greasy/spicy foods, cream of wheat
- » Call office if maximum dose ineffective
- » Report AEs: when and to whom
- » Encourage increased oral fluid intake with water and electrolyte-replacing drinks (Gatorade or Pedialyte if appropriate)
- » Schedule for electrolyte assessment and replace fluids through IV hydration if oral not possible

- Staff education

Taking baseline measurements is essential to assessing changes that are treatment-related. Educating the patient on what to expect and how to address AEs preventively is also critical, as is educating any staff who interface with the patient (NCCN, 2017).

For this particular patient, it is critical to treat her diarrhea with hydration and diet, more so if it is sufficiently severe, using loperamide or diphenoxylate after each episode until it subsides. Rash that is not severe may not affect the completion of the current cycle of treatment, but treatment with minocycline or a corticosteroid may be required.

## AGENTS IN DEVELOPMENT, INCLUDING THE UNMET NEED OF TARGETED THERAPIES FOR BRAIN METASTASES IN HER2+ MBC

Although considerable progress has been made in the treatment of HER2+ MBC there is still a need for additional treatments for these patients. Standard first-line therapy in the metastatic setting is a taxane, trastuzumab, and pertuzumab based on the CLEOPATRA trial (Swain et al., 2015). T-DM1 is often used as second-line therapy based on the EMILIA trial (Diéras et al., 2017). However, for third-line therapy and beyond, several new agents are under investigation. One new agent is margetuximab (Burris et al., 2015; Rugo et al., 2016), which expresses an enhanced antibody-dependent cellular cytotoxicity leading to tumor cell destruction.

Margetuximab is being evaluated in SOPHIA, a phase III trial comparing a chemotherapy backbone plus margetuximab vs. chemotherapy plus trastuzumab in the treatment of HER2+ MBC. On February 6, 2019, positive results from this trial were released (MacroGenetics, 2019). Patients in the margetuximab arm experienced a 24% risk

reduction of disease progression or death vs. patients in the trastuzumab arm (HR, 0.76;  $p = .033$ ). Of note, approximately 85% of patients in SOPHIA were CD16A (FcγRIIIa) 158F allele carriers, previously linked to a diminished clinical response to trastuzumab and other antibodies. For this margetuximab arm subgroup there was a 32% risk reduction of disease progression or death vs. trastuzumab (HR, 0.68;  $p = .005$ ). These findings are noteworthy as there are currently no approved agents for the treatment of patients with metastatic HER2+ BC who have previously received trastuzumab, pertuzumab, and TDM1.

Breast cancer metastatic to the brain continues to be a troubling occurrence for many women (Frisk et al., 2017; Jin et al., 2018; Leone & Leone, 2015; Shen et al., 2015). While there has been little to offer these patients, there have been recent advances and an appreciation of new strategies to address this unmet need. In regard to brain metastases, promising results have been reported with the use of tucatinib, also known as ONT-380. Tucatinib has a high selectivity for HER2 ( $IC_{50(nM)} = 8$  for HER2;  $IC_{50(nM)} = > 10,000$  for EGFR; Moulder et al., 2017).

When comparing cellular selectivity to HER2 or to EGFR, these data suggest that tucatinib may have less skin and GI toxicity as compared to other anti-HER2 agents. In a phase 1b study when combined with capecitabine with or without trastuzumab in women with HER2+ MBC, the objective response rate was 61% with a median PFS of nearly 8 months. In June 2017, tucatinib was given an orphan drug designation by the FDA for the treatment of BC with brain metastases (Cascadian Therapeutics, 2017). A phase II trial of tucatinib plus capecitabine plus placebo vs. tucatinib in combination with capecitabine and trastuzumab in HER2+ BC is underway, the primary endpoint being PFS with secondary endpoints of overall response rate, duration of response, clinical benefit response, safety, and tolerability (NCT02614794; ClinicalTrials.gov, 2019).

Another option for patients with HER2+ MBC with brain metastases is neratinib plus capecitabine, which is listed as a Category 2A recommendation treatment option by NCCN (in the central nervous system section of the NCCN Guidelines; 2018b). The recommendation was based on a phase II trial, the TBCRC 022 study. In

addition, there is a Category 2B recommendation for neratinib plus paclitaxel for this same group of patients. The ongoing NALA trial is a phase III randomized controlled trial of neratinib plus capecitabine vs. lapatinib plus capecitabine in patients with third-line HER2+ MBC. A press release in December 2018 indicated this was a positive trial with further results expected shortly (Puma Biotechnology, Inc., 2018).

### Key Points

- APs should educate patients treated with neratinib to monitor for and prevent diarrhea; dietary precautions and treatment with loperamide and colestipol are helpful in reducing frequency and severity
- New approaches for patients with brain metastases are on the horizon
- Consider enrollment in clinical trials for patients with HER2+ MBC and central nervous system metastases with the option of neratinib plus capecitabine, to be considered per NCCN Guidelines

### Case 4: Therapy De-Escalation and Cardiac Toxicity

The final case features a 65-year-old woman with a history of obesity, hypertension, high cholesterol, borderline diabetes mellitus, and prior myocardial infarction, presenting with 1.5 cm, node-negative, ER+/HER2+ BC. She had a lumpectomy and then received weekly paclitaxel/trastuzumab (paclitaxel weekly  $\times$  12 weeks with trastuzumab to complete 1 year). She received post-lumpectomy radiation and was started on adjuvant hormonal therapy. Six months into the year of trastuzumab, she developed a symptomatic drop in ejection fraction that did not resolve by withholding the drug or with the use of cardiac medications as recommended by her cardiologist.

### THERAPY DE-ESCALATION AND CARDIAC TOXICITY

Data supporting de-escalation of therapy as administered in this case is found in the APT trial by Tolaney and colleagues. This was a single-arm, phase II nonrandomized trial to evaluate if 12 weeks of adjuvant paclitaxel in combination with trastuzumab was effective in node-negative,

small ( $< 3$  cm), HER2+ BC. A total of 410 patients were enrolled. The overall 7-year DFS was 93.3% and the overall 7-year relapse-free interval was 97.5%. It is important to note that two-thirds of patients had HR-positive tumors, and recurrences in this subset may be seen well after 3 years (Tolaney et al., 2015, 2017).

This case also highlights the studies that have evaluated shorter durations (less than 1 year) of adjuvant trastuzumab. Multiple studies have failed to demonstrate noninferiority of shorter durations of trastuzumab, and the HERA trial failed to demonstrate the superiority of 2 years of trastuzumab therapy as compared to 1 year of trastuzumab therapy.

The only study demonstrating noninferiority was the recently presented PERSEPHONE study (Earl et al., 2018), in which patients were given chemotherapy  $\times$  6 cycles and then given 6 months or 1 year of trastuzumab concurrently/sequentially with chemotherapy. Although the noninferiority endpoint was met, several caveats from the study are worth mention. This trial included a fairly good-risk population, with 70% of patients having ER+ disease and 30% of patients having ER- disease (Earl et al., 2018). Few patients today receive only anthracycline-based or taxane-based therapy, but in PERSEPHONE some did, and a few received cyclophosphamide, methotrexate, and fluorouracil, which is not standard therapy for patients with HER2+ BC. Approximately 60% of patients were node-negative and 40% were node-positive. In 2018, an updated analysis at a median follow-up at 5.4 years was presented where non-inferiority to a shorter duration of adjuvant trastuzumab (6 months vs. 1 year) was met (Earl et al., 2018). Subset analyses indicated the longer duration of trastuzumab was superior in patients with ER- disease than in those patients who received sequential as opposed to concurrent trastuzumab therapy (Earl et al., 2018). Therefore, results of this trial should not be broadly generalized, and 1 year of adjuvant trastuzumab remains the standard of care. However, for patients such as the one described in case 4, shorter durations of therapy may be considered based on these results.

### Key Points

- Although 1 year of adjuvant trastuzumab is the standard of care, a shorter duration

of therapy may be considered for some patients based on their unique characteristics and disease history; multiple studies have failed to demonstrate the noninferiority of shorter durations of trastuzumab

- It is important to obtain cardiac echo or MUGA scans every 3 months to monitor for potential cardiotoxicity for patients receiving trastuzumab (alone or in combination with pertuzumab) and to appropriately hold therapy as per guidelines.

## CONCLUSIONS

The discovery of the *HER2* gene and HER2 targeted therapies has resulted in decreases in BC-associated morbidity and mortality. However, patients with HER2+ BC remain at risk for recurrent disease, which is not considered curable and is associated with a decrease in overall survival. Therefore, there is room to further improve outcomes for early-stage HER2+ BC patients who receive treatment in the adjuvant setting and neoadjuvant settings.

Several data sets highlighted in this article support the consideration of neoadjuvant chemotherapy with trastuzumab and pertuzumab in patients with node-positive disease and/or tumors of 2 cm or greater in size. For patients with residual disease following neoadjuvant therapy, the KATHERINE trial supports a new standard of care for the use of T-DM1 in the adjuvant setting. Based on results from the APHINITY and the ExteNET trials, there is now data to support the addition of concurrent pertuzumab for high-risk patients in the adjuvant setting or the sequential use of neratinib in HR+ patients after a year of trastuzumab in the extended adjuvant setting.

In the metastatic setting there are several novel agents under investigation that appear promising, and a focus on developing therapies for patients with brain metastases, as this is an area of high unmet need. It is important to be mindful of therapy-associated toxicities of all these treatments and to institute early management strategies to adequately support patients through treatment. As treatment continues to be refined, future efforts should remain focused on identifying biomarkers for improving patient selection in order

to successfully exclude those who are unlikely to benefit from these expensive interventions.

## CLINICAL PEARLS

To optimize care for patients with HER2+ BC, APs should:

- Stay abreast of emerging data regarding current and novel neoadjuvant, adjuvant, extended adjuvant and metastatic therapies; discuss the clinical implications with their care team to ensure evolving data can be safely and effectively integrated into practice
- Be proactive in monitoring for and treating AEs and encourage patients and their caregivers to do so as well
- Educate patients treated with neratinib to remain hydrated; avoid high-fat greasy, spicy, or fried foods; and take medication to prevent diarrhea
- It is important to obtain cardiac echo or MUGA scans every 3 months to monitor for potential cardiotoxicity for patients receiving trastuzumab (alone or in combination with pertuzumab) and to appropriately hold therapy as per guidelines.
- Be aware of the higher risk of brain metastases in HER2+ MBC and recognize there are agents under investigation for this area of high unmet need. ●

## Disclosure

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## References

- American Cancer Society. (2018). *Cancer Facts & Figures 2018*. Atlanta, GA: American Cancer Society.
- Benson, A. B., 3rd, Ajani, J. A., Catalano, R. B., Engelking, C., Kornblau, S. M., Martenson, J. A., Jr.,...Wadler, S. (2004). Recommended guidelines for the treatment of cancer treatment-induced diarrhea. *Journal of Clinical Oncology*, 22(14), 2918–2926. <https://doi.org/10.1200/JCO.2004.04.132>
- Burris, H. A., Giaccone, G., Im, S.-A., Bauer, T. M., Oh, D.-Y., Jones, S. F.,...Bang, Y.-J. (2015). Updated findings of a first-in-human, phase I study of margetuximab (M), an Fc-optimized chimeric monoclonal antibody (MAb), in patients (pts) with HER2-positive advanced solid tumors [Abstract 523]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts)*, 33(15 suppl). [https://doi.org/10.1200/JCO.2015.33.15\\_suppl.523](https://doi.org/10.1200/JCO.2015.33.15_suppl.523)

- org/10.1200/jco.2015.33.15\_suppl.523
- Burstein, H. J. (2005). The distinctive nature of HER2-positive breast cancers. *New England Journal of Medicine*, 353(16), 1652–1654. <https://doi.org/10.1056/NEJMp058197>
- Burstein, H. J., Lacchetti, C., Anderson, H., Buchholz, T. A., Davidson, N. E., Gelmon, K. E.,...Griggs, J. J. (2016). Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline Update on Ovarian Suppression. *Journal of Clinical Oncology*, 34(14), 1689–1701. <https://doi.org/10.1200/JCO.2015.65.9573>
- Cascade Therapeutics. (2017). FDA grants orphan drug designation to tucatinib for brain metastases. Retrieved from <https://www.healio.com/hematology-oncology/breast-cancer/news/online/%7Bbdcef13f-c984-4195-9a4b-ef06fcd8510%7D/fda-grants-orphan-drug-designation-to-tucatinib-for-brain-metastases>
- Chan, A., Delalogue, S., Holmes, F. A., Moy, B., Iwata, H., Harvey, V. J.,...Martin, M. (2016). Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): A multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncology*, 17(3), 367–377. [https://doi.org/10.1016/S1470-2045\(15\)00551-3](https://doi.org/10.1016/S1470-2045(15)00551-3)
- ClinicalTrials.gov. (2019). A study of tucatinib vs. placebo in combination with capecitabine & trastuzumab in patients with advanced HER2+ breast cancer (HER2CLIMB). Retrieved from <https://clinicaltrials.gov/ct2/show/NCT02614794>
- Diéras, V., Miles, D., Verma, S., Pegram, M., Welslau, M., Baselga, J.,...Gianni, L. (2017). Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): A descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncology*, 18(6), 732–742. [https://doi.org/10.1016/S1470-2045\(17\)30312-1](https://doi.org/10.1016/S1470-2045(17)30312-1)
- Earl, H. M., Hiller, L., Vallier, A. L., Loi, S., Howe, D., Higgins, H. B.,...Dunn, J. (2018). PERSEPHONE: 6 versus 12 months of adjuvant trastuzumab in patients with HER2-positive breast cancer [Abstract 506]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts)*, 36(suppl). Retrieved from <https://meetinglibrary.asco.org/record/160257/abstract>
- Frisk, G., Tinge, B., Ekberg, S., Eloranta, S., Bäcklund, M., Lidbrink, E., & Smedby, K. E. (2017). Survival and level of care among breast cancer patients with brain metastases treated with whole brain radiotherapy. *Breast Cancer Research and Treatment*, 166, 887–896. <https://doi.org/10.1007/s10549-017-4466-3>
- Genentech, Inc. (2012). Perjeta (pertuzumab) package insert. Retrieved from [https://www.accessdata.fda.gov/drugatfdocs\\_docs/label/2012/125409lbl.pdf](https://www.accessdata.fda.gov/drugatfdocs_docs/label/2012/125409lbl.pdf)
- Gianni, L., Pienkowski, T., Im, Y.-H., Roman, L., Tseng, L.-M., Liu, M.-C.,...Valagussa, P. (2012). 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 Oncology*, 13(1), 25–32. [https://doi.org/10.1016/S1470-2045\(11\)70336-9](https://doi.org/10.1016/S1470-2045(11)70336-9)
- Gianni, L., Pienkowski, T., Im, Y.-H., Tseng, L.M., Liu, M.C., Lluch, A.,...Valagussa, P. (2016). 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 Oncology*, 17(6), 791–800. [https://doi.org/10.1016/S1470-2045\(16\)00163-7](https://doi.org/10.1016/S1470-2045(16)00163-7)
- Goldhirsch, A., Gelber, R. D., Piccart-Gebhart, M. J., de Azambuja, E., Procter, M., Suter, T. M.,...Baselga, J. (2013). 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): An open-label, randomised controlled trial. *Lancet*, 382(9897), 1021–1028. [https://doi.org/10.1016/S0140-6736\(13\)61094-6](https://doi.org/10.1016/S0140-6736(13)61094-6)
- Howlader, N., Altekruse, S. F., Li, C. I., Chen, V. W., Clarke, C. A., Ries, L. A. G., & Cronin, K. A. (2014). US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *Journal of the National Cancer Institute*, 106(5), dju055. <https://doi.org/10.1093/jnci/dju055>
- Hurvitz, S., Chan, A., Iannotti, N., Ibrahim, E., Chien, J., Chan, N.,...Rugo, H. S. (2017). Abstract P3-14-01: Effects of adding budesonide or colestipol to loperamide prophylaxis on neratinib-associated diarrhea in patients with HER2+ early-stage breast cancer: The CONTROL trial [Abstract P3-14-01]. Presented at the San Antonio Breast Cancer Symposium. Retrieved from <https://www.sabcs.org/Portals/SABCS2016/Documents/SABCS-2017-Abstracts.pdf>
- Jin, J., Gao, Y., Wang, L., Wang, B., Cao, J., Shao, Z., & Wang, Z. (2018). Incidence, pattern and prognosis of brain metastases in patients with metastatic triple negative breast cancer. *BMC Cancer*, 18, 446. <https://doi.org/10.1186/s12885-018-4371-0>
- Leone, J. P., & Leone, B. A. (2015). Breast cancer brain metastases: The last frontier. *Experimental Hematology & Oncology*, 4, 33. <https://doi.org/10.1186/s40164-015-0028-8>
- Martin, M., Holmes, F. A., Ejlersten, B., Delalogue, S., Moy, B., Iwata, H.,...Chan, A. (2017). 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 Oncology*, 18(12), 1688–1700. [https://doi.org/10.1016/S1470-2045\(17\)30717-30719](https://doi.org/10.1016/S1470-2045(17)30717-30719)
- Moulder, S. L., Borges, V. F., Baetz, T., Mcspadden, T., Fernetich, G., Murthy, R. K.,...Chia, S. K. (2017). Phase I study of ONT-380, a HER2 inhibitor, in patients with HER2+ advanced solid tumors, with an expansion cohort in HER2+ metastatic breast cancer (MBC). *Clinical Cancer Research*, 23(14), 3529–3536. <https://doi.org/10.1158/1078-0432.CCR-16-1496>
- National Comprehensive Cancer Network. (2017). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. V2.2017. Retrieved from <https://jnccn.org/abstract/journals/jnccn/15/6/article-p804.xml>
- National Comprehensive Cancer Network. (2018). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. V3.2018. Retrieved from [https://www.nccn.org/professionals/physician\\_gls/pdf/breast.pdf](https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf)
- National Comprehensive Cancer Network. (2018). NCCN Clinical Practice Guidelines in Oncology: Central nervous system cancers. V2.2018. Retrieved from [https://www.nccn.org/professionals/physician\\_gls/pdf/cns.pdf](https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf)
- Perez, E. A., Romond, E. H., Suman, V. J., Jeong, J. H., Sledge, G., Geyer, C. E., Jr.,...Wolmark, N. (2014). Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: Planned joint analysis of overall survival from NSABP B-31 and

- NCCTG N9831. *Journal of Clinical Oncology*, 32(33), 3744–3752. <https://doi.org/10.1200/JCO.2014.55.5730>
- Puma Biotechnology, Inc. (2017). Nerlynx (neratinib) package insert. Retrieved from [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/208051s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208051s000lbl.pdf)
- Puma Biotechnology, Inc. (2018). Puma biotechnology announces top line results of the phase III NALA trial of neratinib in patients with HER2-positive metastatic breast cancer. Retrieved from <https://investor.pumabiotechnology.com/press-release/puma-biotechnology-announces-top-line-results-phase-iii-nala-trial-neratinib-patients>
- Romond, E. H., Perez, E. A., Bryant, J., Suman, V. J., Geyer, C. E., Jr., Davidson, N. E.,...Wolmark, N. (2005). Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *New England Journal of Medicine*, 353(16), 1673–1684. <https://doi.org/10.1056/NEJMoa052122>
- Rugo, H. S., Pegram, M. D., Gradishar, W. J., Cortes, J., Curigliano, G., Wigginton, J. M.,...Cardoso, F. (2016). SOPHIA: A phase 3, randomized study of margetuximab plus chemotherapy (CTX) vs trastuzumab plus CTX in the treatment of patients with HER2+ metastatic breast cancer [Abstract TPS630]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts)*, 34(suppl 15). Retrieved from <https://meetinglibrary.asco.org/record/126836/abstract>
- Schneeweiss, A., Chia, S., Hickish, T., Harvey, V., Eniu A., Hegg, R.,...Cortez, J. (2013). 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). *Annals of Oncology*, 24(9), 2278–2284. <https://doi.org/10.1093/annonc/mdt182>
- Shen, Q., Sahin, A. A., Hess, K. R., Suki, D., Aldape, K. D., Sawaya, R., & Ibrahim, N. K. (2015). Breast cancer with brain metastases: Clinicopathologic features, survival, and paired biomarker analysis. *Oncologist*, 20(5), 466–473. <https://doi.org/10.1634/theoncologist.2014-0107>
- Slamon, D., Eiermann, W., Robert, N., Pienkowski, T., Martin, M., Press, M.,...Crown, J. (2011). Adjuvant trastuzumab in HER2-positive breast cancer. *New England Journal of Medicine*, 365(14), 1273–1283. <https://doi.org/10.1056/NEJMoa0910383>
- Slamon, D. J., Eiermann, W., Robert, N. J., Giermek, J., Martin, M., Jasiowka, M.,...Crown, J. (2015). Ten year follow-up of BCIRG-006 comparing doxorubicin plus cyclophosphamide followed by docetaxel with doxorubicin plus cyclophosphamide followed by docetaxel and trastuzumab with docetaxel, carboplatin, and trastuzumab in HER2-positive early breast cancer [Abstract S5-04]. Presented at the San Antonio Breast Cancer Symposium. Retrieved from [https://www.abstracts2view.com/sabcs15/view.php?nu=SABCS15L\\_1030&terms=](https://www.abstracts2view.com/sabcs15/view.php?nu=SABCS15L_1030&terms=)
- Swain, S. M., Baselga, J., Kim, S.-B., Ro, J., Semiglazov, V., Campone, M.,...Cortés, J. (2015). Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *New England Journal of Medicine*, 372(8), 724–734. <https://doi.org/10.1056/NEJMoa1413513>
- Tolaney, S. M., Barry, W. T., Dang, C. T., Yardley, D. A., Moy, B., Marcom, P. K.,...Winer, E. P. (2015). Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *New England Journal of Medicine*, 372(2), 134–141. <https://doi.org/10.1056/NEJMoa1406281>
- Tolaney, S. M., Barry, W. T., Guo, H., Dillon, D., Dang, C. T., Yardley, D. A.,...Winer, E. A. (2017). Seven-year follow-up of adjuvant paclitaxel and trastuzumab (APT trial) for node-negative, HER2-positive breast cancer [Abstract 511]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts)*, 35(suppl). Retrieved from <https://meetinglibrary.asco.org/record/145548/abstract>
- von Minckwitz, G., Huang, C. S., Mano, M. S., Loibl, S., Mamounas, E. P., Untch, M.,...Geyer, C. E. (2019). Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *New England Journal of Medicine*, 380, 617–628. <https://doi.org/10.1056/NEJMoa1814017>
- von Minckwitz, G., Procter, M., de Azambuja, E., Zardavas, D., Benyunes, M., Viale, G.,...Baselga, J. (2017). Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *New England Journal of Medicine*, 377(2), 122–131. <https://doi.org/10.1056/NEJMoa1703643>

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