Current neoadjuvant treatment options for HER2-positive breast cancer

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Abstract: Approximately one quarter of patients with breast cancer demonstrate amplification of the human epidermal receptor type 2 (HER2) gene, the expression of which is associated with a relatively poor prognosis independent of other clinical and pathologic variables. Trastuzumab, a humanized recombinant monoclonal antibody specifically directed against the HER2 receptor, has been shown to be biologically active and of considerable clinical utility in HER2-positive breast cancer patients. Neoadjuvant chemotherapy has been used in breast cancer to downstage the tumor and increase the opportunity for breast-conserving surgery. Preoperative chemotherapy can also serve as an in vivo testing of chemotherapy sensitivity. Additionally, a pathologic complete response is usually a surrogate marker of disease-free survival. Following the successful use of trastuzumab in the metastatic and adjuvant settings, many clinical trials have recently reported the successful use of anti-HER2 therapy in combination with different chemotherapy regimens in the neoadjuvant setting with a significantly higher pathologic complete response. With the recent introduction of new anti-HER2 drugs, interest has shifted toward dual HER2 blockade. Two such studies were recently reported, both showing a significant advantage of dual anti-HER2 therapy using lapatinib or pertuzumab in addition to trastuzumab and chemotherapy. However, several key questions need to be investigated further, such as the preferred combination chemotherapy and the optimal duration of trastuzumab in patients who achieve a pathologic complete response following preoperative chemotherapy with trastuzumab. These issues and others are discussed in this review.

Keywords: neoadjuvant, breast cancer, trastuzumab, pertuzumab, lapatinib

Introduction

Neoadjuvant therapy, also known as primary systemic treatment, was initially introduced for the treatment of inoperable locally advanced or inflammatory breast cancer. Increasingly, primary systemic treatment is now considered for women with large but operable disease. The rationale of this approach is to provide early chemotherapy that allows theoretical downstaging of the tumor, higher rates of breast-conserving surgeries, and in vivo testing of tumor response to the chosen chemotherapy.1–5 Despite the various definitions of pathologic complete response in the neoadjuvant trials, the correlation of pathologic complete response with improved disease-free survival and overall survival has already been demonstrated in several studies and is currently used as a surrogate marker for chemotherapy benefit in the neoadjuvant setting.6–8

Neoadjuvant chemotherapy has been compared with adjuvant chemotherapy using the same drug regimens in patients with operable breast cancer, with no difference in overall survival or disease-free survival. In the National Surgical Adjuvant Breast
and Bowel Project (NSABP) B18 trial, patients with clinical T1-3, N0-1 breast cancer were randomly assigned to neoadjuvant or adjuvant chemotherapy utilizing four cycles of adriamycin + cyclophosphamide. There was no statistically significant difference between neoadjuvant and adjuvant chemotherapy in nine-year overall survival. 9 At 16 years of follow-up, the difference in overall survival between the two groups remained statistically insignificant (hazard ratio [HR] 0.99; 95% confidence interval [CI] 0.85–1.16). 10

Similar conclusions were reached utilizing different chemotherapy regimens. The European Organisation for Research and Treatment of Cancer 10902 trial randomized patients with clinical T1c–T4b breast cancer to neoadjuvant or adjuvant chemotherapy with four cycles of fluorouracil + epirubicin + cyclophosphamide. At a median follow-up of 56 months, there was no significant difference between neoadjuvant and adjuvant chemotherapy in terms of four-year overall survival (82% versus 84%) or progression-free survival (65% versus 70%). 11

Many neoadjuvant clinical trials have been reported utilizing different chemotherapeutic agents, the more recent of which have utilized taxanes (paclitaxel or docetaxel) and anthracyclines (adriamycin [doxorubicin] or epirubicin) in their regimens. The NSABP B27 trial utilized four cycles of adriamycin + cyclophosphamide with or without four cycles of docetaxel, with the surgery performed before or after the docetaxel. Compared with preoperative adriamycin + cyclophosphamide alone, preoperative adriamycin + cyclophosphamide followed by docetaxel increased the clinical complete response rate (40.1% versus 63.6%; \( P < 0.001 \)), the overall clinical response rate (85.5% versus 90.7%; \( P < 0.001 \)), the pathologic complete response rate (13.7% versus 26.1%; \( P < 0.001 \)), and the proportion of patients with negative nodes (50.8% versus 58.2%; \( P < 0.001 \)). 12 Similar results were also achieved in the Aberdeen trial utilizing different docetaxel-based neoadjuvant chemotherapy. 13

Approximately one quarter of patients with breast cancer demonstrate overamplification of the human epidermal receptor type 2 (HER2) gene, resulting in overexpression of the HER2 receptor, a transmembrane tyrosine kinase receptor, the activation of which is known to result in increased activity of a variety of molecular pathways associated with tumor growth and progression. 14 Extensive published data have demonstrated that patients whose cancers overexpress HER2 have a relatively poor prognosis independent of other clinical and pathologic variables, like tumor size and nodal status. 15–17

Trastuzumab, a humanized recombinant monoclonal antibody specifically directed against the HER2 receptor, has been shown to be biologically active and of considerable clinical utility in HER2-positive breast cancer patients. 18 Trastuzumab was approved by the US Food and Drug Administration in 1998 after a landmark Phase III trial in women with HER2-positive metastatic breast cancer showed dramatic improvement in overall response rates and overall survival with the addition of trastuzumab to standard first-line chemotherapy consisting of doxorubicin + cyclophosphamide or paclitaxel. 19 Many Phase II trials have reported similar clinical benefit when this drug is combined with a number of other chemotherapeutic agents including docetaxel, vinorelbine, capecitabine, and gemcitabine, in both front-line and pretreated metastatic settings. 20–25

So far, the results of five Phase III randomized trials exploring the benefit of adding trastuzumab to adjuvant chemotherapy for early HER2-positive breast cancer patients have been reported. 26–31 All trials demonstrated significant improvement in disease-free survival. The HERA (Herceptin Adjuvant) trial 26,27 and the joint analysis of two other studies, NSABP B31 and North Central Cancer Treatment Group N31, 10 also showed an improved overall survival.

The encouraging data from published clinical trials resulted in enormous interest in incorporating trastuzumab into the neoadjuvant setting in women with HER2-positive breast cancer, hoping to improve the outcome of such patients. The present paper reviews the present clinical trials in this regard and outline the main results and their impact on clinical practice.

**First randomized trial**

The use of concurrent chemotherapy and trastuzumab in the preoperative setting has been investigated in several studies. In one of the initial trials, Buzdar et al from the MD Anderson Cancer Center randomized patients with HER2-positive, early-stage operable breast cancer to receive four cycles of paclitaxel every three weeks followed by four cycles of fluorouracil + epirubicin + cyclophosphamide with or without concomitant weekly trastuzumab. The addition of trastuzumab to neoadjuvant chemotherapy significantly increased the pathologic complete response rate from 26.3% in the chemotherapy arm alone to 65.2% in the trastuzumab arm (\( P = 0.016 \)). 32 The study was closed prematurely after recruiting only 42 patients, and a third, open-label, nonrandomized cohort (n = 22) was added to the study, and all were assigned to the trastuzumab arm. Among the 45 patients who received chemotherapy plus trastuzumab, the pathologic
complete response rate was 60% (95% CI 44.3–74.3). Both the one-year, disease-free survival rate (100% versus 94.7% in the chemotherapy plus trastuzumab and chemotherapy alone arms, respectively) and the three-year, disease-free survival rate (100% versus 85.3%, respectively) improved with the addition of trastuzumab which was significant ($P = 0.041$) among the randomized arms. However, the addition of trastuzumab to neoadjuvant therapy had a minimal effect on the rate of breast-conserving therapy performed (52.6% and 56.5% of patients in the chemotherapy alone and chemotherapy with trastuzumab arms, respectively).

**Larger Phase III trials**

The use of trastuzumab was also assessed in larger clinical trials in patients with newly diagnosed locally advanced or inflammatory breast cancer. The NOAH (Neoadjuvant Herceptin) trial was a large, international Phase III trial designed to assess the efficacy and safety of sequential doxorubicin + paclitaxel followed by paclitaxel, then cyclophosphamide + methotrexate + 5-fluouracil with ($n = 117$) or without ($n = 118$) concomitant trastuzumab, in patients with newly diagnosed locally advanced breast cancer. A third arm of patients ($n = 99$) with HER2-negative disease who received the same regimen but without trastuzumab was also included. Patients with HER2-positive disease who received neoadjuvant chemotherapy with concurrent trastuzumab had a significantly improved overall response rate (87% versus 74%; $P = 0.009$) and pathologic complete response rate in breast tissue (43% versus 22%; $P = 0.0007$) compared with those who received neoadjuvant chemotherapy alone. A significant improvement in the pathologic complete response rate was also observed in a subgroup analysis of patients with inflammatory breast cancer who received trastuzumab compared with those who did not (39% versus 20%; $P = 0.002$). At a median follow-up of 3.2 years, the three-year, event-free survival improved significantly in patients with HER2-positive disease who received chemotherapy plus trastuzumab compared with those who received chemotherapy alone (71% versus 56%, HR 0.59; $P = 0.013$). For HER2-positive patients, the three-year overall survival of trastuzumab arm as compared with chemotherapy alone arm was 87% (95% CI 79–92) and 79% (95% CI 70–86), respectively ($P = 0.114$).

The German Breast Group/Gynecologic Oncology Study Group (GeparQuattro) trial was also designed to evaluate the effect of trastuzumab on pathologic complete response rates in a group of 1509 patients with either locally advanced (T3 or T4), hormone receptor-negative or hormone receptor-positive but lymph node-positive tumors. All patients were scheduled to receive four cycles of epirubicin 90 mg/m$^2$ and cyclophosphamide 600 mg/m$^2$ and were then randomly assigned to three treatment arms; the first arm received four cycles of docetaxel 100 mg/m$^2$ (EC-D), the second arm received four cycles of docetaxel 75 mg/m$^2$ + capcitabine 1800 mg/m$^2$ (EC-DX) while the third arm received four cycles of docetaxel 75 mg/m$^2$ followed by four cycles of capcitabine 1800 mg/m$^2$ on days 1–14 (EC-D-X). In each arm, patients with HER2-positive disease received trastuzumab starting from the initiation of the EC for 52 weeks. Patients with HER2-negative tumors received chemotherapy only. In total, 445 patients with HER2-positive tumors were included. Pathologic complete response rate, defined as no invasive or in situ residual tumors in the breast, was 31.7% for patients who had received neoadjuvant trastuzumab plus chemotherapy and 15.7% for patients who received chemotherapy alone ($P < 0.001$). In the HER2-positive group, a pathologic complete response was observed in 48 (32.9%) of 146 patients treated with EC-D, 45 (31.3%) of 144 patients treated with EC-DX, and 47 (34.6%) of 136 patients treated with EC-D-X. The rate of breast-conserving surgery was comparable among patients in the HER2-positive group (63.1%) and the HER2-negative reference group (64.7%). Results of these major trastuzumab-based neoadjuvant trials are summarized in Table 1.

**Newer anti-HER2 drugs**

The HER family consists of four transmembrane receptors that mediate a complex network of signaling pathways, and HER1, HER2, and HER3 are all implicated in the development and progression of cancer. While the role of the HER4 receptor in breast cancer is unclear, the HER3 receptor is gaining increasing interest in cancer research.

Ligand binding to the extracellular domain of the HER receptor initiates a conformational rearrangement, exposing the dimerization (receptor pairing) domain that forms the core of the dimer interface with another HER receptor. HER2 has no identified ligands and exists in an open conformation that allows dimerization with other HER receptors. HER2 and HER3 are highly complementary to each other, ie, HER3 binds ligand yet lacks intrinsic kinase activity while HER2 has intrinsic tyrosine kinase activity but no identified ligand. HER2 dimerizes preferentially with HER3 to drive downstream signaling.

Pertuzumab is the first of a new class of targeted anti-cancer agents known as the HER2 dimerization inhibitors. It is a humanized monoclonal antibody that binds to the...
The dimerization domain of HER2, which is an extracellular region essential for HER activation and signaling. The mechanism of action of pertuzumab, ie, inhibition of HER2 dimerization, is unique compared with that of other HER-targeted therapies. By blocking the pairing of the most potent signaling HER dimer, ie, HER2:HER3, pertuzumab affects key signaling pathways that mediate cell proliferation and survival in some cancers such as the breast. In vitro and in vivo studies have shown that pertuzumab works synergistically with trastuzumab to inhibit breast tumor cells survival.

Lapatinib is an orally active small molecule which reversibly inhibits both HER1 and HER2 tyrosine kinase domains. This concurrent inhibition in HER1-expressing and HER2-expressing tumors blocks the activating signaling cascades in the MAPK and PI3 K pathways, resulting in growth arrest and/or apoptosis, as shown in cell line and xenograft models. As a single agent, lapatinib has efficacy similar to that of trastuzumab monotherapy in the first-line treatment of HER2-positive metastatic breast cancer, and was approved by the US Food and Drug Administration in 2006 based on a Phase III trial demonstrating improved progression-free survival with the combination of lapatinib and capecitabine compared with capecitabine alone in patients with trastuzumab-refractory disease. Because lapatinib is a small molecule that can penetrate the blood–brain barrier, it is now being extensively studied for the treatment and prevention of central nervous system metastasis.

### Dual anti-HER2 blockade

With the recent introduction of new anti-HER2 drugs, interest was shifted toward dual HER2 blockade. The initial results of the Neo-ALTTO trial were recently presented at the 33rd San Antonio Breast Cancer Symposium. The study included 450 HER2-positive patients who had tumors that were 2 cm or larger in diameter and were randomly assigned to one of three arms, ie, lapatinib, trastuzumab, or the combination of both. Anti-HER2 therapy alone was given for six weeks, and then weekly paclitaxel was added for 12 weeks followed by surgery at week 18. Following surgery, patients received three cycles of fluorouracil + epirubicin + cyclophosphamide were then continued on the same anti-HER2 therapy that they were on previously for up to a year. The overall response rate was significantly higher with lapatinib plus trastuzumab versus trastuzumab alone after six weeks and at the time of surgery. The pathologic complete response with the combination of lapatinib and trastuzumab was 51.3% compared with 29.5% for trastuzumab (P = 0.0001). The overall response rate for the lapatinib alone arm was 52.6% while 24.7% achieved a...
pathologic complete response. Although no significant cardiac toxicity was reported, patients in the lapatinib arm suffered more toxicity than those in the trastuzumab arm including an increased incidence of diarrhea, hepatotoxicity, neutropenia, and skin disorders. More patients discontinued treatment because of adverse events with combination therapy. This concept of dual anti-HER2 therapy is being tested in the adjuvant setting in the ALTTO trial which is about to conclude, having accrued its target of 8200 patients.48

The other major dual anti-HER-2 neoadjuvant trial is NeoSphere, which looked at a combined blockade using trastuzumab + pertuzumab versus trastuzumab alone. This study was unique in including an arm that did not receive any chemotherapy, just the dual blockade. In this study, which was also presented at the 33rd San Antonio Breast Cancer Symposium, women with operable, locally advanced, or inflammatory breast cancer were randomized to receive four cycles every three weeks of docetaxel + trastuzumab or docetaxel + trastuzumab + pertuzumab. The other two arms received docetaxel + pertuzumab or the doublet of the two monoclonal antibodies, trastuzumab + pertuzumab, without chemotherapy. After surgery, all patients received three cycles of fluorouracil + epirubicin + cyclophosphamide + trastuzumab every three weeks for one full year. The pathologic complete response rate was 45.8% for the combined regimen of two monoclonals compared with 29% for the trastuzumab arm ($P = 0.014$) and 24% for the pertuzumab arm ($P = 0.003$). The pathologic complete response in women who received the two monoclonals without chemotherapy was 16.8%, thus raising the question whether a subgroup of breast cancer patients can be treated with monoclonal agents and thus avoid chemotherapy. One patient developed congestive heart failure with trastuzumab and pertuzumab.49

Results of these dual anti-HER2 blockade neoadjuvant trials are summarized in Table 2.

### Significance of pathologic complete response

Pathologic complete response has been almost universally adopted in the neoadjuvant trials as a reliable endpoint and has been shown to correlate with both disease-free survival and overall survival in many of these trials.10,12,50 However, the precise definition among different trials varies; earlier trials referred to pathologic complete response as absent tumor histologically in both the breast and axilla. Later, it was regarded as absence of tumor cells in breast tissues only. In addition, some trials looked at both invasive and noninvasive (carcinoma in situ) components in the residual tumor following the neoadjuvant therapy.

Several trials have shown that the extent of residual breast cancer burden and lymph node metastases correlates with disease-free survival. In one trial, Hennessy et al reviewed response data for 925 patients treated in five prospective neoadjuvant trials, including 403 patients with cytologically confirmed axillary lymph node metastases. Eighty-nine patients (22%) achieved a pathologic complete response in the axillary lymph nodes following neoadjuvant therapy. The outcome for patients who achieved axillary lymph node pathologic complete response with neoadjuvant chemotherapy was compared with those having residual disease in the axillary lymph nodes. Median follow-up was 64 (range 15–178) months. The five-year overall survival and relapse-free survival rates were significantly better in patients with a pathologic complete response in the axillary lymph nodes (93% [95% CI 87.5–98.5] and 87% [95% CI 79.7–94.3] versus 72% [95% CI 66.5–77.5] and 60% [95% CI 54.1–65.9], respectively; $P < 0.0001$).51

Updated follow-up data from both the NSABP-B18 and B27 trials have shown similar trends.10 The TECHNO trial also addressed this issue after neoadjuvant chemotherapy and trastuzumab. In this trial, over 200 HER2-positive patients

### Table 2 Summary of pCR with dual anti-HER2 blockade in neoadjuvant breast cancer trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Chemotherapy regimens</th>
<th>Patients</th>
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<th>$P$ value</th>
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</thead>
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<tr>
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<td>24.7%</td>
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<td>Trastuzumab + paclitaxel</td>
<td>149</td>
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<tr>
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<td></td>
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<td>107</td>
<td>29%</td>
<td>**</td>
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<td>24%</td>
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<tr>
<td>NeoSphere49</td>
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<td>16.8%</td>
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</table>

**Notes:** $^*$ $P$ values as compared with trastuzumab + paclitaxel; $^{**}$ $P$ values as compared with trastuzumab + docetaxel. Neo-ALTTO: lapatinib 1500 mg/day, if combined with trastuzumab 1000 mg/day, reduced to 750 mg/day with paclitaxel in 2008. Paclitaxel 80 mg/m2/week. Trastuzumab 4 mg/kg loading then 2 mg/kg/week. NeoSphere: pertuzumab 840 mg loading dose and 420 mg maintenance; trastuzumab 8 mg/kg loading dose and 6 mg/kg maintenance; docetaxel 75 mg/m2 with escalation to 100 mg/m2 if the starting dose was well tolerated.

**Abbreviation:** pCR, pathologic complete response.
received neoadjuvant epirubicin + cyclophosphamide for four
cycles every three weeks followed by paclitaxel 175 mg/m²
once every three weeks + trastuzumab 6 mg/kg every three
weeks after a loading dose of 8 mg/kg. Chemotherapy was
followed by surgery. Trastuzumab was continued after
surgery until completion of 12 months of treatment. The
three-year median follow-up data were recently presented
and showed a three-year, disease-free survival of 88% compared
with a rate of 73% among the patients who failed to achieve
pathologic complete response ($P$ = 0.011). Similarly, overall
survival was also better (96%) compared with a rate of 86%
($P$ = 0.025). 52

Cardiac toxicity
Cardiac toxicity was an unexpected finding during the clinical
development of trastuzumab. Therefore, baseline cardiac
evaluation or prospective monitoring were not mandated in
early clinical trials in the metastatic setting. Also, patients
with underlying cardiac disease were not excluded. In the
adjuvant setting, trastuzumab was associated with a low but
real risk of severe congestive heart failure or cardiac death,
ranging from 0.6% in the HERA trial 26–27 to 3.9% in NSABP-
B31 18 in patients who had prior anthracyclines. The majority
of the observed trastuzumab-related cardiac events were
asymptomatic decreases in left ventricular ejection fraction
(LVEF), and both symptomatic and asymptomatic events
were largely reversible.

In a meta-analysis including 10,955 patients treated in
adjuvant trials, the risk of symptomatic, clinically significant
(stage 3 to 4) heart failure following one year of trastuzumab
versus chemotherapy not containing trastuzumab was 1.9%
versus 0.3%, while the risk of an asymptomatic decrease in
LVEF in patients treated with trastuzumab versus no trastu-
zumab was 13.3% versus 6.1%. 53

Simultaneous administration of trastuzumab + epirubicin
in the MD Anderson Cancer Center study has raised the
concern for cardiac toxicity. Among patients randomized
to fluorouracil + epirubicin + cyclophosphamide and tras-
tuzumab, the median LVEF decreased from 65% to 60% by
the end of follow-up, but the LVEF range remained nearly
constant. None of the 45 patients treated with chemotherapy
and trastuzumab in the initial and the assigned cohort experi-
enced clinical cardiac dysfunction, and there were no cardiac
deaths in this study. 32

In the GeparQuattro Study, congestive heart failure and
cardiac ischemia were reported in two patients each treated
with chemotherapy alone and in one patient treated with
chemotherapy and trastuzumab. A decrease in LVEF to 45%
was reported in five patients and an LVEF decrease of more
than 10% from baseline was reported in two patients treated
with trastuzumab. 32 Similar trends were also noted in the
NOAH trial. 34

The risk of cardiac toxicity can be reduced by close
cardiac monitoring during therapy and by avoiding treat-
ing patients with a baseline LVEF $<$ 50%. Older patients
with baseline LVEF 50%–55% and cardiac risk factors
such as smoking, hypertension, body mass index $>$ 25,
and diabetes mellitus should be treated cautiously with
close cardiac surveillance. Extending the window between
the completion of anthracycline chemotherapy and initia-
tion of trastuzumab, and administering trastuzumab with
a nonanthracycline chemotherapy regimen may be a good
option for high-risk patients with underlying cardiac dis-
ease or borderline LVEF. Biomarkers such as troponin and
brain natriuretic peptide are being explored as potential
drug markers of cardiac injury, as is the prophylactic use
of cardiac medications. 54

Future directions
A larger randomized Phase III clinical trial, ie, NSABP-B41,
is currently ongoing to evaluate pathologic complete response
rate with the administration of adriamycin + cyclophos-
phamide followed by weekly paclitaxel in combination with
trastuzumab, lapatinib, or a combination of both trastu-
zumab and lapatinib, in the preoperative setting for patients
with palpable and operable HER-2 positive breast cancer
(NCT00486668). 55

There is growing interest in identifying biologic mark-
kers that would help tailoring treatment to individuals by
recognizing reliable response predictors. Such markers may
be related to cell proliferation, cell cycles, angiogenesis, or
signal transduction. In the previously discussed NeoSphere
study, tumor and blood specimens from $>$95% of patients
have been collected and are being probed. 49

HER2-specific vaccines are an interesting new concept
that have been evaluated in preclinical studies, with the
hypothesis that generation of an anti-HER2 immune response
may lead to slower tumor development at early stages.
Different vaccine strategies are being tested. 56

Several other key questions need to be investigated fur-
ther, such as the preferred chemotherapy for combination
with trastuzumab (anthracycline versus nonanthracycline-
based therapy) and the optimal duration of trastuzumab
in patients who achieve pathologic complete response
after preoperative chemotherapy with trastuzumab.
Lastly, a randomized clinical trial comparing the benefit
of trastuzumab in combination with chemotherapy in the preoperative versus postoperative setting is also needed to determine the best strategy to administer trastuzumab-based chemotherapy.

**Conclusion**

Many good quality clinical studies suggest that trastuzumab should be incorporated in the preoperative treatment of women with HER2-positive disease, a fact that is already incorporated into the current National Comprehensive Cancer Network guidelines. As discussed in this paper, several key questions still need to be addressed, including the preferred combination chemotherapy and the optimal duration of trastuzumab in patients who achieve a complete pathologic response after preoperative chemotherapy.

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**Disclosure**

The authors report no conflict of interest in this work.

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