Adjuvant systemic therapy for HER2-positive breast cancer

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INTRODUCTION

Globally, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in females. In the United States, breast cancer is the most common female cancer, the second most common cause of cancer death in women, and the main cause of death in women ages 40 to 49 years. The lifetime probability of developing invasive breast cancer is one in eight.

Breast cancer is a heterogeneous, phenotypically diverse disease composed of several biologic subtypes that have distinct behavior. Amplification or overexpression of the human epidermal growth factor receptor 2 (*HER2*) oncogene is present in approximately 15 percent of primary invasive breast cancers [1]. Women with early-stage breast cancer that meet criteria for HER2 positivity are treated with chemotherapy and trastuzumab as adjuvant treatment.

This topic review will cover the use of adjuvant HER2-directed therapy plus chemotherapy in patients with HER2-positive, early-stage breast cancer (stage I to III). Where clinical guidance is provided in this topic, the anatomic staging system set forth in the eighth edition of the American Joint Committee on Cancer Staging Manual is used (table 1); however, it is recognized that the studies cited may have used previous editions of the staging system, which is a limitation of existing data. (See "Tumor, node, metastasis (TNM) staging classification for breast cancer".)

Other relevant topics, including principles of testing for HER2 expression on breast cancer tumor tissue, indications for neoadjuvant therapy versus adjuvant therapy in HER2-positive disease, and treatment protocols for HER2-positive disease are discussed elsewhere.

- (See "HER2 and predicting response to therapy in breast cancer".)
- (See "Neoadjuvant therapy for patients with HER2-positive breast cancer", section on 'Indications'.)
- (See "Overview of the treatment of newly diagnosed, invasive, non-metastatic breast cancer".)
- (See "Treatment protocols for breast cancer", section on 'Regimens for HER2-positive breast cancer'.)

PATIENT ELIGIBILITY

All newly diagnosed breast cancers are tested for HER2 overexpression because HER2-directed therapy is a critical component of the adjuvant treatment of HER2-positive breast cancer. Testing algorithms for tumor HER2 status were developed by a joint consensus panel convened by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (table 2 and algorithm 1) [2].

Patients are eligible for adjuvant HER2-directed treatment if they have HER2-positive breast cancer defined as:

- Immunohistochemical stain of 3+, defined as uniform intense membrane staining for HER2 in 10 percent or more of tumor cells, or
- A *HER2*/chromosome enumeration probe 17 (CEP17) fluorescent in situ hybridization amplification ratio ≥2.0 and *HER2* copy number signals/cell ≥4 [3].

Our approach to HER2 testing and interpretation of the results is included in the algorithm (algorithm 1), and is consistent with ASCO guidelines [2].

Further details regarding the recommendations from the joint panel regarding optimal performance, interpretation, and reporting of individual assays are discussed in detail elsewhere. (See "HER2 and predicting response to therapy in breast cancer", section on 'Testing for HER2 expression'.)

TREATMENT OVERVIEW

General considerations

- Patients with HER2-positive non-metastatic breast cancer generally warrant adjuvant or neoadjuvant treatment with chemotherapy and trastuzumab, though other HER2-directed agents also may play a role in management (algorithm 2). Patients with stage II or III HER2-positive cancers will receive neoadjuvant therapy. Surgery as initial treatment is appropriate for those with smaller, node-negative tumors. Indications for neoadjuvant versus adjuvant therapy for HER2-positive breast cancer are discussed elsewhere. (See "Neoadjuvant therapy for patients with HER2-positive breast cancer", section on 'Indications'.)

- Benefits of adjuvant chemotherapy in early breast cancer have been demonstrated in a large meta-analysis [4], which included patients with early breast cancer, irrespective of HER2 status. These results are discussed elsewhere. (See "Selection and administration of adjuvant chemotherapy for HER2-negative breast cancer", section on 'Benefit of adjuvant chemotherapy'.)

- All of the trials establishing the benefit of trastuzumab limited eligibility to women with either node-positive or node-negative high-risk breast cancer (usually defined as tumor size >1 cm [5-7] or >2 cm [8]). We recommend chemotherapy plus trastuzumab for all women with HER2-positive, node-positive breast cancer and for women with HER2-positive, node-negative tumors >5 mm. We sometimes offer chemotherapy and trastuzumab for even smaller tumors (3 to 4 mm), especially if they are hormone receptor negative. We typically do not offer HER2-directed therapy or chemotherapy for node-negative tumors that are 1 to 2 mm in size. (See 'Node-negative tumors <1 cm' below.)

- Trastuzumab should be administered concomitantly with the non-anthracycline components of chemotherapy, rather than sequentially after chemotherapy. Although administration of trastuzumab sequentially after completion of all chemotherapy has demonstrated activity, it appears to be less effective than when given concurrently.

Patients who were treated with neoadjuvant therapy — Patients who were treated with neoadjuvant chemotherapy and trastuzumab (with or without pertuzumab) are treated with HER2-directed therapy in the adjuvant setting, with choice of therapy directed according to their response to neoadjuvant treatment (algorithm 2).

Residual disease — For those with residual disease after neoadjuvant HER2-directed therapy, we switch to ado-trastuzumab emtansine (T-DM1) in the adjuvant setting and continue for 14 cycles [9]. No further chemotherapy is administered with or after T-DM1.

T-DM1 — Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate of trastuzumab and the cytotoxic agent emtansine (DM1), a maytansine derivative and microtubule inhibitor [10]. For those with residual disease after neoadjuvant therapy for HER2-positive breast cancer, we administer T-DM1 in the adjuvant setting, continuing for 14 cycles, rather than trastuzumab or trastuzumab with pertuzumab.

In a randomized, open-label trial of 1486 women with HER2-positive early breast cancer with residual invasive disease after neoadjuvant taxane-containing chemotherapy (with or without anthracyclines) and trastuzumab, adjuvant treatment with 14 cycles of T-DM1 versus trastuzumab improved three-year invasive DFS (88 versus 77 percent; hazard ratio [HR] 0.50, 95% CI 0.39-0.64) [10,11]. The risk of distant recurrence was substantially lower with T-DM1 compared with trastuzumab (HR 0.60, 95% CI 0.45-0.79). Furthermore, the benefit of postoperative TDM-1 compared with trastuzumab was similar regardless of the preoperative choice of anti-HER2 therapy. Among patients who received neoadjuvant trastuzumab plus a second HER2-directed therapy with chemotherapy (typically pertuzumab), there was a nonsignificant trend towards improved invasive DFS with postoperative T-DM1 compared with trastuzumab (HR 0.54, 95% CI 0.27-1.06).

Serious adverse events occurred in 13 percent receiving T-DM1 and 8 percent receiving trastuzumab. Relative efficacy of T-DM1 compared with pertuzumab and trastuzumab in the adjuvant setting is unknown. Adverse events leading to discontinuation of the trial drug occurred in 18 percent of those receiving T-DM1 versus 2 percent of the trastuzumab group. In the T-DM1 group, the most common adverse events leading to discontinuation of the drug were laboratory abnormalities (decreased platelet count, 4.2 percent; increased bilirubin, 2.6 percent; increased aspartate aminotransferase or alanine aminotransferase, 1 to 2 percent each), peripheral sensory neuropathy (1.5 percent), and decreased ejection fraction (1.2 percent).

No residual disease

Trastuzumab, with or without pertuzumab — For those with pathologic complete response following HER2-directed therapy, we continue adjuvant trastuzumab, with or without pertuzumab, to complete a year of HER2-directed therapy. Neratinib following adjuvant trastuzumab has also shown benefits in DFS, particularly for those with estrogen receptor-positive disease, although we typically do not offer it if pertuzumab has been used as there are no trials evaluating it in this setting. (See 'Dual anti-HER2 therapy in high-risk disease' below.)

Patients who have not received neoadjuvant therapy — Many patients with HER2-positive disease will be treated with neoadjuvant therapy. However, for those with smaller, node-negative tumors, initial surgical treatment may be appropriate, followed by adjuvant therapy. In

such patients with tumors that are <2 cm and node negative, we typically offer adjuvant therapy with paclitaxel plus trastuzumab for 12 weeks, followed by trastuzumab alone to complete a year of treatment. (See 'Node-negative tumors <2 cm' below.)

Other adjuvant chemotherapy regimens, with or without pertuzumab, are available for those with larger tumors who were not treated neoadjuvantly. (See 'Choice of chemotherapy' below and 'Dual anti-HER2 therapy in high-risk disease' below.)

TRASTUZUMAB-BASED TREATMENT

Benefits — For patients who are treated with adjuvant chemotherapy, we treat concurrently with trastuzumab and continue treatment to complete a year of therapy. Adjuvant trastuzumab is also used for those who were treated neoadjuvantly with chemotherapy and HER2-directed therapy and experience a pathologic complete response.

There are substantial clinical benefits for including anti-HER2 therapy in management of early-stage, HER2-positive breast cancer. The benefits of adding trastuzumab to adjuvant chemotherapy in patients with HER2-positive tumors were confirmed in a 2021 meta-analysis of seven trials of chemotherapy plus trastuzumab versus chemotherapy alone involving nearly 14,000 patients [12]:

- Improvement in breast cancer recurrence (hazard ratio [HR] 0.66, 95% CI 0.62-0.71). Absolute 10-year recurrence risk was reduced by 9.0 percent.
    - The reduction in recurrence was largest in years 0 to 1 after randomization (HR 0.53), with benefits persisting through years 2 to 4 (HR 0.73) and 5 to 9 (HR 0.80), with little follow-up beyond year 10. Reductions in recurrence risks occurred irrespective of patient characteristics and tumor estrogen receptor (ER) status. The higher-risk the tumor, the greater the absolute reductions in five-year recurrence (eg, 5.7 percent in N0 disease, 6.8 percent in N1 to N3 disease, and 10.7 percent in N4+ disease).
- Improvement in breast cancer mortality (HR 0.67, 95% CI 0.61-0.73). 10-year breast cancer mortality was reduced by 6.4 percent.

These results are consistent with those from a previous meta-analysis as well [13]. Subsequent data show that the addition of trastuzumab to adjuvant chemotherapy results in durable survival benefits for patients with HER2-positive breast cancer. This was shown in the combined analysis of the North Central Cancer Treatment Group N9831 trial and the National Adjuvant Breast and Bowel Project B-31 clinical trials [14,15]. With a median on-study time of 8.4 years,

the addition of trastuzumab resulted in a 37 percent improvement in OS (HR 0.63, 95% CI 0.54-0.73) and a 40 percent improvement in DFS (HR 0.60, 95% CI 0.53-0.68).

It should be noted that adjuvant use of trastuzumab appears to also increase the risks of cardiac toxicities, including congestive heart failure and left ventricular ejection fraction declines. These risks and monitoring for cardiac function for patients on trastuzumab are discussed below. (See 'Assessing risks and benefits of treatment' below and "Cardiotoxicity of trastuzumab and other HER2-targeted agents".)

Dual anti-HER2 therapy in high-risk disease — Patients are treated with adjuvant trastuzumab either because they did not receive neoadjuvant treatment or because they had a pathologic complete response after neoadjuvant treatment. In either of these instances, the option for using a second anti-HER2 agent exists if the initial disease was considered to be high risk [16].

- **Addition of pertuzumab** – Our approach is to offer the concurrent adjuvant pertuzumab with trastuzumab for patients with high-risk disease (typically node positive or >2 cm), as evidence exists for improvements in DFS.

  The data to support adjuvant pertuzumab come from the phase III APHINITY trial, in which over 4800 patients with node-positive or high-risk, node-negative, HER2-positive, operable breast cancer were randomly assigned to chemotherapy and trastuzumab with either pertuzumab or placebo [17]. At a median follow-up of approximately six years, patients receiving pertuzumab experienced improved six-year invasive DFS relative to those receiving placebo (91 versus 88 percent; HR 0.76, 95% CI 0.64-91). Six-year overall OS rates were 95 versus 94 percent, respectively. Preplanned subgroup analysis showed that pertuzumab improved the three-year DFS among those with node-positive disease (88 versus 83 percent; HR 0.72, 95% CI 0.59-0.87). By contrast, the recurrence rate was low among patients with node-negative disease, with no difference between those receiving pertuzumab versus placebo. Among patients with hormone receptor-positive tumors, there was a statistically significant improvement in invasive DFS with the addition of pertuzumab (91 versus 88 percent; HR 0.73, 95% CI 0.59-0.92), but the difference was not statistically significant in the hormone receptor-negative group (90 versus 88 percent; HR 0.83, 95% CI 0.63-1.10). Grade 3 or higher adverse events were more frequent with pertuzumab (64 versus 57 percent), with diarrhea, anemia, and neutropenia being the most common [18]. Primary cardiac side effects were infrequent in both groups (<1 percent).

- **Neratinib, in highly selected cases of high-risk, ER-positive disease** – There are no data on the safety or efficacy of neratinib in patients whose adjuvant therapy included pertuzumab, and as such we use it very selectively only in cases of ER-positive disease at the highest risk of recurrence (eg, stage III, ER-positive disease).

  Neratinib has been shown to improve recurrence rates when used in the adjuvant setting following treatment with single-agent trastuzumab, particularly in patients with HER2-positive tumors that are larger and ER positive, and when treatment is started within a year of trastuzumab [19,20]. In a phase III trial neratinib after a year of adjuvant trastuzumab improved five-year invasive DFS (90.2 versus 87.7 percent; HR 0.73, 95% CI 0.57-0.92) relative to placebo [19], although OS was similar at eight years follow-up [21]. There was a nonsignificant trend toward greater improvements for those with hormone receptor-positive disease compared with hormone receptor-negative disease (HR of 0.60 and 0.95, respectively). Among those receiving neratinib, the frequency of grade 3 to 4 diarrhea was 40 percent without diarrhea prophylaxis versus 2 percent among those receiving placebo.

Further discussion of adjuvant management, including radiation, and for those with hormone-positive disease, endocrine therapy, is found elsewhere. (See "Adjuvant radiation therapy for women with newly diagnosed, non-metastatic breast cancer", section on 'Patients treated with breast-conserving surgery' and "General principles of neoadjuvant management of breast cancer", section on 'Adjuvant treatment' and "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer".)

Prescribing information and formulations — Trastuzumab is administered with a loading dose (weekly schedule: 4 mg/kg; three-weekly schedule: 8 mg/kg) prior to the usual dose (weekly schedule: 2 mg/kg; three-weekly schedule: 6 mg/kg). Adjuvant treatment is typically started within four to six weeks after surgery. Earlier treatment is not necessarily better, but a delay of more than 12 weeks may be detrimental [22]. For patients who miss a dose by more than one week (whether that be treatment intended for weekly or every-three-weeks administration), 2015 guidance from the US Food and Drug Administration (FDA) recommends that a reloading dose be administered prior to resumption of the usual dosing schedule [23]. In addition, for women who are of reproductive potential, the FDA guidance recommends the use of effective contraception during treatment and for at least seven months after receiving the last dose of trastuzumab.

Subcutaneous (SC) forms of trastuzumab as well as trastuzumab and pertuzumab have received approval by the FDA based on similar pathologic complete response rates as the intravenous (IV) forms of these therapies when used with chemotherapy in the neoadjuvant setting [24-27].

However, the IV formulations were used in all canonical trials of therapy for both early- and late-stage, HER2-positive breast cancer. Pending further data, we continue to prefer the IV over the SC formulation in the adjuvant/neoadjuvant setting when travel to an infusion center is feasible and deemed safe; however, the SC formulation is an available alternative. Further data are discussed elsewhere. (See "Neoadjuvant therapy for patients with HER2-positive breast cancer", section on 'Alternative formulations'.)

Biosimilars for trastuzumab have also been approved by the FDA [23,28].

Treatment duration — The standard course of adjuvant trastuzumab is one year [13,29].

However, other durations have also been studied. Results from randomized trials demonstrate no improvement with extension to two years [30-32]. For example:

- In the HERA trial, over 5000 women with HER2-positive breast cancer who had completed adjuvant chemotherapy were randomly assigned to observation or to the addition of trastuzumab for one or two years [6,32-34]. With 11-year follow-up, there was no difference in 10-year DFS between women treated with one versus two years of trastuzumab (69 percent in both arms; HR 1.02, 95% CI 0.89-1.17, versus 63 percent among those in the observation arm) [32]. Trastuzumab for one year improved OS relative to observation, but there was no further improvement with extension to two years (79 and 80 percent in the one- and two-year trastuzumab groups, respectively, versus 73 percent among those in the observation arm). Incidence of cardiotoxicity was less frequent among those receiving one versus two years of trastuzumab (4.4 and 7.3 percent, respectively, versus 0.9 percent among those in the observation arm). (See "Cardiotoxicity of trastuzumab and other HER2-targeted agents".)

Trials of 6 versus 12 months of adjuvant trastuzumab have shown discordant results. For example:

- In the PHARE trial, 3380 women were randomly assigned to treatment with 6 or 12 months of trastuzumab [30]. At a median follow-up of 7.5 years, DFS events occurred in 20.4 and 21.2 percent, respectively, such that noninferiority based on prespecified criteria could not be claimed (HR 1.08, 95% CI 0.93-1.25, which includes the prespecified HR for noninferiority of 1.15) [35]. The 7-year survival rates for the 6- and 12-month groups were 82.3 and 80.6 percent, respectively.

  While cardiac dysfunction occurred at a higher frequency in the 12-month group compared with the 6-month group, the incidence was low and reversible in most instances after discontinuation of trastuzumab [36].

Similarly, in the HORG trial of 481 women with node-positive or high-risk, node-negative, HER2-positive early breast cancer, 6 months of adjuvant trastuzumab treatment failed to demonstrate non-inferiority compared with 12 months (three-year DFS, 95.7 versus 93.3 percent for 12 versus 6 months, respectively; HR 1.57, 95% CI 0.86-2.10). The non-inferiority margin had been defined at 1.53 [37].

- By contrast, in the PERSEPHONE trial, among 4089 patients with HER2-positive early breast cancer, 85 percent of whom received adjuvant chemotherapy, those randomly assigned to six months of adjuvant trastuzumab experienced non-inferior four-year DFS rates relative to those receiving 12 months (89.4 versus 89.8 percent, respectively; HR 1.07, 95% CI 0.93-1.24), with fewer cardiac events leading to trastuzumab discontinuation (3 versus 8 percent, respectively) [38].

A possible explanation for the differing outcomes of these trials is the difference in prespecified noninferiority criteria [39]. Moreover, in the subset of the PERSEPHONE trial that most mirrors contemporary practice, with concurrent chemotherapy and trastuzumab, there was a benefit for 12 over 6 months of trastuzumab (HR 1.53, 95% CI 1.16-2.01).

Moreover, for stage II or III patients in the United States, adding adjuvant pertuzumab for one year is common, and pertuzumab requires concurrent trastuzumab administration [18].

Given these considerations, and the fact that observed cardiotoxicity is reversible (and typically lower than observed in PERSEPHONE), we continue to suggest one year of trastuzumab in the adjuvant setting. For patients who, for whatever reason, cannot tolerate 12 months of therapy, data from PERSEPHONE are reassuring that the greatest amount of benefit is achieved within the first 6 months.

CHOICE OF CHEMOTHERAPY

Tumors >2 cm and/or node positive — Several chemotherapy regimens used with trastuzumab have been evaluated in large prospective studies. For most patients with stage II and III disease, we use **either** a sequential regimen of anthracyclines followed by taxanes with trastuzumab (and pertuzumab) or the non-anthracycline regimen, docetaxel plus carboplatin plus trastuzumab, with or without pertuzumab (TCH[P]).

Anthracycline-based therapy — Data regarding the combination of anthracycline-based chemotherapy plus trastuzumab come largely from two North American Cooperative Group trials that were initially designed as parallel clinical trials [5]. These trials examined the benefit of the addition of trastuzumab to anthracycline and taxane-based chemotherapy. A non-

anthracycline versus anthracycline regimen was examined in BCIRG-006, discussed below. (See 'Non-anthracycline-based therapy' below.)

In both randomized studies, all patients received doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) given every three weeks for four cycles. Otherwise, the specific eligibility and taxane-based schema was as follows:

- NSABP B-31 – In the NSABP B-31 trial, women with HER2-positive, node-positive disease received four courses of single agent paclitaxel given every three weeks (175 mg/m^2 over three hours) with or without weekly trastuzumab (initial loading dose 4 mg/kg, then 2 mg/kg weekly for one year), beginning with the first dose of paclitaxel.

- NCCTG-coordinated Intergroup trial N-9831 – In the N-9831 trial, women with HER2-positive, node-positive or high-risk, node-negative disease (>1 cm estrogen receptor [ER]-negative or >2 cm ER-positive) were then treated with one of three regimens: weekly paclitaxel (80 mg/m^2) for 12 weeks followed by no further treatment, weekly paclitaxel followed by sequential trastuzumab for 52 weeks, or weekly paclitaxel with concurrent trastuzumab for 12 weeks followed by trastuzumab alone for 40 weeks.

With a median follow-up of 3.9 years, chemotherapy plus adjuvant trastuzumab resulted in significantly superior rates of disease-free survival (DFS; 86 versus 74 percent, hazard ratio [HR] 0.52) and overall survival (OS; 93 versus 86 percent, HR 0.61) at four years [40].

When administering anthracycline-based therapy, we administer it in a dose-dense fashion. Data to support this dosing strategy come from a large meta-analysis including patients with HER2-positive as well as HER2-negative disease. This is discussed in detail elsewhere. (See "Selection and administration of adjuvant chemotherapy for HER2-negative breast cancer", section on 'Dose-dense schedule preferred'.)

Non-anthracycline-based therapy — For most patients with stage II and III disease, we use either an anthracycline-based regimen, as discussed above, or the non-anthracycline regimen, docetaxel plus carboplatin plus trastuzumab, with or without pertuzumab (TCH[P]). Women with contraindications to anthracyclines (eg, pre-existing cardiac conditions, borderline ejection fraction at baseline, or prior anthracycline exposure) or personal preferences to receive non-anthracycline-based therapy should be treated with a non-anthracycline regimen (TCH[P]). Being overweight or obese may be a risk factor for cardiotoxicity from anthracyclines and trastuzumab and is another potential reason to favor a non-anthracycline regimen. (See "Cardiotoxicity of trastuzumab and other HER2-targeted agents", section on 'Risk factors'.)

The efficacy and safety of combining trastuzumab with a non-anthracycline-containing chemotherapy regimen was evaluated in the BCIRG-006 trial of 3222 women with HER2-positive, node-positive or high-risk, node-negative disease [7]. Patients with negative lymph nodes (no evidence of involvement in review of a minimum of six axillary nodes or a negative sentinel node biopsy) were eligible if they had at least one high-risk feature (ie, age <35 years, tumor >2 cm, ER-/progesterone receptor-negative, or histologic and/or nuclear tumor grade 2 or 3).

All patients were randomly assigned to adjuvant treatment with one of the following regimens:

- ACT – Doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every three weeks for four cycles, followed by docetaxel (100 mg/m^2) every three weeks for four cycles.
- ACTH – ACT plus trastuzumab for one year (weekly during chemotherapy, then every three weeks).
- TCH – Docetaxel (75 mg/m^2) plus carboplatin (area under the curve 6) every three weeks for six cycles, with trastuzumab (weekly during chemotherapy, then every three weeks) for one year.

Compared with TCH, ACTH demonstrated a trend toward improved DFS and OS that did not reach statistical significance but was associated with a small but significantly greater toxicity than TCH. Both trastuzumab-containing arms (ACTH or TCH) resulted in improved survival outcomes when compared with ACT [7,41]:

- At five years, both ACTH and TCH were associated with improved DFS (84 and 81 percent, respectively, versus 75 percent with ACT) and OS (92 and 91 percent, respectively, versus 87 percent with ACT) [7].
- Preliminary reporting of 10-year outcomes in abstract form similarly suggests that both ACTH and TCH led to significantly improved DFS (75 and 73 percent, respectively, versus 68 percent for ACT) and OS (86 and 83 percent, respectively, versus 79 percent for ACT) [41].
- While the differences in DFS and OS outcomes between ACTH and TCH were not statistically significant at either 5 or 10 years, the study was not powered to detect equivalence between ACTH and TCH.

When compared with ACTH, TCH resulted in the following differences in adverse events:

- Lower rates of severe (grade 3/4) neutropenia (66 versus 72 percent) and leukopenia (48 versus 60 percent), but significantly higher rates of severe anemia (6 versus 3 percent) and thrombocytopenia (6 versus 2 percent).

- Lower incidence of congestive heart failure (0.4 versus 2 percent, respectively). By comparison, congestive heart failure was seen in 0.7 percent of women receiving ACT alone.

- Lower incidence of subclinical and sustained loss of mean left ventricular ejection fraction (LVEF; defined as >10 percent relative loss of LVEF, 9.4 versus 18.6 percent). By comparison, this incidence was 11.2 percent among women treated with ACT. In 33 percent of cases, the decrease in LVEF persisted for at least four years after randomization. The long term significance of these changes in LVEF is not known.

- Lower rates of sensory neuropathy (36 versus 50 percent), motor neuropathy (4 versus 6 percent), nail changes (29 versus 44 percent), and myalgias (39 versus 56 percent).

These findings are consistent with the other trials that demonstrate improved DFS and OS when trastuzumab is added to combination chemotherapy [13]. Unlike the other trials, however, there was little or no crossover to trastuzumab by the arm that was assigned to no trastuzumab. (See 'Anthracycline-based therapy' above.)

Incorporation of anti-HER2 agents

- For stage II/III cancers, we typically include pertuzumab with trastuzumab-based treatments, either as TCH(P) or AC/THP. The APHINITY trial, discussed above, suggests that in these higher-risk tumors, the addition of pertuzumab reduces the risk of tumor recurrence. We also extrapolate from the neoadjuvant setting, in which the addition of pertuzumab in high-risk disease improves the rates of complete pathologic response. (See "Neoadjuvant therapy for patients with HER2-positive breast cancer", section on 'Addition of pertuzumab' and 'Dual anti-HER2 therapy in high-risk disease' above.)

  - This is in contrast to patients with stage I, node-negative breast cancers, for whom we typically recommend trastuzumab-based but not pertuzumab plus trastuzumab-based anti-HER2 treatments. (See 'Node-negative tumors <2 cm' below.)

- As noted above, patients with residual disease after chemotherapy and trastuzumab (with or without pertuzumab)-based neoadjuvant therapy should receive maintenance ado-trastuzumab emtansine (T-DM1), rather than trastuzumab. (See 'T-DM1' above.)

- The use of neratinib following adjuvant trastuzumab is usually limited to higher-risk (by stage), HER2-positive breast cancers. There are no data for the benefit of neratinib in women who have received pertuzumab or T-DM1 as part of their neoadjuvant treatments. (See 'Dual anti-HER2 therapy in high-risk disease' above.)

Node-negative tumors <2 cm — Although it has never been compared directly with ACTH or TCH, we generally prefer the paclitaxel-trastuzumab (TH) regimen for patients with node-negative, HER2-positive tumors <2 cm given excellent DFS rates that have been observed in this population with this regimen. Although T-DM1 has shown promising activity in this setting, it is associated with early therapy discontinuation.

In a phase II study that enrolled 410 patients with node-negative disease up to 3 cm (31 percent with T1b lesions and 17 percent with T1a lesions), treatment with paclitaxel (80 mg/m^2) weekly for 12 weeks plus trastuzumab for one year was associated with the following [42-44]:

- The three-year rate of survival free from invasive disease was 98.7 percent (95% CI 97.6-99.8). The three-year rate of recurrence-free survival was 99.2 percent (95% CI 98.4-100.0). There was no difference seen when patients were stratified by tumor size (≤1 versus >1 cm).
- Outcomes at longer-term follow-up remained satisfactory, with seven-year and 10-year DFS of 93 and 91 percent, respectively, and OS of 95 and 94 percent, respectively.
- Overall toxicity was minimal, with only 13 patients (3 percent) reporting at least one episode of grade 3 neuropathy, two patients reporting grade 3 left ventricular systolic dysfunction, and 13 patients who required discontinuation of trastuzumab due to a significant asymptomatic decline in the ejection fraction.

The efficacy and safety of adjuvant T-DM1 in this setting was explored in the ATEMPT trial [45]. In this randomized phase II trial, 497 patients with stage I HER2-positive breast cancer were assigned in a 3:1 ratio to T-DM1 versus TH. At a median follow-up of 3.9 years, the three-year DFS for T-DM1 was 97.8 percent (95% CI 96.3-99.3) versus 93.4 percent (95% CI 88.7-98.2) with TH, but the study was not powered to detect efficacy differences between the two adjuvant regimens. Clinically relevant toxicities were similar between the two groups. Approximately 17 percent receiving T-DM1 discontinued for adverse events (versus 6 percent among those receiving TH). Because of concerns over tolerability and the limited follow-up of patients in this single trial, T-DM1 is not a standard adjuvant regimen for small, HER2-positive tumors.

SPECIAL POPULATIONS

Hormone receptor-positive disease — For patients who have hormone receptor-positive, HER2-positive disease, we recommend endocrine therapy concurrently with HER2-directed therapy during maintenance treatment (following completion of adjuvant chemotherapy) [46]. There are no data to support the use of trastuzumab plus endocrine therapy (without prior use

of chemotherapy) for women with estrogen receptor (ER)-positive, HER2-positive breast cancer, and we consider this approach to be investigational. (See "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer", section on 'Additional considerations for HER2-positive disease'.)

Node-negative tumors <1 cm — Whether HER2-directed treatment is indicated for patients with node-negative, small HER2-positive breast cancers (ie, tumor ≤10 mm) is not entirely clear. However, these patients appear to be at a higher risk of recurrence compared with similar patients with HER2-negative disease. Therefore, we treat patients with HER2-positive breast cancers that are 5 to 10 mm with adjuvant trastuzumab and paclitaxel. (See 'Node-negative tumors <2 cm' above.)

Small tumors recur less frequently, and therefore, the absolute benefit derived from anti-HER2 therapy is likely to be less. Nevertheless, we often also treat tumors that are as small as 3 to 4 mm with these agents, especially if they are hormone receptor-negative, which portends a worse prognosis. For tumors that are 1 to 2 mm, we typically do not treat with adjuvant trastuzumab and chemotherapy, given an expected low likelihood of recurrence. In addition to the considerations above, for tumors of any size that are hormone receptor-positive, we treat with adjuvant endocrine therapy. This is generally consistent with the guidelines from the National Comprehensive Cancer Network [47].

Several retrospective studies suggest that patients with a small HER2-positive tumor have a higher risk of relapse than HER2-negative cancers. For example [48-51]:

- In a study of 2026 women with node-negative disease who underwent tissue microarray, 206 women (10 percent) were HER2 positive [50]. Ten percent of the HER2-positive group and 17 percent in the HER2-negative group had a tumor size <10 mm. The majority of women in this subset (82 percent) did not receive chemotherapy. Although there was a trend towards worse relapse-free survival in women with HER2-positive disease, there was no difference in breast cancer-specific survival.

- In another study of 965 patients with T1a (>1 mm but ≤5 mm) or T1b (>5 mm but ≤10 mm) node-negative breast cancer, those with HER2-positive tumors had significantly worse five-year rates of recurrence-free survival (77 versus 94 percent) and distant recurrence-free survival (86 versus 97 percent) when compared with HER2-negative disease [49]. In this cohort, 86 percent of the women had hormone receptor-positive tumors.

Therefore, given the higher risk of relapse and proven benefit of trastuzumab in HER2-positive disease, it is reasonable to offer trastuzumab-based adjuvant therapy to patients with small HER2-positive tumors.

Male breast cancer — Breast cancer is a rare diagnosis in men, but decisions regarding adjuvant chemotherapy do not differ by gender. The prognosis for men and women with breast cancer is similar. Male breast cancer is covered in detail elsewhere. (See "Breast cancer in men".)

Breast cancer in pregnancy — The use of trastuzumab during pregnancy is contraindicated. The agent has not been studied in pregnancy, and there are theoretical concerns that exposure to trastuzumab in utero could result in oligohydramnios, which in some cases can result in pulmonary hypoplasia and neonatal death [23]. Mothers are advised to either discontinue nursing if they wish to receive trastuzumab or to discontinue trastuzumab if they want to continue nursing.

Most chemotherapy agents for breast cancer carry a risk of teratogenicity in humans. However, chemotherapy administered outside of the first trimester has a low-risk profile. Breast cancer during pregnancy is covered in detail elsewhere. (See "Gestational breast cancer: Treatment".)

Patients with cardiac risk factors — Potential risk factors associated with the development of trastuzumab-related cardiotoxicity include previous or concurrent anthracycline use, age greater than 50, pre-existing cardiac dysfunction, high body mass index, and treatment with antihypertensive agents. For patients with cardiac risk factors who are candidates for adjuvant HER2-directed treatment, we recommend careful monitoring of cardiac function during and after treatment. However, the presence of cardiac risk factors alone should not exclude HER2-positive patients from HER2-targeted therapy. (See 'Assessing risks and benefits of treatment' below and "Cardiotoxicity of trastuzumab and other HER2-targeted agents".)

ASSESSING RISKS AND BENEFITS OF TREATMENT

The use of adjuvant trastuzumab improves survival outcomes in women with breast cancer [13]. However, treatment is associated with a fivefold higher risk for congestive heart failure (CHF) and a twofold higher risk of left ventricular ejection fraction declines [13,52]. These cardiac risks should not prevent HER2-positive patients from receiving adjuvant trastuzumab. The overall incidence of cardiac toxicity was low in prospective clinical trials, ranging from 1 to 4 percent [5-7,29,33,40,53,54]. In addition, trastuzumab-related cardiac toxicity is also reversible, especially if detected early, and responds well to medical treatment [55]. (See "Cardiotoxicity of trastuzumab and other HER2-targeted agents".)

A discussion of the benefits of therapy should be balanced with the risk for cardiac toxicity, particularly in patients at a lower risk of recurrence (ie, tumor size <1 cm). The survival benefit

and the risk of CHF associated with adjuvant trastuzumab plus chemotherapy can be estimated as follows [13]:

- For patients with high-risk, HER2-positive breast cancer, trastuzumab is associated with an absolute risk reduction (ARR) of death of 13.3 percent (mortality rate, 36.7 versus 50 percent in controls). The number of patients needed to treat (NNT) to save one life is 8. For patients with low-risk disease, the ARR is 3.3 percent (10 versus 6.7 percent, respectively). The NNT is 31.

- For patients at high risk for CHF prior to trastuzumab treatment, the absolute risk increase (ARI) of CHF associated with trastuzumab is 21 percent (26 versus 5 percent in controls). The number of patients needed to harm (NNH) is 5. However, for patients at low risk for CHF, the ARI is 2.1 percent (2.6 versus 0.5 percent, respectively). The NNH in this group is 48.

For all patients receiving trastuzumab, routine cardiac monitoring is suggested. (See 'Patients with cardiac risk factors' above and "Cardiotoxicity of trastuzumab and other HER2-targeted agents".)

For patients receiving pertuzumab, side effects including diarrhea, neutropenia, and anemia are increased. (See 'Dual anti-HER2 therapy in high-risk disease' above.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Breast cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient education: Treatment of early HER2-positive breast cancer (Beyond the Basics)" and "Patient education: Treatment of early-stage, hormone-responsive breast cancer in premenopausal women (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Defining HER2 positivity** – It is essential that all patients with newly diagnosed breast cancer be tested for human epidermal growth factor receptor 2 (HER2) overexpression because HER2-directed therapy is a critical component of the adjuvant treatment of HER2-positive breast cancer. Patients are eligible for adjuvant HER2-directed treatment if they have HER2-positive breast cancer, characterized by immunohistochemical stain of 3+ on their tumor or a *HER2*/chromosome enumeration probe 17 (CEP17) fluorescent in situ hybridization amplification ratio ≥2.0, and if the *HER2* copy number signals/cell is ≥4 (algorithm 1). (See 'Patient eligibility' above.)

- **Indications for HER2-directed therapy** – We recommend systemic treatment with HER2-directed therapy plus chemotherapy rather than chemotherapy alone for those with HER2-positive breast cancers ≥1 cm and/or nodal involvement (**Grade 1A**), and also suggest it for those whose tumors are node negative and ≥5 mm (**Grade 2B**). Some patients with smaller HER2-positive tumors and high-risk features (eg, hormone receptor-negative) may also benefit from this approach. (See 'General considerations' above and 'Node-negative tumors <1 cm' above.)

- **Neoadjuvant versus adjuvant treatment** – Discussion of appropriate candidates for neoadjuvant versus adjuvant therapy is found elsewhere. (See "Neoadjuvant therapy for patients with HER2-positive breast cancer", section on 'Indications'.)

- **Adjuvant treatment for patients who received neoadjuvant chemotherapy** – Patients who were treated with neoadjuvant chemotherapy and trastuzumab (with or without pertuzumab) are treated with HER2-directed therapy in the adjuvant setting, with choice of therapy directed according to their response to neoadjuvant treatment (algorithm 2). (See 'Patients who were treated with neoadjuvant therapy' above.)

  - For those with residual disease after neoadjuvant therapy, we recommend maintenance ado-trastuzumab emtansine (T-DM1) in the adjuvant setting rather than

continuing trastuzumab, with or without pertuzumab (**Grade 1B**). Further chemotherapy is not administered either with or following T-DM1.

- For those with pathologic complete response after neoadjuvant therapy, we suggest continuing adjuvant trastuzumab, with or without pertuzumab, to complete a year of HER2-directed therapy, rather than a shorter treatment course or a change in therapy (**Grade 2B**).

- **Dual adjuvant anti-HER2 therapy for select patients** – For patients who were diagnosed with node-positive disease or node-negative tumors >2 cm, and who will be receiving trastuzumab in the adjuvant setting (either because they did not receive neoadjuvant therapy or had a pathologic complete response following neoadjuvant therapy), we suggest the addition of adjuvant pertuzumab to complete a year of treatment (**Grade 2C**). However, given risk of toxicity and small benefit, a reasonable alternative is to treat with trastuzumab maintenance alone. (See 'Dual anti-HER2 therapy in high-risk disease' above.)

- **Choice of chemotherapy** – Regarding choice of chemotherapy to be used:

  - For most patients with HER2-positive, node-negative tumors >2 cm in size or node-positive tumors, we suggest, in addition to trastuzumab, either dose-dense doxorubicin and cyclophosphamide followed by paclitaxel, or the combination of docetaxel and carboplatin (**Grade 2C**), rather than other regimens. Those with contraindications to anthracyclines (eg, pre-existing cardiac conditions, borderline ejection fraction at baseline, or prior anthracycline exposure) should receive docetaxel and carboplatin with trastuzumab (with or without pertuzumab), if cardiac function permits. (See 'Choice of chemotherapy' above.)

  - For HER2-positive, smaller (<2 cm), node-negative tumors, we suggest adjuvant paclitaxel (weekly for 12 weeks) with trastuzumab, rather than either doxorubicin and cyclophosphamide followed by paclitaxel with trastuzumab, or T-DM1 (**Grade 2C**). (See 'Node-negative tumors <2 cm' above.)

- **Risk of cardiac toxicity with** trastuzumab – Patients receiving trastuzumab have an increased risk for cardiac toxicity (ie, congestive heart failure or left ventricle fraction declines). These risks should be taken into account when prescribing trastuzumab. All patients receiving adjuvant trastuzumab should undergo routine cardiac monitoring during treatment. Concurrent administration of pertuzumab and trastuzumab with anthracyclines should be avoided. (See 'Patients with cardiac risk factors' above.)

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Topic 773 Version 112.0

GRAPHICS

Breast carcinoma TNM anatomic stage group AJCC UICC 8th edition

When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	IA
T0	N1mi	M0	IB
T1	N1mi	M0	IB
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB
T0	N2	M0	IIIA
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC

Any T	Any N	M1	IV

- The anatomic stage group table should only be used in global regions where biomarker tests are not routinely available.
- Cancer registries in the US must use the prognostic stage group table for case reporting.

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Graphic 110848 Version 8.0

Summary of the joint ASCO/CAP guideline recommendations for assessment of HER2 status

Optimal FISH testing requirements
Test is rejected and repeated if:
Controls are not as expected
Observer cannot find and count as least two areas of invasive tumor
>25 percent of signals are unfavorable due to weak signals
>10 percent of signals occur over cytoplasm
Nuclear resolution is poor
Autofluorescence is strong
The entire ISH slide should be scanned prior to counting at least 20 cells or use IHC to define the areas of potential HER2 amplification
If there is a second population of cells with increased HER2 signals/cell and consists of more than 10 percent of tumor cells on the slide, a separate counting of at least 20 non-overlapping cells must also be performed with this cell population and reported
Counting should compare patterns in normal breast and tumor cells if bright-field ISH is used; if the tumor cell pattern is neither normal nor clearly amplified, expert opinion should be sought
Optimal IHC testing requirements
Test is rejected and repeated or tested by FISH if:
Controls are not as expected
Artifacts involve most of sample
Sample has strong membrane staining of normal breast ducts (internal controls)
Interpretation follows guideline recommendation
Positive HER2 result requires homogeneous, dark circumferential (chicken wire) pattern in >10 percent of invasive tumor
Interpreters have method to maintain consistency and competency
Sample is subjected to confirmatory FISH testing if equivocal based on initial results
Report must include guideline-detailed elements
Optimal tissue handling requirements
Time from tissue acquisition to fixation should be within one hour; samples from HER2 testing are fixed in 10 percent neutral buffered formalin for 6 to 72 hours; any exceptions to this process must be included in reporting

Samples should be sliced at 5 to 10 mm intervals after appropriate gross inspection and margins designation and placed in sufficient volume of neutral buffered formalin
Sections should ideally not be used for HER2 testing if cut >6 weeks earlier; this may vary with primary fixation or storage conditions
Time to fixation and duration of fixation if available should be recorded for each sample
Optimal internal validation procedure
Validation of test must be done before test is offered
Laboratories performing these tests should be following all accreditation requirements
Initial testing validation should conform to the published 2010 ASCO/CAP recommendations for IHC testing of ER and RT guidance validation requirements with 20 negative and 20 positive FDA-approved assays and 40 negative and 40 positive for laboratory-developed tests; laboratories are responsible for ensuring the reliability and accuracy of their testing results
Optimal internal QA procedures
Initial test validation
Ongoing quality control and equipment maintenance
Initial and ongoing laboratory personnel training and competency assessment
Use of standard operating procedures including routine use of control materials
Revalidation of procedure if changed
Ongoing competency assessment and education of pathologists
Optimal external proficiency assessment
Participation in external proficiency testing program with at least two testing events (mailings)/year
Satisfactory performance requires at least 90 percent correct responses on graded challenges for either test
Unsatisfactory performance will require laboratory to respond according to accreditation agency program requirements
Optimal laboratory accreditation
Onsite inspection every other year with annual requirement for self-inspection
Reviews laboratory validation, procedures, QA results and processes, results and reports
Unsatisfactory performance results in suspension of laboratory testing for HER2 for that method

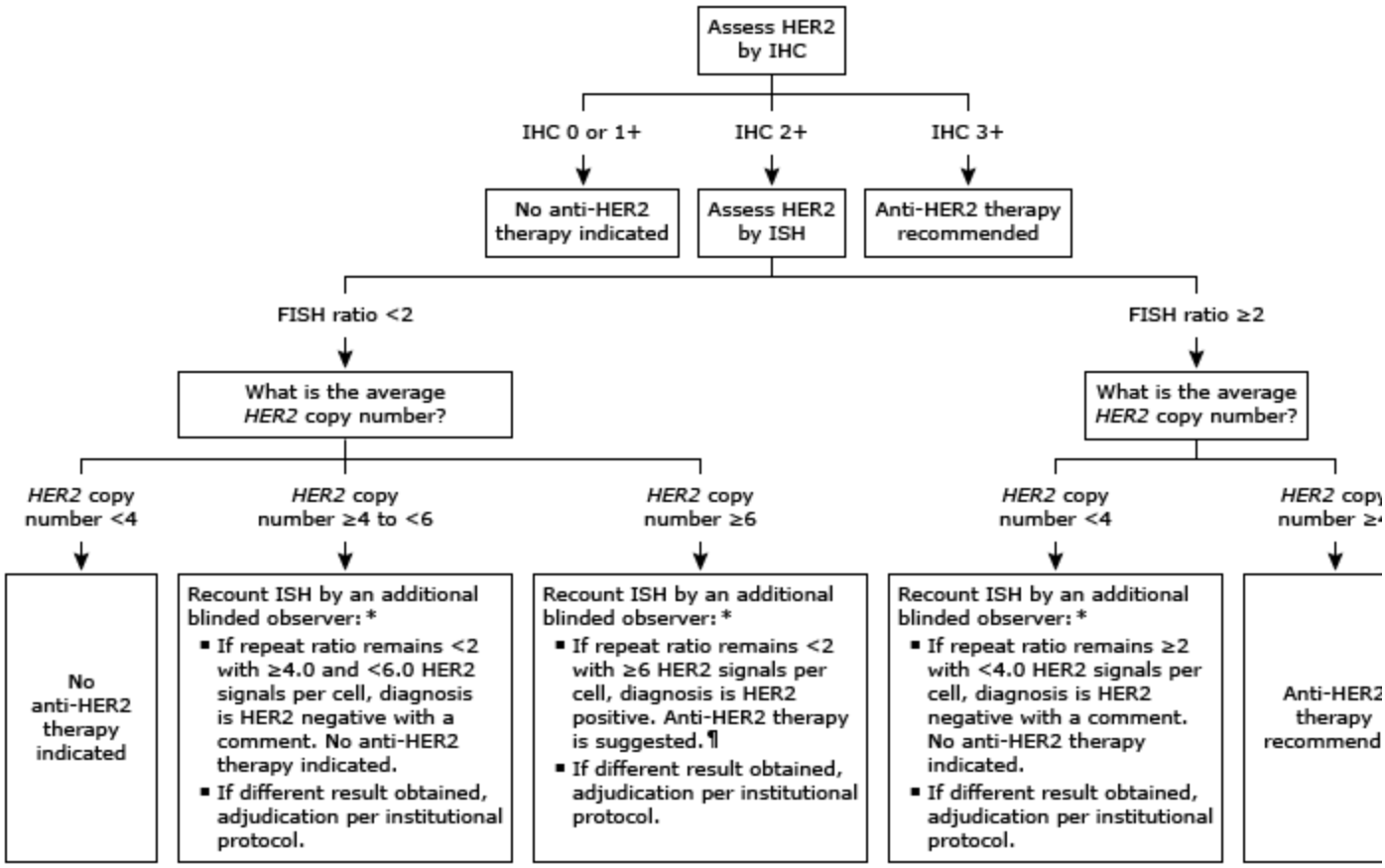
ASCO: American Society of Clinical Oncology; CAP: College of American Pathologists; HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; FISH: fluorescent in situ hybridization; CEP17: chromosome 17 centromere; QA: quality assurance.

Revised with information from:

1. *Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update. J Clin Oncol 2013. DOI: JCO.2013.50.9984.*

Graphic 75536 Version 7.0

HER2 assessment for breast cancer



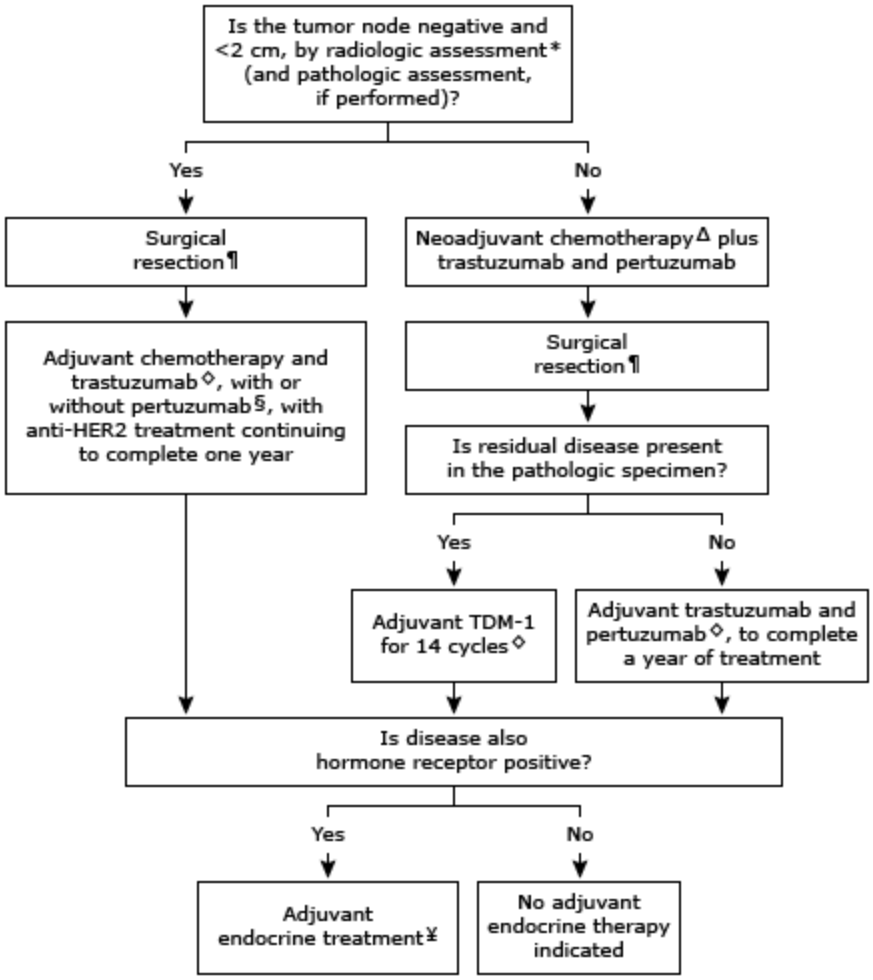
HER2: human epidermal growth factor receptor 2; IHC: immunohistochemistry; ISH: in situ hybridization.

* ISH should be recounted by an additional observer, blinded to previous ISH results; count should be at lea 20 cells that include the area of invasive cancer with IHC 2+ staining.

¶ The predictive value of this finding of benefit from anti-HER2 therapy is unknown, and it therefore is also reasonable to omit anti-HER2 therapy.

Graphic 131428 Version 1.0

Systemic treatment for early HER2-positive breast cancer



HER2: human epidermal growth factor receptor 2; T-DM1: ado-trastuzumab emtansine; MRI: magnetic resonance imaging.

* Radiographic assessment typically includes mammography and ultrasonography, with or without MRI.

¶ Surgical resection may consist of breast-conserving surgery or mastectomy, depending on patient preference, tumor features, and response to therapy, if neoadjuvant treatment was administered.

Δ Preferred chemotherapy regimens include docetaxel/carboplatin as well as doxorubicin/cyclophosphamide, followed by a taxane. Further details and other options are discussed in UpToDate content on neoadjuvant therapy for patients with HER2-positive breast cancer.

◇ Radiation, if indicated, may be administered concurrently with anti-HER2 therapy (ie, trastuzumab, pertuzumab, or TDM-1, as indicated).

§ Chemotherapy selection is guided by results from surgical pathology. For node-negative tumors <2 cm, paclitaxel alone is an appropriate choice for chemotherapy. For larger or node-positive tumors, preferred chemotherapy regimens are according to the footnote above.[Δ] Pertuzumab is usually added for tumors that are >2 cm or node positive.

¥ Endocrine therapy, if indicated, is administered concurrently with adjuvant anti-HER2 therapy (ie, trastuzumab, with or without pertuzumab; or T-DM1), after completion of any indicated adjuvant chemotherapy. While endocrine therapy may be administered concurrently with radiation, our approach is to delay until after completion, for those who will be treated with adjuvant radiation. Duration and choice of endocrine therapy are discussed in UpToDate topics on adjuvant endocrine therapy for hormone receptor-positive breast cancer.

Contributor Disclosures

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