Breast Cancer, Version 3.2024

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Abstract

Breast cancer is treated with a multidisciplinary approach involving surgical oncology, radiation oncology, and medical oncology. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer include recommendations for clinical management of patients with carcinoma in situ, invasive breast cancer, Paget's disease, Phyllodes tumor, inflammatory breast cancer, and management of breast cancer during pregnancy. The content featured in this issue focuses on the recommendations for overall management of systemic therapy (preoperative and adjuvant) options for nonmetastatic breast cancer. For the full version of the NCCN Guidelines for Breast Cancer, visit NCCN.org.

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Overview

Breast cancer is the most common malignancy in females in the United States and is second only to lung cancer as a cause of cancer death. The American Cancer Society has estimated that 313,510 Americans will be diagnosed with breast cancer and 42,780 will die of disease in the United States in 2024.[1,2] The therapeutic options for patients with noninvasive or invasive breast cancer are complex and varied. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer include guidelines for clinical management of patients with carcinoma in situ, invasive breast cancer, Paget's disease, Phyllodes tumor, inflammatory breast cancer, male breast cancer, and breast cancer during pregnancy. These guidelines have been developed and are updated continuously by a multidisciplinary panel of representatives from NCCN Member Institutions with breast cancer-focused expertise in the fields of medical oncology, surgical oncology, radiation oncology, pathology, reconstructive surgery, and patient advocacy. This section focuses on systemic therapies (neoadjuvant/adjuvant) for nonmetastatic breast cancer.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; antiracist, anticlassist, antimisogynist, antiageist, antiableist, and anti–weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate nongendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms "men," "women," "female," and "male" when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies

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To view disclosures of external relationships for the NCCN Guidelines panel, go to https://www.nccn.org/guidelines/guidelines-panels-and-disclosure/disclosure-panels

The full NCCN Guidelines for Breast Cancer are not printed in this issue of *JNCCN*. The complete and most recent version of these guidelines is available free of charge at NCCN.org.

and organizations to use more inclusive and accurate language in their future analyses.

Guidelines Update Methodology

The complete details of the "Development and Update of the NCCN Guidelines" are available at NCCN.org.

Literature Search Criteria

Prior to the update, an electronic search of the PubMed database was performed to obtain key literature in breast cancer. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[3]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies. The potential relevance of the PubMed search was examined. The data from key PubMed articles selected by the panel for review during the Guidelines update meeting as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

Systemic Therapies (Preoperative and Adjuvant)

Preoperative Systemic Therapy

The NCCN panel has outlined the rationale, appropriate patient selection, and response assessment for preoperative systemic therapy in a section titled, "Principles of Preoperative Chemotherapy" (Figures 1 and 2).

Randomized clinical trials have found no significant differences in long-term outcomes when systemic chemotherapy is given before or after surgery.[4,5] Historically, a primary advantage of administering preoperative systemic therapy has been to improve surgical outcomes. Preoperative systemic therapy can convert inoperable tumors to operable and also downstage a significant number of patients with operable breast cancer to allow for more limited breast conservation procedures.[6] Results from large clinical trials and retrospective reviews indicate that breast conservation rates are improved with preoperative systemic therapy.[5,7] Clinicians need to carefully consider the extent of disease in the breast, tumor biology, and likelihood of adequate tumor response before recommending preoperative systemic therapy to improve the likelihood of successful breast conservation.

In addition, use of preoperative systemic therapy may provide important prognostic information based on response to therapy. Experiencing a pathologic complete response (pCR) to neoadjuvant therapy is associated with favorable disease-free survival (DFS) and overall survival (OS) in early-stage breast cancer. The correlation between pathologic response and long-term outcomes in patients with early-stage breast cancer is strongest for patients with triple-negative breast cancer (TNBC), less so for HER2-positive disease, and least for hormone-positive disease.[8–10]

Other benefits of preoperative systemic therapy include allowing time for appropriate genetic testing and for planning potential breast reconstruction in patients proceeding with mastectomy. For those with significant residual disease after standard preoperative systemic therapy, it may provide an opportunity to identify patients who may benefit from further adjuvant therapy after surgery. It may allow sentinel lymph node biopsy alone or allow for limited radiation fields if clinically node positive disease becomes clinically node negative after preoperative systemic therapy. In addition, preoperative systemic therapy also serves as an excellent research platform to test novel therapies and predictive biomarkers by providing tumor specimens and blood samples before and during systemic treatment.

Selection of Patients for Preoperative Therapy

Not all patients are appropriate candidates for preoperative systemic therapy (Figures 1 and 2). According to the NCCN panel, among those with inoperable breast tumors, preoperative systemic therapy is indicated in patients with locally advanced or inoperable breast cancer, including those with inflammatory breast cancer; those with bulky or matted cN2 axillary nodes; cN3 regional lymph node nodal disease; and cT4 tumors.

In patients with operable tumors, preoperative systemic therapy is the preferred approach for the following scenarios: for patients with TNBC and HER2-positive breast cancer that is clinical stage T2N0 and higher or is clinically node positive;

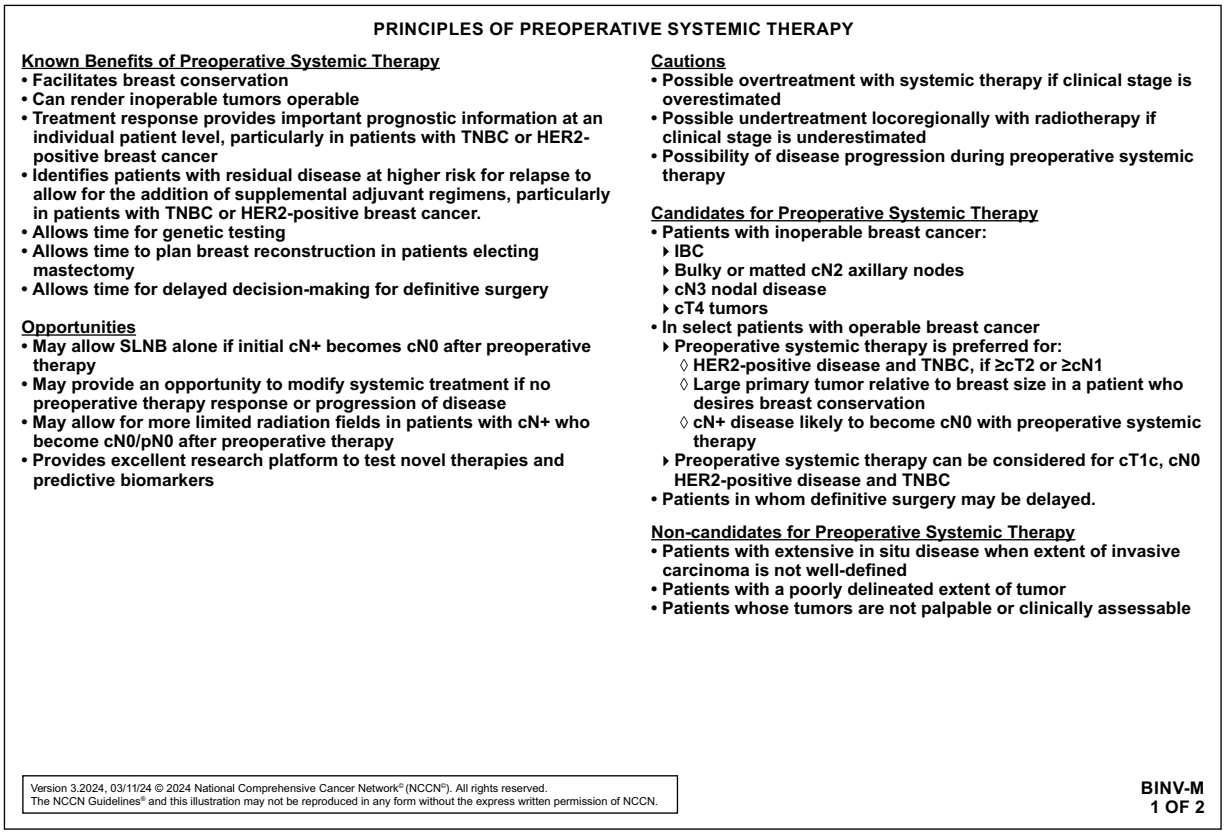

Figure 1. BINV M 1 of 2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer, Version 3.2024.

if the patient's breast cancer subtype is associated with a high likelihood of response; or if a patient desires breast-conserving surgery and the size of the tumor is large relative to that of the breast.

When preoperative systemic therapy is used to improve the likelihood of successful breast conservation, the surgical plan should consider the possibility that clear surgical margins may not always be obtained, and a follow-up mastectomy may be required, with or without breast reconstruction. This consideration is especially important when oncoplastic breast reduction techniques or contralateral breast symmetry procedures are added to the breast-conserving surgery to achieve optimal cosmetic outcomes.

The NCCN panel cautions that preoperative systemic therapy is not appropriate for certain patients. Preoperative systemic therapy should not be offered in patients with extensive in situ disease when the extent of invasive disease cannot be defined; in patients where the extent of the tumor is poorly delineated; or in those whose tumors are not clinically assessable. The decision to use preoperative therapy should be made in the context of a coordinated and collaborative multidisciplinary team.

For predicting the response of preoperative endocrine therapy for postmenopausal women with estrogen receptor (ER)–positive, HER2-negative, cN0 breast cancer, data from the TransNEOS study demonstrate a significant correlation between 21 gene assay recurrence score (RS) and clinical response to preoperative letrozole. Those whose tumors had an RS between 0 and 17 were significantly more likely to respond to preoperative letrozole compared with RS of 31 to 100.[11]

For predicting the response to preoperative chemotherapy for postmenopausal patients with ER-positive, HER2-negative disease with T1/T2, node-negative tumors, another study evaluated the role of the RS with pathologic response rates after preoperative systemic therapy. Their findings suggest high RS are associated with a higher likelihood of pCR after preoperative chemotherapy.[12]

Based on the 2 studies that showed the use of 21-gene RS in predicting response to preoperative chemotherapy,[11,12] the NCCN panel has added a footnote for considering the use of a gene expression assay during workup when contemplating preoperative endocrine or systemic therapy for postmenopausal patients with cN0, operable ER-positive, HER2-negative disease, to aid in predicting response to preoperative therapy.

Preoperative Therapy Options

Chemotherapy

A number of chemotherapy regimens have activity in the preoperative setting. According to the NCCN panel, those regimens recommended in the adjuvant setting may be considered in the preoperative setting. In both settings, the underlying aim remains the same: eradication or control of undiscovered distant metastases.

Endocrine Therapy

Preoperative endocrine therapy alone may be offered to those with strongly HR-positive tumors based on comorbidities or low-risk luminal biology based on clinical characteristics and/or

PRINCIPLES OF PREOPERATIVE SYSTEMIC THERAPY

- **Pathology evaluation of surgical resection specimens following preoperative systemic therapy should include the standardized tissue sampling and reporting elements of the Residual Cancer Burden (RCB) (category 2B).[a]**
- **Randomized trials of chemotherapy demonstrate similar long-term outcomes when patients are given the same treatment preoperatively compared with postoperatively.[b]**
- **Pathologic complete response (pCR) to preoperative systemic therapy is associated with an extremely favorable disease-free and overall survival (OS), particularly in situations in which all treatment is given preoperatively. The correlation between pathologic response and long-term outcome is strongest for TNBC, somewhat less so for HER2-positive disease, and least for ER-positive disease.[c,d]**
- **A number of chemotherapy regimens have activity in the preoperative setting. In general, those chemotherapy regimens recommended in the adjuvant setting may be considered in the preoperative setting. See Preoperative/Adjuvant Therapy Regimens (BINV-L).**
- **Preoperative endocrine therapy alone may be considered for patients with ER-positive disease based on comorbidities or low-risk luminal biology based on clinical characteristics and/or genomic signatures (until desired effect is achieved). Data shows that optimal duration for response if achieved between 4–6 months.[e]**
- **Patients with HER-2 positive, ≥cT2 and/or cN+ should be considered for HER2-directed therapy preoperatively.[f] See Preoperative/Adjuvant Therapy Regimens (BINV-L).**
- **Some studies suggest an increased risk of locoregional recurrence following use of preoperative chemotherapy.[g] These trials delivered chemotherapy regimens that are no longer standard, did not include targeted therapies, did not use modern imaging techniques, and/or used non-standard locoregional management. Care should be taken to follow the procedures outlined in BINV-12* and BINV-14* to asure appropriate locoregional management. Not all patients are appropriate candidates for preoperative systemic therapy. Accurate clinical staging at baseline prior to initiation of preoperative systemic therapy is critical. See Potentially Operable Disease: Breast and Axillary Evaluation Prior to Preoperative Systemic Therapy (BINV-12*).**
- **Tumor response should be routinely assessed by clinical exam and imaging studies (see footnote uu on BINV-13*) during delivery of preoperative therapy. It is preferred that the standard regimen is completed prior to surgery. If all intended treatment is not completed prior to surgery, the remainder may be given in the adjuvant setting. Patients with operable breast cancer experiencing progression of disease during preoperative systemic therapy may be given an alternate systemic regimen or proceed to surgery if deemed resectable. Locoregional therapy principles should be applied in the same manner as in patients treated with adjuvant systemic therapy.**

[a] Yau C, Osdoit M, van der Noorda M, et al. Residual cancer burden after neoadjuvant chemotherapy and long-term survival outcomes in breast cancer: a multicentre pooled analysis of 5161 patients. Lancet Oncol 2022;23:149-160.
[b] Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: Updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008;26:778-785.
[c] von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol 2012;30:1796-1804.
[d] Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384:164-172.
[e] Hunt KK, Suman VJ, Wingate HF, et al. Local-regional recurrence after neoadjuvant endocrine therapy: Data from ACOSOG Z1031 (Alliance), a Randomized Phase 2 neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal eomen with estrogen receptor-positive clinical stage 2 or 3 breast cancer. Ann Surg Oncol 2023;30:2111-2118.
[f] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[g] Early Breast Cancer Trialists' Collaborative Group (EBTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: metaanalysis of individual patient data from ten randomised trials. Lancet Oncol 2018;19:27-39.

*Available online, in these guidelines, at NCCN.org.

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Figure 2. BINV-M 2 of 2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer, Version 3.2024.

genomic signatures (until desired effect is achieved).[13–20] The results of the ACOSOG Z1031 trial show that preoperative endocrine therapy is effective in reducing residual disease and enabling breast-conserving surgery for many patients with low rates of local-regional recurrence postsurgery.[21]

According to the NCCN panel, the endocrine therapy options include an aromatase inhibitor (AI) (with ovarian function suppression [OFS] for premenopausal patients) or tamoxifen (with or without OFS for premenopausal patients). The preferred endocrine therapy option for postmenopausal patients is an AI. The panel has added a comment that the optimal response to endocrine therapy, if achieved, is anywhere between 4 and 6 months based on the previously cited trials.

HER2-Targeted Therapy

For patients with HER2-positive breast cancer that are candidates for preoperative systemic therapy, chemotherapy and trastuzumab-based therapy is recommended.[22] Chemotherapy and dual anti-HER2 blockade associated with trastuzumab plus pertuzumab has shown significant improvements in the pCR rate when compared with chemotherapy and trastuzumab in the preoperative setting.

In the TRYPHAENA trial, preoperative therapy with pertuzumab and trastuzumab given along with anthracycline-containing or anthracycline-free standard chemotherapy regimens to patients with operable, locally advanced, or inflammatory HER2-positive breast cancer showed pCR rates in all treatment arms ranging from 57% to 66%.[23] In the Neosphere trial, the addition of pertuzumab to trastuzumab and docetaxel preoperatively led to a statistically significant increase in pCR in the breast, which in turn led to improved outcomes in those with node-positive disease.[24,25] The NCCN panel supports the FDA-approved indication that a pertuzumab-containing regimen may be administered preoperatively to patients with greater than or equal to cT2, or greater than or equal to cN1, HER2-positive, early-stage breast cancer.

Immunotherapy

A randomized phase III multicenter, double-blind, placebo-controlled trial (KEYNOTE-522) compared preoperative carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide in combination with either pembrolizumab (n=784) or placebo (n=390), followed by pembrolizumab or placebo administered every 3 weeks for up to 9 cycles after surgery, in patients with previously untreated stage II–III TNBC.[26] After a median follow-up of 39.1 months, a significant improvement in event-free survival (EFS) was seen with the addition of pembrolizumab compared with placebo plus chemotherapy. The 3-year EFS rates were 84.5% and 76.8%, respectively (hazard ratio [HR], 0.63, 95% CI, 0.48–0.82; $P<.001$).[26]

The 5-year follow-up of KEYNOTE-522 trial results showed an improvement in EFS rate in patients treated with chemotherapy plus pembrolizumab compared with the placebo arm (81.3% vs 72.3%), with reduction in risk for recurrence, progression, complications, or death of 37% (HR, 0.63; 95% CI, 0.49–0.81).[27] Among patients in the trial who had a pCR and received adjuvant pembrolizumab, the 5-year EFS rate was 92.2% compared with 88.2% in patients who received only chemotherapy.[27] There are

no data comparing adjuvant pembrolizumab with other newer adjuvant therapies such as adjuvant capecitabine and/or olaparib in patients who meet criteria for treatment with one or more of these agents.

Response Assessment During Preoperative Chemotherapy

The NCCN panel recommends that tumor response be routinely assessed by clinical exam during the delivery of preoperative systemic therapy. Patients with operable breast cancer experiencing progression of disease while undergoing preoperative systemic therapy should be taken promptly to surgery. Imaging during preoperative systemic therapy should not be done routinely but may be considered if tumor progression is suspected. Imaging before surgery should be determined by a multidisciplinary team.

In a multicenter analysis of patients (n=5,161), the residual cancer burden (RCB) after preoperative chemotherapy was seen to be prognostic within each breast cancer subtype.[28] Higher RCB scores were significantly associated with worse EFS, with hazard ratios ranging from 1.55 to 2.16 across different breast cancer subtypes.

This study highlights RCB as a prognostic factor for outcomes in patients with breast cancer undergoing preoperative chemotherapy.[28]

As noted under the "workup" section, to have a standardized method of pathology reporting, the NCCN endorses the CAP protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast. On the "Principles of Preoperative Therapy" page, the panel encourages that the pathology report from definitive surgery after preoperative systemic therapy include the standardized tissue sampling and reporting elements of the RCB. However, since RCB reporting is currently not mandatory given its main purpose for prognostication only, there is inconsistent reporting of RCB across institutions and no uniform agreement among the panel that RCB is required in the pathology report, rendering it a category 2B recommendation.

Adjuvant Systemic Therapy

After surgical treatment, adjuvant systemic therapy should be considered. In patients with early-stage breast cancer, systemic adjuvant therapy is administered to reduce risk of cancer recurrence. The decision is often based on individual risk of relapse and predicted sensitivity to a particular treatment (eg, ER/progesterone receptor [PR] and HER2 status). The decision to use systemic adjuvant therapy requires considering and balancing risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of the therapy, and comorbidity. The decision-making process requires collaboration between the health care team and patient.

Stratification for Systemic Adjuvant Therapy

The NCCN Guidelines stratify patients with breast cancer based on their HR-status and HER2 expression. Patients are then further stratified based on risk of disease recurrence based on anatomic and pathologic characteristics (ie, tumor grade, tumor size, axillary lymph node [ALN] status, angiolymphatic invasion) (Figure 3).

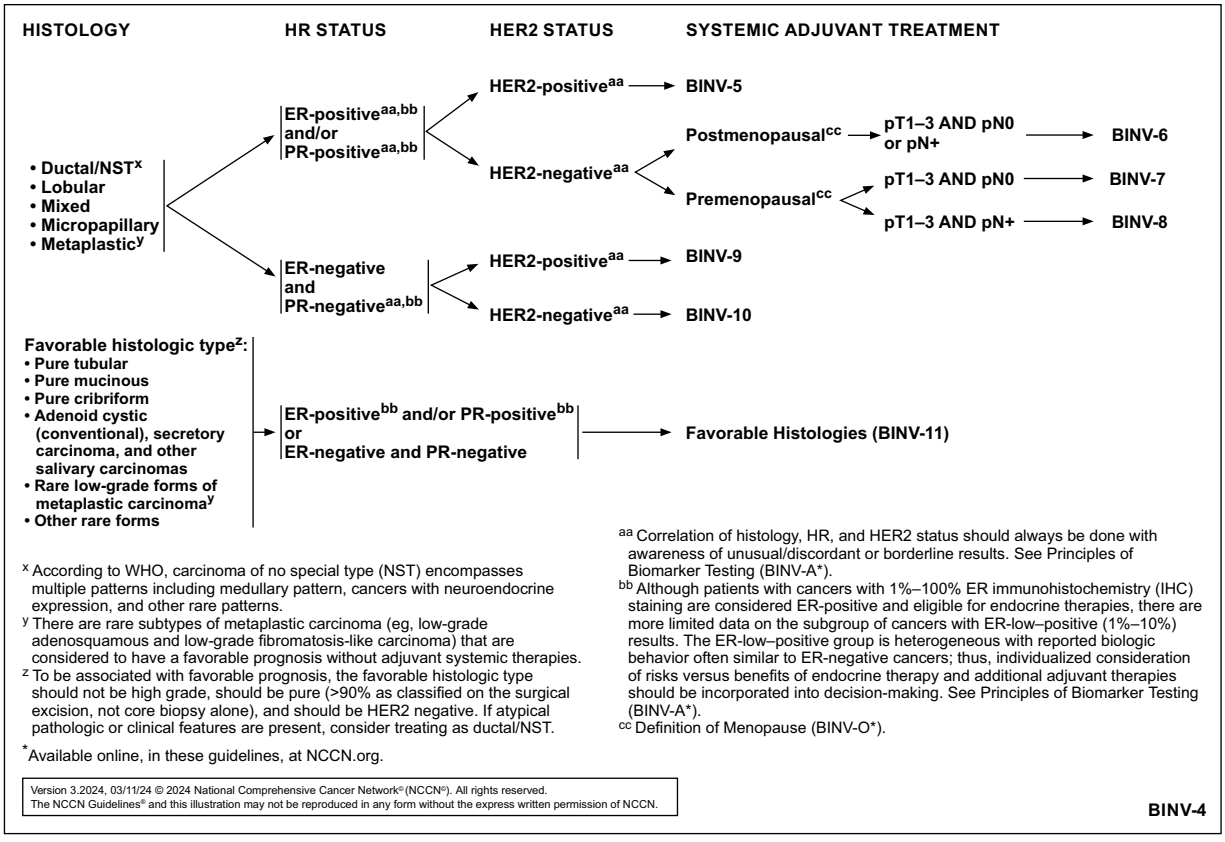

Figure 3. BINV-4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer, Version 3.2024.

Adjuvant Systemic Therapy for HR-Positive, HER2-Negative Tumors

Patients with HR positive, HER2-negative tumors receive adjuvant endocrine therapy to reduce the risk of recurrence, and those deemed at high risk for distant recurrence despite adjuvant endocrine therapy receive adjuvant chemotherapy. The NCCN Guidelines call for the determination of ER and PR content in all primary invasive breast cancers[29] to determine whether a patient is a candidate for endocrine therapies. Patients with cancers with 1%–100% ER immunohistochemistry staining are considered ER-positive and eligible for endocrine therapies. Given the limited efficacy data on the ER-low-positive (1%–10%) group, with ER-low-positive cancers reported to be a heterogeneous group with a natural history/biologic behavior often similar to ER-negative cancers, individualized consideration of risks versus benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making. Patients with ER-negative, PR-positive cancers may also be considered for endocrine therapies; however, the efficacy data on this group are also limited. The same overall interpretation principles apply, but PR should be interpreted as either positive (if 1%–100% of cells have nuclear staining) or negative (if <1% or 0% of cells have nuclear staining). For the purposes of this guideline, any ER and/or PR-positive tumors is referred to as "hormone receptor (HR)-positive," given that the majority of all breast cancers are ER-positive or ER- and PR-positive and the subgroup of ER-negative/PR-positive tumors are relatively uncommon.

The magnitude of risk reduction from adjuvant endocrine therapy is dependent on level of ER expression and on RS of gene expression assay test results. Low level of ER expression is less likely to benefit from endocrine therapy and a high RS will gain less benefit with endocrine therapy alone versus those with low RS.

Patients with invasive breast cancers that are HR-positive should be considered for adjuvant endocrine therapy regardless of patient age, lymph node status, or whether adjuvant chemotherapy is to be administered.[30] Selected studies suggest that HER2-positive breast cancers may be less sensitive to some endocrine therapies, although other studies have failed to confirm this finding.[31–39] A retrospective analysis of tumor blocks collected in the ATAC trial indicated that HER2 amplification is a marker of relative endocrine resistance independent of type of endocrine therapy.[40] However, given the favorable toxicity profile of the available endocrine therapies, the panel recommends the use of adjuvant endocrine therapy in the majority of patients with HR-positive breast cancer regardless of menopausal status, age, or HER2 status of the tumor (Figure 4).

Tamoxifen

The most firmly established adjuvant endocrine therapy is tamoxifen for both premenopausal and postmenopausal patients.[41] In patients with ER-positive breast cancer, adjuvant tamoxifen decreases the annual odds of recurrence by 41% and the annual odds of death by 31% irrespective of the use of chemotherapy, patient age, menopausal status, or ALN status.[41] In patients receiving both tamoxifen and chemotherapy, chemotherapy should be given first, followed by sequential tamoxifen.[42] Prospective

PRINCIPLES OF ADJUVANT ENDOCRINE THERAPY
(for pT1-3pN+M0)

General Principles
- Hormone receptor-positive (HR+) tumors: Breast tumors may be positive for estrogen receptors (ER+), progesterone receptors (PR+) or both (ER+/PR+). See Principles of Biomarker Testing (BINV-A*).
  - ER+ tumors: ER testing should be used to determine if a patient is a candidate for endocrine therapies.[a] Patients with cancers with 1%–100% ER IHC staining are considered ER+ and eligible for endocrine therapies, there are limited efficacy data on the subgroup of cancers with ER-low-positive (1%–10%) results. The ER-low-positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers; thus, individualized consideration of risks versus benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making.
  - PR+ tumors: Patients with ER-negative, PR+ cancers may be considered for endocrine therapies, but the data on this group are noted to be limited. The same overall interpretation principles apply but PR should be interpreted as either positive (if 1%–100% of cells have nuclear staining) or negative (if <1% or 0% of cells have nuclear staining).
- Considering that majority of all HR+ breast cancers are ER+ or ER+/PR+ and ER-negative/PR+ tumors are relatively uncommon, ER and/or PR+ tumors are referred to as HR+ throughout the guidelines.
- The magnitude of risk reduction from adjuvant endocrine therapy is dependent on:
  - Level of ER expression: Low ER+ expression is less likely to benefit from endocrine therapy.
  - Recurrence score (RS) on gene expression assay test results: Patients with high RS will gain relatively less benefit from adjuvant endocrine alone compared to those with low RS.

Candidates for ovarian suppression + endocrine therapy
- Premenopausal
- Endocrine sensitive tumors with high enough recurrence risk where the additional absolute decrease in recurrence compared with tamoxifen alone is worth the additional toxicity (young age, high-grade tumor, lymph node involvement).[b]

Ovarian function assessment
- Menopausal status cannot be determined while receiving OFS.[a]
- Monitor estradiol and follicle-stimulating hormone (FSH)/LH levels:
  - If under 60 y and amenorrheic for ≤12 months prior to treatment with adjuvant endocrine therapy
  - Amenorrheic after chemotherapy or after tamoxifen +/- ovarian function suppression (OFS).
  - After switching from tamoxifen to an AI, or if taken off OFS
  - Prior to next dose of GNRH agonist, particularly in women under the age of 45. Frequency of testing of estradiol and FSH/LH levels should be individualized.
- AI can stimulate ovarian function. If vaginal bleeding occurs while on AI, contact physician immediately.

Methods for OFS
- GNRH agonists
  - Goserelin 3.6 mg SC every 4w or 10.8 mg SC every 12w
  - Leuprolide 3.75–7.5 mg IM every 4w or 11.25–22.5 mg IM every 12w
- Radiation therapy
- Bilateral oophorectomy

Initiation of OFS
- With start of chemotherapy (neoadjuvant or adjuvant)
- If no chemotherapy planned, then OFS should be started alone for at least 1-2 cycles or concurrently with tamoxifen until estradiol level in postmenopausal range at which time an aromatase inhibitor could considered.
  - Concurrently with RT or upon completion

Duration of OFS
- 5 years optimal according to SOFT and TEXT trial. No efficacy or safety date to support prolonged OFS. It is encouraged to complete a minimum 2 years of OFS (The 8-year DFS was 85.4% with OFS + tamoxifen versus 80.2% with tamoxifen alone.[c]
- Premenopausal patients wishing to continue adjuvant endocrine therapy after OFS stopped should use tamoxifen.

[a] Definition of Menopause (BINV-O*).
[b] A balanced discussion of the risks and benefits associated with ovarian suppression therapy is critical, including the potential side effects of premature menopause. Aromatase inhibitor or tamoxifen for 5 years plus ovarian suppression should be considered, based on SOFT and TEXT clinical trial outcomes, for premenopausal patients at higher risk of recurrence (ie, young age, high-grade tumor, lymph node involvement).
[c] Baek SY, Noh WC, Ahn SH, et al. Adding ovarian suppression to tamoxifen for premenopausal women with hormone receptor-positive breast cancer after chemotherapy: An 8-year follow-up of the ASTRRA Trial. J Clin Oncol 2023;41:4864-4871.

*Available online, in these guidelines, at NCCN.org.

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Figure 4. BINV-K 1 of 2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer, Version 3.2024.

randomized trials have demonstrated that 5 years of tamoxifen is more effective than 1 to 2 years of tamoxifen.[41,43]

The ATLAS trial randomly allocated pre- and postmenopausal patients to 5 or 10 years (extended therapy) of tamoxifen. The outcome analyses of 6,846 patients with ER-positive disease showed that by extending adjuvant treatment to 10 years, the risk of relapse and breast cancer-related mortality was reduced.[44] The risk of recurrence during years 5 to 14 was 21.4% for patients receiving tamoxifen versus 25.1% for controls (absolute recurrence reduction 3.7%). Patients who received tamoxifen for 10 years had a greater reduction in risk of progression, possibly due to a "carryover effect." The reduction in risk of recurrence was 0.90 (95% CI, 0.79–1.02) during 5 to 9 years of tamoxifen treatment and 0.75 (0.62–0.90) after 10 years of treatment. There were decreases in the incidence of contralateral breast cancer as well. Furthermore, reduced mortality was also apparent after completion of 10 years of treatment with tamoxifen. With regards to toxicity, the most important adverse effects noted in all patients in the ATLAS trial after 10 years of tamoxifen treatment were an increased risk for endometrial cancer and pulmonary embolism.[44] The results of the aTTom trial confirm the significant reduction in recurrence and death from breast cancer seen in the ATLAS trial with 10 versus 5 years of tamoxifen therapy.[45]

Aromatase Inhibitors

Several studies have evaluated AIs in the treatment of postmenopausal patients with early-stage breast cancer. These studies have used AI as initial adjuvant therapy, as sequential therapy after 2 to 3 years of tamoxifen, or as extended therapy after 4.5 to 6 years of tamoxifen. The AIs are not active in the treatment of patients with functioning ovaries and should not be used in patients whose ovarian function cannot reliably be assessed owing to treatment-induced amenorrhea.

The results from 2 prospective, randomized clinical trials have provided evidence of an OS benefit for patients with early-stage breast cancer receiving initial endocrine therapy with tamoxifen followed sequentially by anastrozole (HR, 0.53; 95% CI, 0.28–0.99; P=.045) or exemestane (HR, 0.83; 95% CI, 0.69–1.00; P=.05 [excluding patients with ER-negative disease]) when compared with tamoxifen as the only endocrine therapy.[46,47] In addition, the NCIC-CTG MA-17 trial showed a survival advantage with extended therapy with letrozole compared with placebo in patients with ALN-positive (but not lymph node-negative), ER-positive breast cancer.[48] Tamoxifen and AIs have different side effect profiles. Both contribute to hot flashes and night sweats and may cause vaginal dryness. AIs are more commonly associated with musculoskeletal symptoms, osteoporosis, and increased rate of bone fracture, while tamoxifen is associated with an increased risk for uterine cancer and deep venous thrombosis.

Two studies have examined initial adjuvant endocrine treatment with either tamoxifen or an AI. The ATAC trial showed that anastrozole is superior to tamoxifen or the combination of tamoxifen and anastrozole in the adjuvant endocrine therapy of postmenopausal patients with HR-positive breast cancer.[49,50] With a median of 100 months follow-up, results in 5,216 postmenopausal patients with HR-positive, early-stage breast cancer enrolled in the ATAC trial demonstrated fewer recurrences (HR for DFS, 0.85; 95% CI, 0.76–0.94; P=.003) with anastrozole compared with tamoxifen.[51] No difference in survival has been observed (HR, 0.90; 95% CI, 0.75–1.07; P=.2). Patients in the combined tamoxifen and anastrozole group gained no benefit over those in the tamoxifen group, suggesting a possible deleterious effect from the weak estrogenic effect of tamoxifen in patients with near complete elimination of endogenous estrogen levels.[50] ATAC trial subprotocols show a lesser effect of anastrozole compared with tamoxifen on endometrial tissue[52]; similar effects of anastrozole and tamoxifen on quality of life, with most patients reporting that overall quality of life was not significantly impaired[53]; a greater loss of bone mineral density with anastrozole[54]; a small pharmacokinetic interference of anastrozole in the presence of tamoxifen of unclear significance[55]; and no evidence for an interaction between prior chemotherapy and anastrozole.[56]

BIG 1-98 is a randomized trial testing the use of tamoxifen alone for 5 years, letrozole alone for 5 years, or tamoxifen for 2 years followed sequentially by letrozole for 3 years, or letrozole for 2 years followed sequentially by tamoxifen for 3 years. An early analysis compared tamoxifen alone versus letrozole alone, including for those patients in the sequential arms during their first 2 years of treatment only.[57] With 8,010 patients included in the analysis, DFS was superior in the letrozole-treated patients (HR, 0.81; 95% CI, 0.70–0.93; log rank P=.003). No interaction between PR expression and benefit was observed. No difference in OS was observed. A comparison of the cardiovascular side effects in the tamoxifen and letrozole arms of the BIG 1-98 trial showed that the overall incidence of cardiac adverse events was similar (letrozole, 4.8%; tamoxifen, 4.7%). However, the incidence of grade 3 to 5 cardiac adverse events was significantly higher in the letrozole arm, and both the overall incidence and incidence of grade 3 to 5 thromboembolic events was significantly higher in the tamoxifen arm.[58] In addition, a higher incidence of bone fracture was observed for patients in the letrozole arm compared with those in the tamoxifen arm (9.5% vs 6.5%).[59] After a longer follow-up (median 71 months), no significant improvement in DFS was noted with either tamoxifen followed by letrozole or the reverse sequence as compared with letrozole alone (HR for tamoxifen followed by letrozole, 1.05; 99% CI, 0.84–1.32; HR for letrozole followed by tamoxifen, 0.96; 99% CI, 0.76–1.21).[60]

Five trials have studied the use of tamoxifen for 2 to 3 years followed sequentially by a third-generation AI versus continued tamoxifen in postmenopausal patients. The Italian Tamoxifen Anastrozole (ITA) trial randomized 426 postmenopausal patients with breast cancer who had completed 2 to 3 years of tamoxifen to either continue tamoxifen or to switch to anastrozole to complete a total of 5 years of endocrine therapy.[61] The HR for relapse strongly favored sequential treatment with anastrozole (HR, 0.35; 95% CI, 0.18–0.68; P=.001) with a trend toward fewer deaths (P=.10).[61] Updated results from this study show the HR for relapse-free survival as 0.56 (95% CI, 0.35–0.89; P=.01); P value for OS analysis remained at 0.1.[62] The IES trial randomized 4,742 postmenopausal patients with breast cancer who had completed a total of 2 to 3 years of tamoxifen to either continue tamoxifen or to switch to exemestane to complete a total of 5 years of endocrine therapy.[63] The results at a median of 55.7 months of follow-up demonstrated the superiority of sequential exemestane in DFS (HR, 0.76; 95% CI, 0.66–0.88; P=.0001) with a significant difference in OS in only patients with ER-positive tumors (HR, 0.83; 95% CI, 0.69–1.00; log rank P=.05).

A prospectively planned, combined analysis of 3,224 patients enrolled in the ABCSG 8 trial and the ARNO 95 trial has also been reported.[64] Patients in this combined analysis had been randomized following 2 years of tamoxifen to complete 5 years of adjuvant tamoxifen or 3 years of anastrozole. With 28 months of median follow-up available, EFS was superior with crossover to anastrozole (HR, 0.60; 95% CI, 0.44–0.81; P=.0009). No statistically significant difference in survival has been observed. An analysis of the ARNO 95 trial alone after 58 months of median follow-up demonstrated that switching from tamoxifen to anastrozole was associated with significant increases in both DFS (HR, 0.66; 95% CI, 0.44–1.00; P=.049) and OS (HR, 0.53; 95% CI, 0.28–0.99; P=.045).[47] A meta-analysis of ABCSG 8, ARNO 95, and ITA studies showed significant improvement in OS (HR, 0.71; 95% CI, 0.52-0.98; P=.04) with a switch to anastrozole.[65]

The TEAM trial compared treatment of exemestane alone versus sequential therapy of tamoxifen for 2.5 to 3.0 years followed by exemestane to complete 5 years of hormone therapy.[66] At the end of 5 years, 85% of patients in the sequential group versus 86% in the exemestane group were disease free (HR, 0.97; 95% CI, 0.88–1.08; P=.60). This is consistent with the data from the BIG 1-98 trial,[60] in which tamoxifen followed by letrozole or the reverse sequence of letrozole followed by tamoxifen was not associated with significant differences in efficacy versus letrozole monotherapy after a median follow-up of 71 months.

The NCCN panel finds no meaningful differences in terms of efficacy or toxicity between the available AIs: anastrozole, letrozole, and exemestane. All 3 have shown similar antitumor efficacy and toxicity profiles in randomized studies in the adjuvant settings.

Ovarian Function Suppression and Endocrine Therapy

OFS is achieved with a gonadotropin-releasing hormone (GnRH) agonist, oophorectomy, or ovarian irradiation. Available GnRH agonists in the United States include goserelin and leuprolide. OFS is generally considered in those who are premenopausal and for tumors with high enough recurrence risk where the additional absolute decrease in recurrence compared with tamoxifen alone is worth the additional toxicity (young age, high-grade tumor, lymph node involvement). A balanced discussion of the risks and benefits associated with OFS is critical, including the potential side effects of premature menopause.

In 2 randomized trials (TEXT and SOFT), premenopausal patients with HR-positive early-stage breast cancer were assigned to receive AI (exemestane) plus OFS or tamoxifen plus OFS for a period of 5 years.[67] Suppression of ovarian estrogen production was achieved with the use of GnRH agonist triptorelin, oophorectomy, or ovarian irradiation. The DFS was 92.8% in the exemestane plus OFS as compared with 88.8% in the tamoxifen plus OFS (HR for recurrence, 0.66; 95% CI, 0.55–0.80; P<.001).[67] The OS did not differ significantly between the 2 groups (HR for death in the exemestane plus OFS group, 1.14; 95% CI, 0.86–1.51; P=.37).[67]

A 9-year median follow-up analysis of the TEXT-SOFT trials showed sustained improvements in DFS with exemestane plus OFS versus tamoxifen plus OFS (HR, 0.77; 95% CI, 0.67–0.90) and in distant recurrence-free interval but not OS (HR, 0.98; 95% CI, 0.79–1.22).[68] Ultimately, with longer follow-up (median, 13 years), an OS was demonstrated for OFS plus exemestane in patients with high risk of recurrence, but not in exemestane plus OFS in patients with lower risk of relapse not receiving chemotherapy.[69]

The benefit of OFS in premenopausal patients with high risk of recurrence was also seen in the results of the ASTRRA trial. This trial studied premenopausal patients (n=1,483) with HR-positive breast cancer younger than 45 years treated with surgery and who received chemotherapy (as adjuvant or preoperative therapy) and received 5 years of tamoxifen alone or 5 years of tamoxifen with OFS for 2 years. The 8-year DFS with tamoxifen plus OFS was 85.4% versus 80.2% with tamoxifen alone (HR, 0.67; 95% CI, 0.51–0.87).[70]

The results of the TEXT–SOFT trials suggest an optimal OFS duration of 5 years, and data from the ASTRA trial suggests a benefit with a minimum of at least 2 years of OFS. The NCCN panel has included OFS plus endocrine therapy for 5 years as an option for premenopausal patients with HR-positive breast cancer at higher risk of recurrence (eg, young age, high-grade tumor, lymph node involvement). Premenopausal patients wishing to continue adjuvant endocrine therapy after ovarian suppression is stopped should continue with tamoxifen versus AI.

Duration of Adjuvant Endocrine Therapy

Adjuvant endocrine therapy is recommended for a minimum of 5 years. A recent retrospective analysis by the Oxford University studied risk of recurrence for years 5 through 20 after 5 years of endocrine therapy.[71] These data showed a considerable risk of recurrence between years 5 and 20 in these patients treated with initial 5 years of endocrine therapy.[71] Data have now emerged showing benefit of extended endocrine therapy in improving DFS.

Data from the ATLAS trial (discussed previously)[44] and the aTTom trial confirm greater reduction in recurrence and death from breast cancer with 10 versus 5 years of tamoxifen therapy.[45]

For those treated initially with adjuvant tamoxifen, there is evidence for benefit from extended adjuvant endocrine therapy from several randomized trials. Results of the MA-17 trial in 5,187 patients who had completed 4.5 to 6 years of adjuvant tamoxifen demonstrated that extended therapy with letrozole provides benefit in postmenopausal patients with HR-positive, early-stage breast cancer.[48,72] With a median follow-up of 64 months, letrozole was associated with improved DFS (HR, 0.52; 95% CI, 0.45–0.61) and an improved OS (HR, 0.61; 95% CI, 0.52–0.71) compared with placebo.[73]

In a separate cohort analysis of the MA-17 trial, the efficacy of letrozole versus placebo was evaluated after unblinding of the study in the 1,579 patients who had been randomly assigned to placebo after 4.5 to 6 years of tamoxifen.[74,75] The median time since completion of tamoxifen was 2.8 years. Both DFS and distant DFS were significantly improved in the group receiving letrozole, thereby providing some evidence for the efficacy of letrozole in patients who had received 4.5 to 6 years of tamoxifen therapy followed by no endocrine therapy for an extended period. A formal quality-of-life analysis demonstrated reasonable preservation of quality of life during extended endocrine therapy, although patients may experience ongoing menopausal symptoms and loss of bone mineral density.[76,77] No data are available regarding use of aromatase inhibitors for more than 5 years or long-term toxic effects from extended treatment. In addition, the ATLAS trial data do not provide clear direction for treatment of

postmenopausal patients.[44] There are no data available to suggest that an AI for 5 years is better for long-term benefit than 10 years of tamoxifen.

In the extension study of ABCSG trial 6, HR-positive postmenopausal patients received 5 years of adjuvant tamoxifen and were randomized to 3 years of anastrozole or no further therapy.[78] At a median follow-up of 62.3 months, patients who received anastrozole (n=387) were reported to have a statistically significantly reduced risk of recurrence compared with patients who received no further treatment (n=469; HR, 0.62; 95% CI, 0.40–0.96; P=.031).[78]

The differences in design and patient populations among the studies of the AIs do not allow for the direct comparison of the results of these studies. A meta-analysis of adjuvant trials of AIs versus tamoxifen alone versus after 2 or 3 years of tamoxifen documented lower recurrence rates with the AI-containing regimen, with no clear impact on OS.[79] It is not known whether initial, sequential, or extended use of adjuvant AIs is the optimal strategy.

In patients initially treated with an AI, a randomized phase III trial (MA17.R) evaluated the effects of extending adjuvant AI therapy from 5 to 10 years.[80] Postmenopausal patients who had completed 4.5 to 6 years of therapy with an AI (with a median duration of prior tamoxifen of 5 years), were randomized to letrozole or placebo for an additional 5 years.[80] Improvement was seen in 5-year DFS in those receiving letrozole compared with those who received placebo (95% [95% CI, 93%–96%] vs 91% [95% CI, 89%−93%]). The annual rate of contralateral breast cancer reported was lower with letrozole (0.49% vs 0.21%; HR, 0.42; 95% CI, 0.22%–0.81%). However, longer duration of AI resulted in more frequent bone-related adverse effects compared with those who received placebo, and no improvement was observed with respect to OS. Bone-related adverse effects included bone pain (18% vs 14%), fractures (14% vs 9%), and new-onset osteoporosis (11% vs 6%).[80] Patients with high-risk of recurrence (eg those with lymph node involvement) may benefit from extended AI duration (7.5–10 years total).[81,82]

NCCN Recommendations

The decision of whether to extend adjuvant treatment based on the evidence available should be individualized. When considering endocrine therapy, the panel recommends the following adjuvant endocrine therapy options for patients with early-stage breast cancer (Figure 5).

Adjuvant Endocrine Therapy for Postmenopausal Patients

The NCCN panel recommends AI as initial adjuvant therapy for 5 years (category 1); and tamoxifen for 2 to 3 years followed by one of the following options: an AI to complete 5 years of adjuvant endocrine therapy (category 1) or 5 years of AI therapy (category 2B); or tamoxifen for 4.5 to 6 years followed by 5 years of AI (category 1) or consideration of tamoxifen for up to 10 years. In postmenopausal patients, the use of tamoxifen alone for 5 years (category 1) or up to 10 years is limited to those who decline or who have a contraindication to AIs.

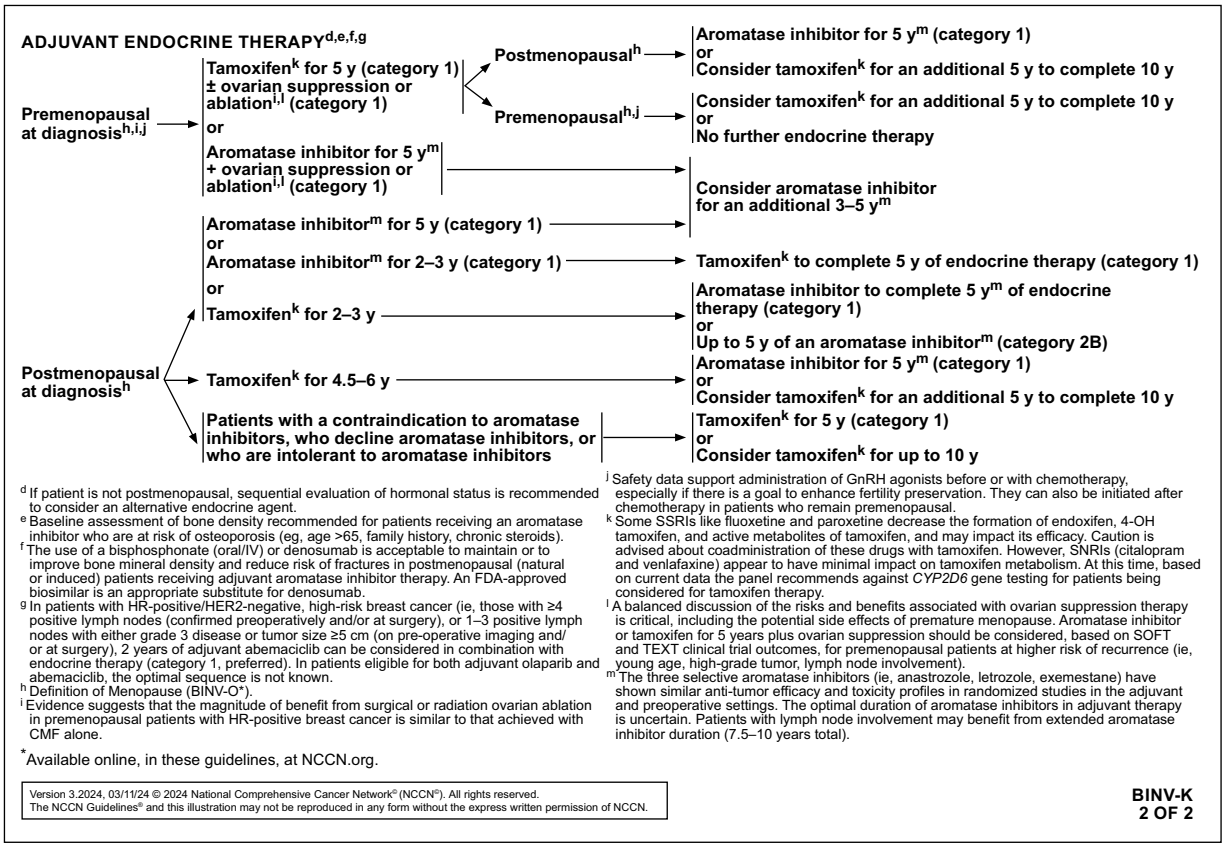


Figure 5. BINV-K 2 of 2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer, Version 3.2024.

Adjuvant Endocrine Therapy for Premenopausal Patients

For patients who are premenopausal at diagnosis, the NCCN panel recommend 5 years of tamoxifen alone (category 1) or tamoxifen with OFS (category 1) or OFS plus AI for 5 years (category 1). Patients who are premenopausal at diagnosis and who become amenorrheic with chemotherapy may have continued estrogen production from the ovaries without menses. Menopausal status cannot be determined while receiving OFS. AI can stimulate ovarian function. To assure a true postmenopausal status, serial assessment of circulating luteinizing hormone, follicle-stimulating hormone, and estradiol is mandatory when considering this subset for AI therapy.[83,84] Frequency of testing of estradiol and follicle-stimulating hormone/luteinizing hormone levels should be individualized.

After 5 years of initial endocrine therapy, for patients who are postmenopausal at that time (including those who have become postmenopausal during the 5 years of tamoxifen therapy), the NCCN panel recommends considering extended therapy with an AI for up to 5 years (category 1) or based on the data from the ATLAS trial considering tamoxifen for an additional 5 years. For those who remain premenopausal after the initial 5 years of tamoxifen, the panel recommends considering continuing up to 10 years of tamoxifen therapy.

Additional Considerations During Adjuvant Endocrine Therapy

Symptom management for patients on adjuvant endocrine therapies often requires treatment of hot flashes and the treatment of concurrent depression.

Venlafaxine, a serotonin-norepinephrine reuptake inhibitor, has been studied and is an effective intervention in decreasing hot flashes.[85–88] There is evidence suggesting that concomitant use of tamoxifen with certain selective serotonin reuptake inhibitors (SSRIs) (eg, paroxetine, fluoxetine) may decrease plasma levels of endoxifen, an active metabolite of tamoxifen.[89,90] These SSRIs/serotonin-norepinephrine reuptake inhibitors s may interfere with the enzymatic conversion of tamoxifen to endoxifen by inhibiting a particular isoform of cytochrome P-450 (CYP450) enzyme. Individuals with wild-type *CYP2D6* alleles are classified as extensive metabolizers of tamoxifen. Those with one or two variant alleles with either reduced or no activity are designated as intermediate metabolizers and poor metabolizers, respectively. The mild CYP2D6 inhibitors such as citalopram, escitalopram, sertraline, and venlafaxine appear to have no or only minimal effect on tamoxifen metabolism.[83,91,92]

With respect to *CYP2D6* mutation status, a large retrospective study of 1,325 patients found that time to disease recurrence was significantly shortened in poor metabolizers of tamoxifen.[93] However, the BIG 1-98 trial reported on the outcome based on *CYP2D6* genotype in a subset of postmenopausal patients with endocrine-responsive, early invasive breast cancer. The study found no correlation between CYP2D6 allelic status and disease outcome or between CYP2D6 allelic status and tamoxifen-related adverse effects.[94] A genetic analysis of the ATAC trial found no association between *CYP2D6* genotype and clinical outcomes.[95,96] Given the limited and conflicting evidence at this time,[97] the NCCN Breast Cancer Panel does not recommend CYP2D6 testing as a tool to determine the optimal adjuvant endocrine strategy. This recommendation is consistent with the ASCO Guidelines.[98] When prescribing an SSRI, it is reasonable to avoid potent and intermediate CYP2D6 inhibiting agents, particularly paroxetine and fluoxetine, if an appropriate alternative exists.

For those on tamoxifen, although age-appropriate gynecologic screening is recommended, the use of routine annual pelvic ultrasound is not recommended. For those receiving AI or who experience ovarian failure secondary to treatment should have monitoring of bone health with a bone mineral density determination at baseline and periodically thereafter. The panel discourages the selective ER modulators to treat osteoporosis or osteopenia in patients with breast cancer. The use of a bisphosphonate (oral/intravenous) or denosumab is recommended to maintain or to improve bone mineral density and reduce risk of fractures in postmenopausal (natural or induced) patients receiving adjuvant AI therapy. Optimal duration of either therapy has not been established. The optimal duration and benefits beyond 3 years is not known. Factors to consider for duration of antiosteoporosis therapy include bone mineral density, response to therapy, and risk factors for continued bone loss or fracture. There are case reports of spontaneous fractures after denosumab discontinuation. Patients treated with bisphosphonates or denosumab should undergo a dental examination with preventive dentistry prior to the initiation of therapy, and should take supplemental calcium and vitamin D.

The incremental benefit of adding adjuvant chemotherapy to endocrine therapy in patients with low clinical risk of recurrence such as those with very small, low grade, lymph node-negative tumors is relatively small.[99] The decision whether to administer adjuvant chemotherapy in patients with HR-positive, HER2-negative tumors is based on many factors including lymph node status, size, grade, lymphovascular invasion, age, comorbid conditions and/or the results of a gene expression profile test using multigene assays.

Several commercially available gene-based assays are useful in determining prognosis by predicting distant recurrence, local recurrence, or survival. Of these, only one, the 21-gene assay (Oncotype Dx) has been clinically validated for predicting the benefit of adding adjuvant chemotherapy to further reduce the risk of recurrence.

21-Gene Assay (Oncotype DX) in Node-Negative, HR-Positive, HER2-Negative Disease

The 21-gene RS is one of the most validated multigene assays. The RS is helpful in determining the prognosis in patients with HR-positive, HER2-negative tumors treated with endocrine therapy alone by predicting locoregional and distant recurrence.[100–102] This assay has also been validated to predict the benefit from adding adjuvant chemotherapy to adjuvant endocrine therapy for patients with HR-positive, HER2-negative, node-negative breast cancer.[39,103,104]

Among patients with T1b/c and T2, lymph node-negative, HR-positive, HER2-negative tumors with RS between 0 and 10, the risk of distant recurrence is low and these patients derive no incremental benefit from the addition of adjuvant chemotherapy to endocrine therapy.[39,105] At the other end of the spectrum, patients with lymph node-negative, HR-positive, HER2-negative cancers with high RS (≥31) have a higher risk of distant recurrence, and secondary analyses of prospective studies demonstrate a clear benefit from adjuvant chemotherapy.[39,106]

For those with intermediate RS (11–25), the TAILORx trial of postmenopausal patients (n=6,711) with lymph node-negative,

HR-positive, HER2-negative breast cancer, showed similar DFS rates at 9 years in those who received adjuvant chemotherapy followed by endocrine therapy compared with endocrine therapy alone.[106] However, in a subset analysis, patients 50 years of age or younger with RS 16 to 25 had lower rates of distance recurrence with the addition of adjuvant chemotherapy to endocrine therapy.[106] The cutoff for low, intermediate, and high RS was different in TAILORx versus NSABP B-20. The NSABP-B20 was the first trial to validate the 21-gene assay both as a prognostic and as a predictive tool and identified RS cutoffs to predict the magnitude of chemotherapy benefit in patients with node-negative, HR-positive breast cancer.[7]

21-Gene Assay (Oncotype DX) in Node-Positive, HR-Positive, HER2-Negative Disease

In the West German Plan B study, patients (n=110) with node-positive, HR-positive, HER2-negative tumors, and an RS of ≤11 were found to have a 5-year DFS of 94.4% when treated with endocrine therapy alone.[107] In a secondary analysis of a prospective registry of patients with HR-positive, HER2-negative, node-positive tumors, the 5-year risk of distant recurrence in patients with an RS of <18 treated with endocrine therapy alone was 2.7%.[108] These results suggest that in patients with limited nodal disease (1–3 positive lymph nodes) and a low RS, the absolute benefit from chemotherapy is likely to be very small.[108,109]

There is a clear benefit from adjuvant chemotherapy in patients with node positive, HR-positive, HER2-negative tumors, if the RS is high (≥31). In a secondary analysis of the SWOG 8814 trial of patients with HR-positive, node-positive tumors, high RS (≥31) was predictive of chemotherapy benefit. This study evaluated breast cancer specimens from postmenopausal patients with node-positive, HR-positive disease (n=367) randomized to endocrine therapy with tamoxifen alone or chemotherapy with CAF (cyclophosphamide, doxorubicin hydrochloride [Adriamycin], and fluorouracil) followed by tamoxifen.[103] Compared with tamoxifen alone, treatment with CAF among patients with a high RS (≥31) resulted in improved 10-year DFS (55% vs 43%; HR, 0.59; 95% CI, 0.35–1.01) and OS (73% vs 54%; HR, 0.56; 95% CI 0.31–1.02).[103]

The Southwest Oncology Group (SWOG) S1007 RxPONDER trial (ClinicalTrials.gov identifier: NCT01272037) assigned patients with 1 to 3 node-positive, HR-positive, HER2-negative breast cancer and an RS ≤25 to standard endocrine therapy with or without adjuvant chemotherapy. The results showed that the addition of adjuvant chemotherapy to endocrine therapy improved invasive DFS among premenopausal—but not postmenopausal—women with HR-positive, HER2-negative, node-positive breast cancer and a 21-gene assay RS up to 25.[110]

70-Gene Assay (MammaPrint)

Results from the randomized MINDACT trial[111] demonstrated that the 70-gene assay can identify a subset of patients who have a low likelihood of distant recurrence despite high-risk clinical features (based on tumor size, grade, nodal status). In this trial, 79% had node-negative disease and 21% had 1 to 3 positive lymph nodes and all patients underwent risk assessment by clinical criteria (using Adjuvant! Online) and genomic risk assessment by the 70-gene assay.

Patients with low-risk disease according to both clinical criteria and genomic assay results did not receive adjuvant chemotherapy, whereas patients categorized as high risk by both assessments received chemotherapy. Patients with discordant results (ie, either high clinical risk/low genomic risk or low clinical risk/high genomic risk) were randomized to the chemotherapy group or the no-chemotherapy group on the basis of either the clinical result or the genomic result. The primary outcome of the study was met with the demonstration that among those with high clinical risk/low genomic risk, the 5-year rate of survival without distant metastasis in those did not receive adjuvant chemotherapy was 94.7% (95% CI, 92.5–96.2).[111]

In the intention-to-treat population, among patients at high clinical risk/low genomic risk by the 70-gene assay, the 5-year rate of survival with no distant metastasis in those who received chemotherapy was 95.9% (95% CI, 94.0–97.2) versus 94.4% (95% CI, 92.3–95.9) in those who did not receive chemotherapy (adjusted HR for distant metastasis or death with chemotherapy vs no chemotherapy 0.78; 95% CI, 0.50–1.21).[111] Among patients at low clinical risk/high genomic risk, 5-year survival with no distant metastasis was 95.8% with chemotherapy (95% CI, 92.9–97.6), compared with a rate of 95.0% (95% CI, 91.8%–97.0%) without chemotherapy (adjusted HR for distant metastasis or death with chemotherapy vs no chemotherapy, 1.17; 95% CI, 0.59–2.28). These data suggest that the results of the 70-gene signature do not provide evidence for making recommendations regarding chemotherapy for patients at low clinical risk.[111]

In a subgroup analysis by nodal status, among node-negative patients with high clinical risk/low genomic risk, the 5-year rate of survival with no distant metastasis was 95.7% (95% CI, 93.0–97.4) in those who received adjuvant chemotherapy compared with 93.2% (95% CI, 90.1–95.4) in those who did not receive chemotherapy.[111] Among patients with 1 to 3 positive lymph nodes, the rates of survival without distant metastases were 96.3% (95% CI, 93.1–98.1) in those who received adjuvant chemotherapy versus 95.6 (95% CI, 92.7–97.4) in those who did not receive adjuvant chemotherapy.[111] These data suggest that the additional benefit of adjuvant chemotherapy in patients with high clinical risk/low genomic risk is likely to be small.

50-Gene Assay (PAM50)

The 50-gene assay (PAM-50) risk of recurrence (ROR) score stratifies patients with HR-positive disease into high-, medium-, and low-risk groups. Several studies have shown the prognostic value of ROR score in estimating risk of disease recurrence.[112–114]

In a study from the Danish Breast Cancer Cooperative Group database, patients with node-negative tumors and low ROR had a distant recurrence risk of 5.0% (95% CI, 2.9%–8.0%) whereas tumors with high ROR had a distant recurrence risk of 17.8% (95% CI, 14.0%–22.0%).[113] Based on these analyses, patients with T1 and T2, HR-positive, HER2-negative, node-negative tumors, a ROR score in the low range, regardless of tumor size, places the individual into the same prognostic category as those with T1a–T1b, N0, M0 tumors.[113]

In patients with 1 to 3 node-positive, HR-positive, HER2-negative disease with low ROR score, the distant recurrence risk was less than 3.5% at 10 years with endocrine therapy alone.[113] In TransATAC study, no distant recurrence was seen at 10 years in a similar group.[114]

12-Gene Assay (EndoPredict)

This assay uses 12 genes to calculate a prognostic score. This assay appears to be useful in identifying a subgroup of patients with ER-positive, HER2-negative tumors with very low risk of recurrence without adjuvant chemotherapy and helpful in identifying patients at low risk for a late recurrence.[115] Based on results of 2 Austrian Breast Cancer Study Group trials-ABCSG-6 and ABCSG-8, patients with HR-positive, HER2-negative, and node-negative disease with a low-risk score by the 12-gene assay had risk of distant recurrence of 4% at 10 years.[115] The prognostic value of the risk score from the 12-gene assay was found to be independent of conventional clinicopathological factors. Patients with T1 and T2 HR-positive, HER2-negative, and node-negative tumors, a 12-gene low-risk score, regardless of T size, places the tumor into the same prognostic category as T1a–T1b, N0, M0.

In TransATAC study, patients with 1 to 3 positive nodes in the low-risk group had a 5.6% risk of distant recurrence at 10 years,[114] suggesting that chemotherapy would be of limited benefit in these patients.

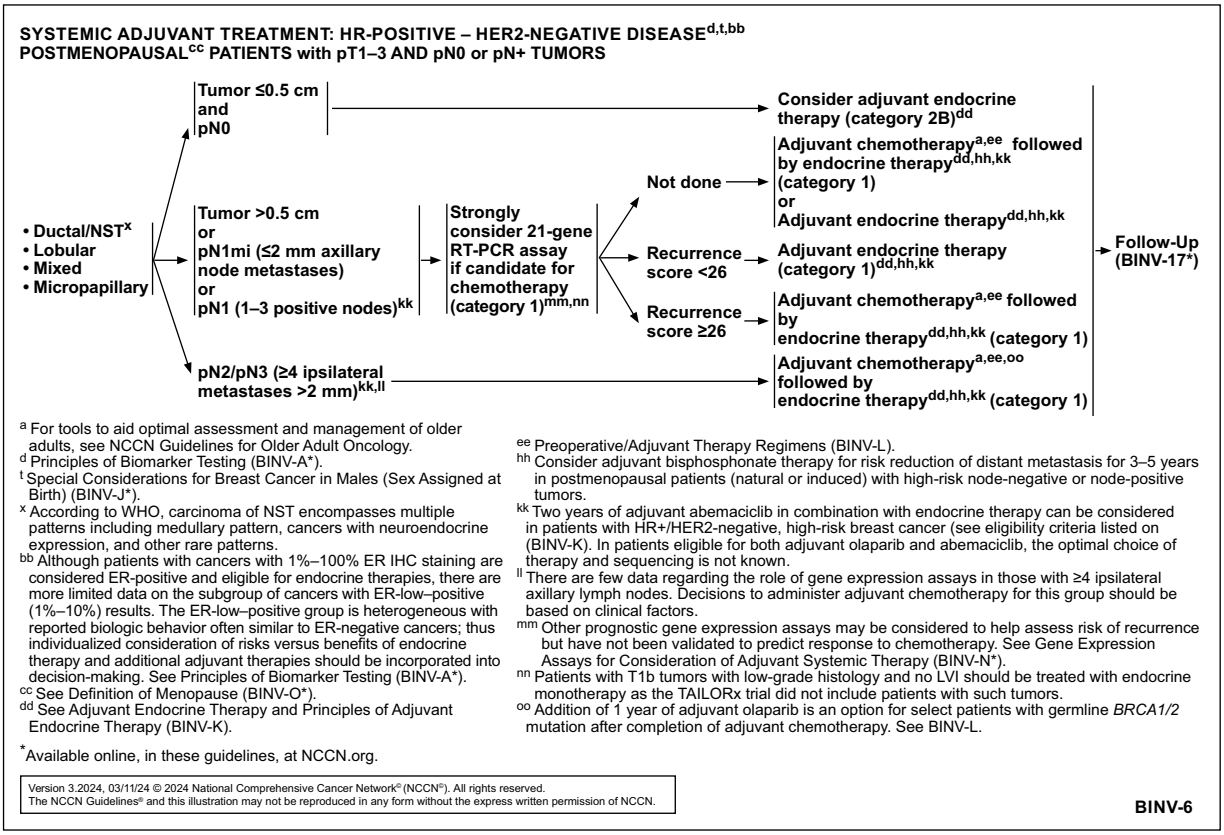
Breast Cancer Index

The Breast Cancer Index (BCI) is a combination of 2 profiles, the HOXB13-to-IL17BR expression ratio (H:I ratio) and the molecular grade index. Compared with clinical prognostic factors (eg, age, tumor size, tumor grade, and lymph node status), the H:I ratio has been shown to be prognostic in the setting of adjuvant tamoxifen monotherapy.[115,116] The addition of the molecular grade index to H:I was determined to provide additional prognostic discrimination, leading to the BCI assay.[116] In a secondary analysis of the ATAC trial, BCI was prognostic in node-negative breast cancer for both early (years 0–5) and late (years 5–10) distant recurrence.[117] For patients with T1 and T2 HR-positive, HER2-negative, and node-negative tumors, a BCI in the low-risk range, regardless of T size, places the tumor into the same prognostic category as T1a-T1b, N0, M0. Secondary analyses of the MA.17, TransaTTom, and IDEAL trials showed that in patients with HR-positive T1–T3 tumors that are lymph-node negative or positive, those that had a high BCI (H:I) demonstrated significant improvements in DFS when adjuvant endocrine therapy was extended, compared with the control arm.[118–120] Considering the ability of the multigene assays to predict benefit of adjuvant systemic chemotherapy and ability to determine prognosis by predicting risk of distant recurrence, the NCCN panel has summarized the treatment implications based on risk scores and nodal status.

Multigene Assays for Axillary Lymph Node–Negative HR-Positive, HER2-Negative Tumors

Small tumors (up to 0.5 cm in greatest diameter) that do not involve the lymph nodes have a favorable prognosis, so adjuvant chemotherapy is not recommended. According to the NCCN panel, adjuvant endocrine therapy may be considered in this group of patients to reduce the risk for a second contralateral breast cancer, as well as the small benefit in reducing the risk of local/regional and distant recurrence (category 2B).

For patients with invasive ductal or lobular tumors greater than 0.5 cm in diameter and no lymph node involvement (node-negative), the NCCN panel recommends strongly considering



[a] For tools to aid optimal assessment and management of older adults, see NCCN Guidelines for Older Adult Oncology.
[d] Principles of Biomarker Testing (BINV-A*).
[t] Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J*).
[x] According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.
[bb] Although patients with cancers with 1%–100% ER IHC staining are considered ER-positive and eligible for endocrine therapies, there are more limited data on the subgroup of cancers with ER-low–positive (1%–10%) results. The ER-low–positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers; thus individualized consideration of risks versus benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making. See Principles of Biomarker Testing (BINV-A*).
[cc] See Definition of Menopause (BINV-O*).
[dd] See Adjuvant Endocrine Therapy and Principles of Adjuvant Endocrine Therapy (BINV-K).
[ee] Preoperative/Adjuvant Therapy Regimens (BINV-L).
[hh] Consider adjuvant bisphosphonate therapy for risk reduction of distant metastasis for 3–5 years in postmenopausal patients (natural or induced) with high-risk node-negative or node-positive tumors.
[kk] Two years of adjuvant abemaciclib in combination with endocrine therapy can be considered in patients with HR+/HER2-negative, high-risk breast cancer (see eligibility criteria listed on (BINV-K). In patients eligible for both adjuvant olaparib and abemaciclib, the optimal choice of therapy and sequencing is not known.
[ll] There are few data regarding the role of gene expression assays in those with ≥4 ipsilateral axillary lymph nodes. Decisions to administer adjuvant chemotherapy for this group should be based on clinical factors.
[mm] Other prognostic gene expression assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy. See Gene Expression Assays for Consideration of Adjuvant Systemic Therapy (BINV-N*).
[nn] Patients with T1b tumors with low-grade histology and no LVI should be treated with endocrine monotherapy as the TAILORx trial did not include patients with such tumors.
[oo] Addition of 1 year of adjuvant olaparib is an option for select patients with germline *BRCA1/2* mutation after completion of adjuvant chemotherapy. See BINV-L.
*Available online, in these guidelines, at NCCN.org.

BINV-6

Figure 6. BINV-6. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer, Version 3.2024.

the 21-gene reverse transcriptase–polymerase chain reaction assay to help estimate likelihood of recurrence *and* benefit from chemotherapy (category 1). The panel has noted that on an exploratory analysis from the TAILORx study,[106] adjuvant chemotherapy may be considered in patients 50 years of age or younger with a 21-gene RS of 16 to 25. Also, patients with T1b tumors with low-grade histology should be considered for endocrine monotherapy, as the TAILORx study[106] did not include patients with such tumors.

The panel notes that other prognostic multigene assays may be considered to help estimate risk of recurrence, but these assays have not been validated to predict the benefit of systemic chemotherapy. Also, among the other assays, the panel has listed the 70-gene assay as a category 1 option based on the results of the prospective MINDACT[111] trial demonstrating the ability of the 70-gene assay to identify a good genomic risk population despite a high clinical risk, in whom chemotherapy may be omitted without a detrimental effect. High clinical risk in the MINDACT trial was defined for grade 1 tumors as >3 cm N0 or T2N1, for grade 2 tumors T2N0–1, and for grade 3 tumors T1c–2N0–1.

Furthermore, given no difference in outcomes with or without chemotherapy in the discordant low clinical risk/high genomic risk group, the MINDACT study suggests that the 70-gene panel is not useful guiding systemic chemotherapy decisions in this subgroup of patients.

Since results of different assays may not be concordant with each other and these assays have not been compared head-to-head prospectively, clinicians should only order one of the available assays for a specific patient and tumor.

Multigene Assays for Axillary Lymph Node–Positive HR-Positive, HER2-Negative Tumors

For patients with 4 or more involved nodes, the panel recommends systemic adjuvant chemotherapy followed by endocrine therapy (category 1).

Patients with fewer than 4 involved nodes or with pN1mi and less than or equal to 2 mm axillary node metastasis are most often candidates for chemotherapy in addition to endocrine therapy. The panel recommends that clinical decision making for adjuvant chemotherapy be based on elements of clinical risk stratification such as clinical characteristics, tumor stage, pathology, and comorbid conditions. If the patient is not a candidate for chemotherapy, the panel recommends adjuvant endocrine therapy alone (category 2A).

For those who are candidates for systemic adjuvant chemotherapy based on clinical characteristics, tumor stage, and pathology, the panel recommends consideration of multigene assays to assess prognosis as a tool to assist with treatment decision making. The panel notes in those with N1mi and N1 tumors, while multigene assays have yet to be proven to be predictive for adjuvant chemotherapy benefit, they are prognostic and can be used to identify low-risk patients who are likely to derive little or no absolute benefit from addition of adjuvant chemotherapy to adjuvant endocrine therapy. A secondary analysis of the prospective SWOG 8814 trial using the 21-gene assay demonstrated no benefit for chemotherapy for patients with 1 to 3 involved axillary lymph nodes and a low RS, and a significant benefit for the addition of adjuvant chemotherapy in those with high RS (≥31).[103] The phase III RxPONDER trial prospectively demonstrated that

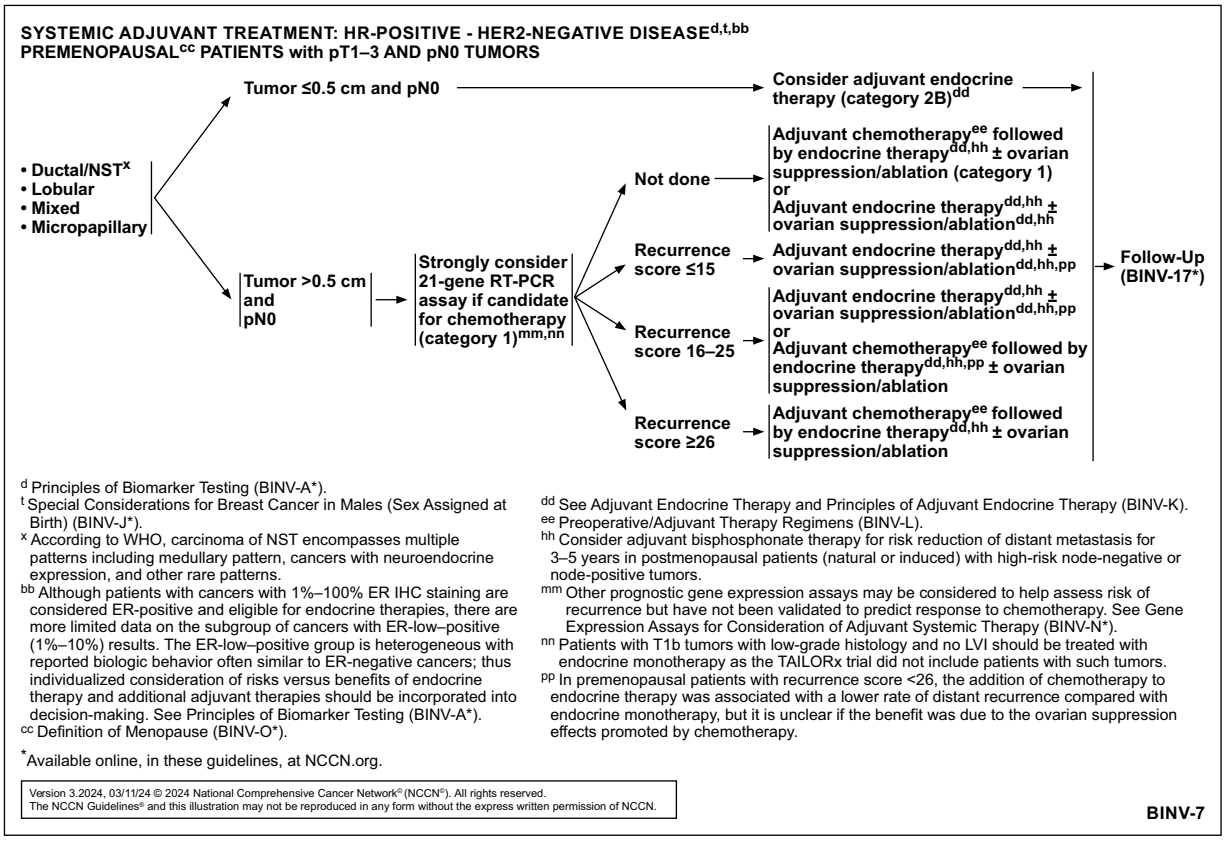


Figure 7. BINV-7. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer, Version 3.2024.

for premenopausal patients with HR-positive, HER2-negative, node-positive breast cancer, a 21-gene assay RS up to 25 had an addition benefit of adjuvant chemotherapy to endocrine therapy for improving invasive DFS.[110] In the MINDACT trial, among patients with 1 to 3 positive nodes who had a high clinical risk of recurrence but low risk by the 70-gene assay, the rates of survival were similar between those who received adjuvant chemotherapy in addition to adjuvant endocrine therapy versus those received adjuvant endocrine therapy alone, suggesting that chemotherapy could be omitted in this group.[111] Other multigene assays have not proven to be predictive of benefit from chemotherapy.

For those who are candidates for systemic adjuvant chemotherapy based on clinical characteristics, tumor stage, and pathology, if multigene assay is not available, the panel recommends systemic adjuvant chemotherapy followed by endocrine therapy (category 1).

Adjuvant Targeted Therapies for HR-Positive, HER2-Negative Tumors

Adjuvant therapies are rapidly evolving, and cyclin-dependent kinase (CDK) 4/6 inhibitors and poly-ADP ribose polymerase inhibitors are now indicated in this setting (Figures 5–9).

Adjuvant CDK 4/6 Inhibitors

In the MonarchE study, the addition of 2 years of abemaciclib to endocrine therapy reduced the absolute risk of recurrence at 4 years by 6.4% (HR, 0.664; 95% CI, 0.578–0.762; $P<.0001$) in patients with HR-positive/HER2-negative, high-risk breast cancer, defined as 4 or more pathologically involved lymph nodes confirmed preoperatively and/or at surgery, or 1 to 3 pathologically involved lymph nodes with additional high-risk features (grade 3 or size ≥5 cm based on preoperative imaging and/or pathologically at surgery).[121]

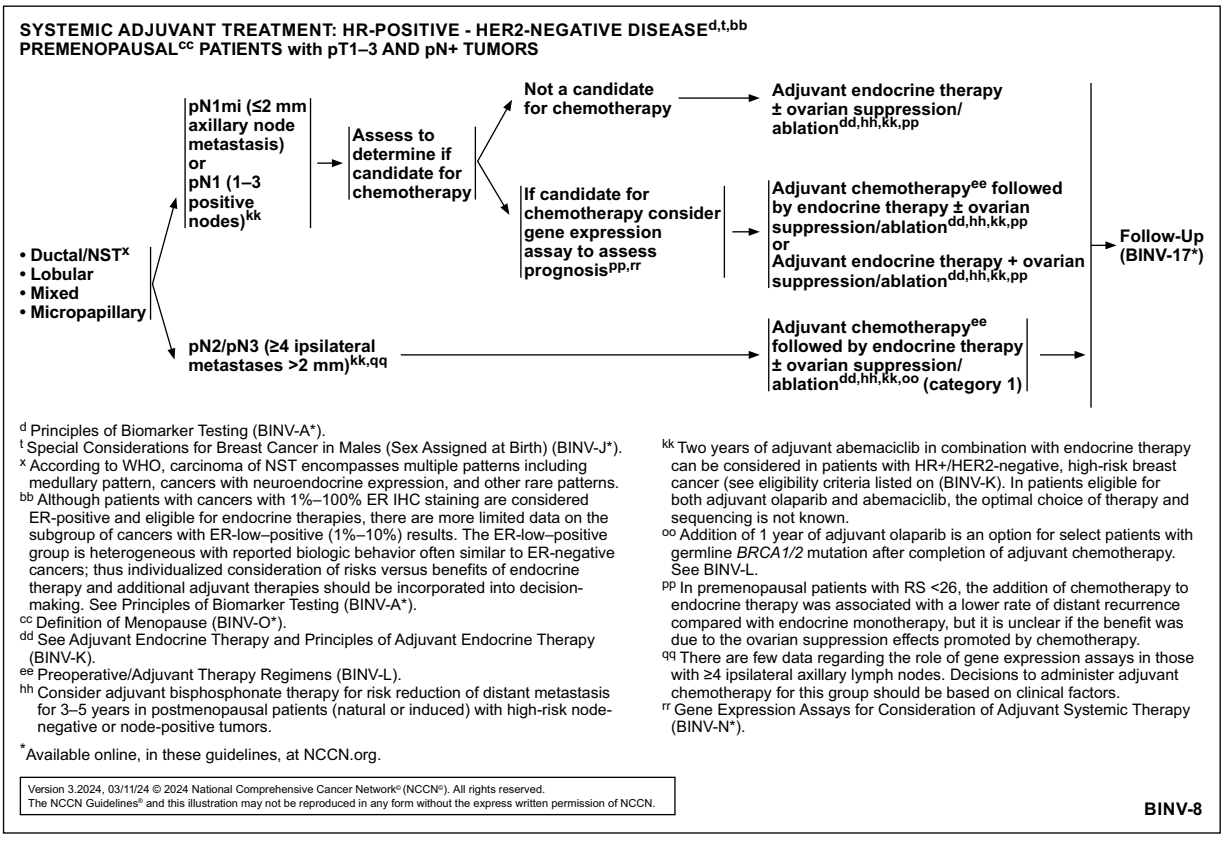
Two trials of palbociclib as adjuvant therapy in HR-positive, HER2-negative early breast cancer did not show benefit of adding palbociclib to adjuvant endocrine therapy in terms of invasive DFS.[122,123]

The results from the NATALEE trial reported after a median follow-up of 34 months, showed a statistically significant improvement (3.3%) in invasive DFS with the addition of ribociclib to adjuvant endocrine therapy (HR, 0.75; 95% CI, 0.62–0.91; $P=.003$) for stage II and stage III HR-positive, HER2-negative breast cancer.[124] Additional follow-up is needed to characterize the long-term efficacy of ribociclib in this setting.

According to the current guidelines, 2 years of adjuvant CDK 4/6 therapy with abemaciclib should be considered in combination with endocrine therapy in patients with HR-positive/HER2-negative, high-risk breast cancer (as detailed previously). This is a category 1, preferred option for this setting.

Adjuvant Olaparib

In patients with germline *BRCA* 1/2 mutations and high-risk HER2-negative tumors, the results of the OlympiA trial showed that the 4-year OS in the group that received 1 year of adjuvant olaparib was 89.8% and 86.4% in the placebo group (95% CI,



[d] Principles of Biomarker Testing (BINV-A*).
[t] Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J*).
[x] According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.
[bb] Although patients with cancers with 1%–100% ER IHC staining are considered ER-positive and eligible for endocrine therapies, there are more limited data on the subgroup of cancers with ER-low–positive (1%–10%) results. The ER-low–positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers; thus individualized consideration of risks versus benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making. See Principles of Biomarker Testing (BINV-A*).
[cc] Definition of Menopause (BINV-O*).
[dd] See Adjuvant Endocrine Therapy and Principles of Adjuvant Endocrine Therapy (BINV-K).
[ee] Preoperative/Adjuvant Therapy Regimens (BINV-L).
[hh] Consider adjuvant bisphosphonate therapy for risk reduction of distant metastasis for 3–5 years in postmenopausal patients (natural or induced) with high-risk node-negative or node-positive tumors.
[kk] Two years of adjuvant abemaciclib in combination with endocrine therapy can be considered in patients with HR+/HER2-negative, high-risk breast cancer (see eligibility criteria listed on (BINV-K). In patients eligible for both adjuvant olaparib and abemaciclib, the optimal choice of therapy and sequencing is not known.
[oo] Addition of 1 year of adjuvant olaparib is an option for select patients with germline *BRCA1/2* mutation after completion of adjuvant chemotherapy. See BINV-L.
[pp] In premenopausal patients with RS <26, the addition of chemotherapy to endocrine therapy was associated with a lower rate of distant recurrence compared with endocrine monotherapy, but it is unclear if the benefit was due to the ovarian suppression effects promoted by chemotherapy.
[qq] There are few data regarding the role of gene expression assays in those with ≥4 ipsilateral axillary lymph nodes. Decisions to administer adjuvant chemotherapy for this group should be based on clinical factors.
[rr] Gene Expression Assays for Consideration of Adjuvant Systemic Therapy (BINV-N*).
*Available online, in these guidelines, at NCCN.org.

BINV-8

Figure 8. BINV-8. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer, Version 3.2024.

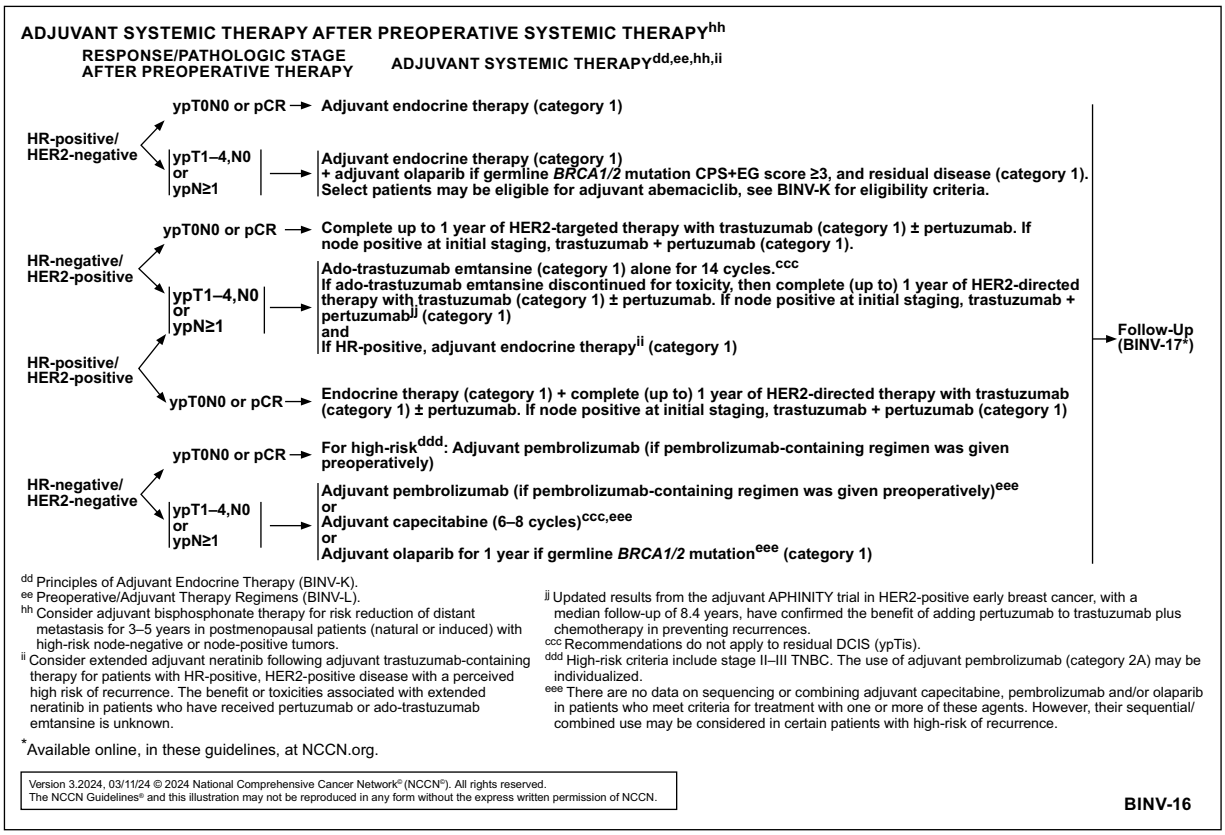


Figure 9. BINV-16. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer, Version 3.2024.

−0.1% to −6.8%). The 4-year invasive DFS for the olaparib group versus placebo group was 82.7% versus 75.4% (95% CI, 3.0%–11.5%) and 4-year distant DFS was 86.5% versus 79.1% (95% CI, 3.6%–11.3%).[125]

According to the NCCN panel, addition of adjuvant olaparib for 1 year may be considered for those with germline *BRCA* 1/2 mutations in patients with HR-positive, HER2-negative tumors with ≥4 positive lymph nodes after adjuvant chemotherapy or residual disease after preoperative therapy and a clinical stage, pathologic stage, ER status, and tumor grade (CPS+EG) score ≥3 (category 2A).

Adjuvant olaparib may be used concurrently with endocrine therapy.

In patients eligible for both adjuvant olaparib and abemaciclib, the optimal sequencing is not known. (For sequencing of olaparib and/or abemaciclib with radiotherapy [RT], see page BINV-I, available in these guidelines at NCCN.org).

Adjuvant Bisphosphonate Therapy

Antiresorptive agents (bisphosphonates and denosumab) have an established role as preventative and therapeutic agents for the management of osteoporosis, hypercalcemia of malignancy, and bone metastases.

Bisphosphonates

In the Austrian Breast and Colorectal Cancer Study Group trial-12 (ABCSG-12) trial, for patients older than 40 years, zoledronic acid significantly reduced the risk of recurrence by 34% (HR, 0.66; P=.014) and the risk of death by 49% (HR, 0.51; P=.020). However, no improvement was seen in either DFS or OS in this post hoc analysis among patients younger than 40 years.[126] In a planned subgroup analysis of the AZURE trial, zoledronic acid improved DFS in patients who were more than 5 years since menopause at trial entry.[127] A meta-analysis of data from 7 adjuvant bisphosphonate trials (AZURE, ABCSG-12, ZO-FAST, Z-FAST, EZO-FAST, NSABP-B34, GAIN), including for only patients known to be older than 50 years, postmenopausal, or with ovarian suppression, showed a significant benefit for the use of adjuvant bisphosphonates in patients with a low-estrogen state and early-stage breast cancer.[128] More recently, the Early Breast Cancer Trialists' Collaborative Group (EBTCG) conducted a meta-analysis of all randomized adjuvant bisphosphonate studies (26 studies) and reported convincing evidence that adjuvant bisphosphonates provide benefits to postmenopausal (natural or induced) patients with breast cancer.[129] With bisphosphonate therapy, the greatest improvement was seen in bone recurrence (RR, 0.83; P=.004) and bone fractures (RR, 0.85; P=.02). No effect was seen on distant recurrence outside bone (RR, 0.98; P=.69).[129] In premenopausal patients, bisphosphonate therapy did not seem to have a significant effect on bone recurrence. However, in postmenopausal patients, zoledronic acid significantly reduced bone recurrence (3.4% vs 4.5%; RR, 0.73; 99% CI, 0.53–1.00); the difference in breast cancer mortality was not statistically significant (7.1% vs 7.9%; RR, 0.88; 99% CI, 0.69–1.11).[129]

Denosumab

In the adjuvant setting, the ABCSG-18 trial studied the effect of denosumab in postmenopausal patients treated with adjuvant

AIs and showed a reduction in clinical fractures (HR, 0.5; $P<.0001$), which was the primary endpoint of this study.[130] The final analysis after a median follow-up of 8 years continued to show a benefit with denosumab. Adjuvant denosumab improved bone metastasis-free survival (88.9% vs 86.4%; HR, 0.81; 95% CI, 0.65–1.00) and OS (90.9% vs 89.9%; HR, 0.80; 95% CI, 0.64–1.01).[131] In contrast, results of the phase III trial (D-Care) failed to demonstrate a difference in bone metastasis-free survival in those receiving denosumab versus placebo.[132]

Due to these conflicting results from phase III trials, denosumab is currently not recommended in the adjuvant setting.[131] The panel recommends considering adjuvant bisphosphonate therapy for risk reduction of distant metastasis for 3 to 5 years in patients with high-risk node-negative or node-positive tumors.

Adjuvant Therapy for HER2-Negative Tumors

Several combination chemotherapy regimens are appropriate to consider for HR-positive or HR-negative and HER2-negative tumors. All adjuvant chemotherapy regimens listed in the NCCN Guidelines have been evaluated in phase III clinical trials and are category 1 unless otherwise noted (Figures 6, 8, 10–13).

Preferred Regimens

Regimens listed as preferred include dose-dense doxorubicin and cyclophosphamide (AC) followed or preceded by paclitaxel either weekly or biweekly; docetaxel plus cyclophosphamide (TC); olaparib for germline *BRCA*1/2 mutations; pembrolizumab for high-risk ER-negative disease; and capecitabine for residual ER-negative disease after preoperative chemotherapy.

Meta-analysis from the Early Breast Cancer Trialists' Collaborative Group has shown that anthracycline and taxane-based combination chemotherapy reduces the risk of breast cancer mortality compared with no chemotherapy. The use of dose-dense schedules has shown to further reduce the risk of breast cancer recurrence or death without increasing mortality.[133]

The results of 2 randomized trials comparing AC chemotherapy with or without sequential paclitaxel chemotherapy in patients with axillary node-positive breast cancer suggest improved disease-free rates and results from one of the trials showed an improvement in OS with the addition of paclitaxel.[134,135] On retrospective analysis, the apparent advantage of the paclitaxel-containing regimen appears greater in patients with ER-negative breast cancers.

A randomized trial evaluated the use of concurrent versus sequential chemotherapy (doxorubicin followed by paclitaxel followed by cyclophosphamide vs doxorubicin plus cyclophosphamide followed by paclitaxel) given either every 2 weeks with filgrastim support or every 3 weeks. The results show no significant difference between the 2 chemotherapy regimens but demonstrate a 26% reduction in hazard of recurrence ($P=.01$) and a 31% reduction in the hazard of death ($P=.013$) for the dose-dense regimens.[136]

The ECOG E1199 study was a 4-arm trial that randomized 4,950 patients to receive AC chemotherapy followed by either paclitaxel or docetaxel given by either an every-3-week schedule or a weekly schedule.[137] In a secondary series of comparisons,

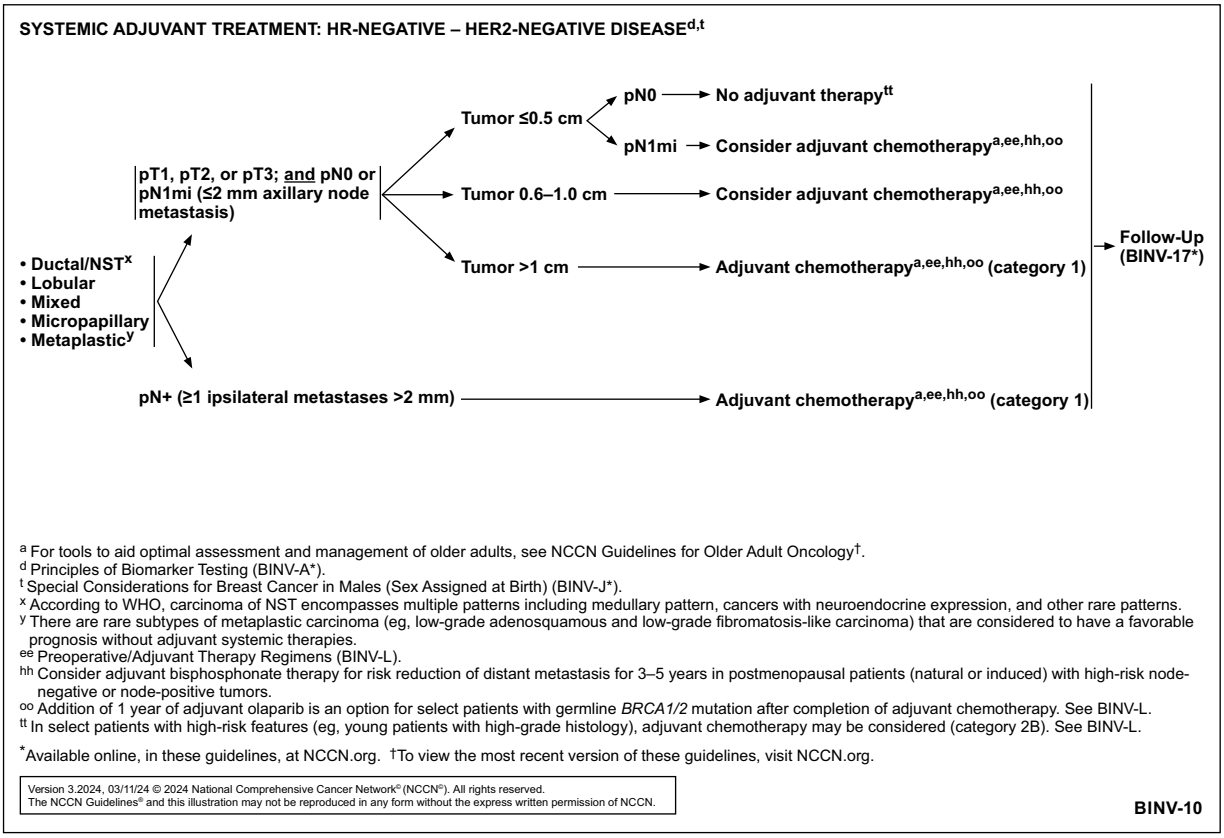
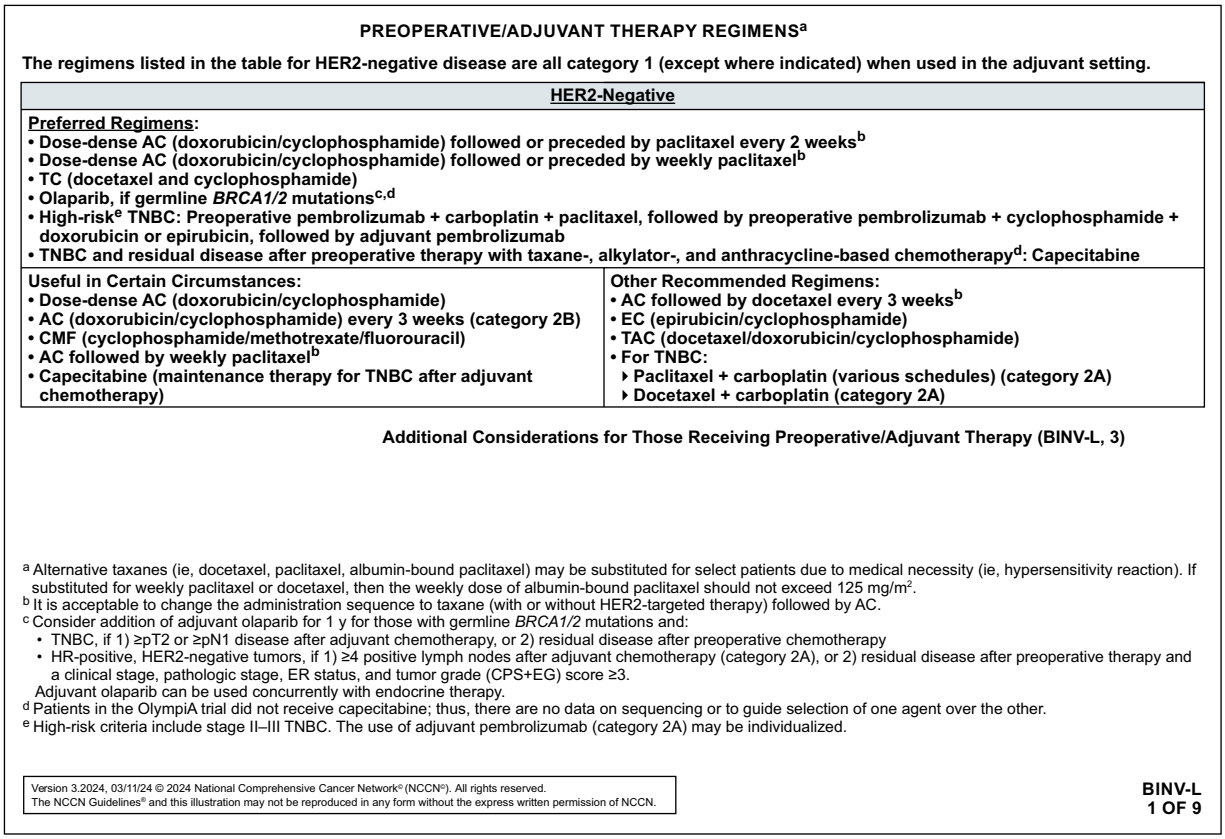


Figure 10. BINV-10. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer, Version 3.2024.



PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a]

The regimens listed in the table for HER2-negative disease are all category 1 (except where indicated) when used in the adjuvant setting.

HER2-Negative

Preferred Regimens:
- **Dose-dense AC (doxorubicin/cyclophosphamide) followed or preceded by paclitaxel every 2 weeks[b]**
- **Dose-dense AC (doxorubicin/cyclophosphamide) followed or preceded by weekly paclitaxel[b]**
- **TC (docetaxel and cyclophosphamide)**
- **Olaparib, if germline *BRCA1/2* mutations[c,d]**
- **High-risk[e] TNBC: Preoperative pembrolizumab + carboplatin + paclitaxel, followed by preoperative pembrolizumab + cyclophosphamide + doxorubicin or epirubicin, followed by adjuvant pembrolizumab**
- **TNBC and residual disease after preoperative therapy with taxane-, alkylator-, and anthracycline-based chemotherapy[d]: Capecitabine**

Useful in Certain Circumstances:
- **Dose-dense AC (doxorubicin/cyclophosphamide)**
- **AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B)**
- **CMF (cyclophosphamide/methotrexate/fluorouracil)**
- **AC followed by weekly paclitaxel[b]**
- **Capecitabine (maintenance therapy for TNBC after adjuvant chemotherapy)**

Other Recommended Regimens:
- **AC followed by docetaxel every 3 weeks[b]**
- **EC (epirubicin/cyclophosphamide)**
- **TAC (docetaxel/doxorubicin/cyclophosphamide)**
- **For TNBC:**
  - **Paclitaxel + carboplatin (various schedules) (category 2A)**
  - **Docetaxel + carboplatin (category 2A)**

Additional Considerations for Those Receiving Preoperative/Adjuvant Therapy (BINV-L, 3)

[a] Alternative taxanes (ie, docetaxel, paclitaxel, albumin-bound paclitaxel) may be substituted for select patients due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of albumin-bound paclitaxel should not exceed 125 mg/m^2.
[b] It is acceptable to change the administration sequence to taxane (with or without HER2-targeted therapy) followed by AC.
[c] Consider addition of adjuvant olaparib for 1 y for those with germline *BRCA1/2* mutations and:
- TNBC, if 1) ≥pT2 or ≥pN1 disease after adjuvant chemotherapy, or 2) residual disease after preoperative chemotherapy
- HR-positive, HER2-negative tumors, if 1) ≥4 positive lymph nodes after adjuvant chemotherapy (category 2A), or 2) residual disease after preoperative therapy and a clinical stage, pathologic stage, ER status, and tumor grade (CPS+EG) score ≥3.

Adjuvant olaparib can be used concurrently with endocrine therapy.
[d] Patients in the OlympiA trial did not receive capecitabine; thus, there are no data on sequencing or to guide selection of one agent over the other.
[e] High-risk criteria include stage II–III TNBC. The use of adjuvant pembrolizumab (category 2A) may be individualized.

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Figure 11. BINV-L 1 of 9. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer, Version 3.2024.

weekly paclitaxel was superior to every-3-week paclitaxel in DFS (HR, 1.27; 95% CI, 1.03–1.57; P=.006) and OS (HR, 1.32; 95% CI, 1.02–1.72; P=.01), and every-3-week docetaxel was superior to every-3-week paclitaxel in DFS (HR, 1.23; 95% CI, 1.00–1.52; P=.02) but not in OS.[137] Based on these results and the findings from the CALGB 9741 trial that showed dose-dense AC followed by paclitaxel every 2 weeks to have a survival benefit when compared with the regimen of AC followed by every-3-week paclitaxel,[136] the every-3-week paclitaxel regimen has been removed from the guidelines.

Combination TC was compared with AC chemotherapy in a trial that randomized 1,016 patients with stage I–III breast cancer.[138] At a median follow-up of 7 years, overall DFS (81% vs 75%; HR, 0.74; 95% CI, 0.56–0.98; P=.033) and OS (87% vs 82%; HR, 0.69; 95% CI, 0.50–0.97; P=.032) were significantly improved with TC compared with AC. Nonanthracycline, taxane-based regimens such as TC may be preferred options in patients for whom anthracyclines are contraindicated.

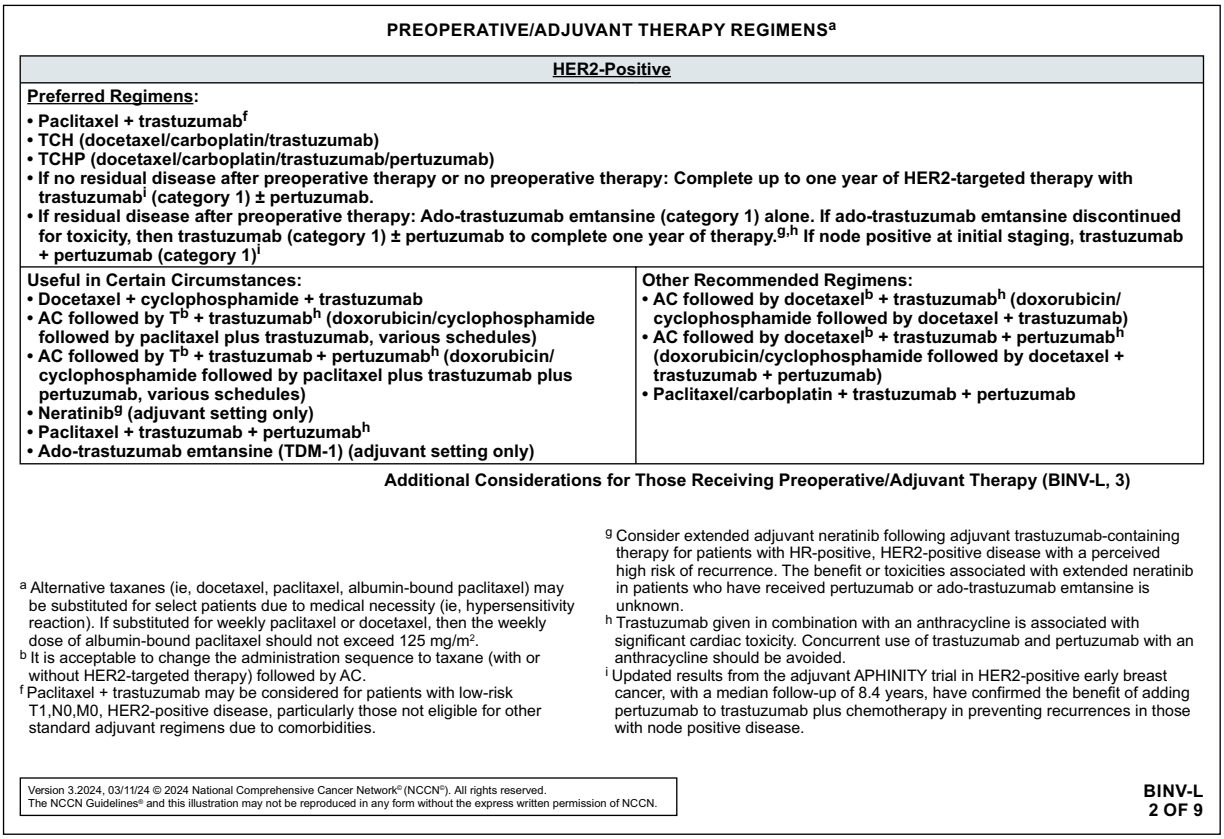
Residual disease after preoperative systemic therapy indicates higher risk (20%–30%) of disease relapse.[9,139] CREATE-X, a multicenter, open-label, randomized phase III trial evaluated the efficacy and safety of adjuvant capecitabine in patients with HER2-negative primary breast cancer who had residual invasive disease after standard (anthracycline and/or taxane-based) preoperative chemotherapy. The results showed improved DFS (HR, 0.70; 95% CI, 0.53–0.92; P=.01) and OS (HR for death, 0.59; 95% CI, 0.39–0.90; P=.01) with adjuvant capecitabine. The OS was higher in those with TNBC (HR for death, 0.52). Results of 2 other similar trials with adjuvant capecitabine have showed a similar impact with adjuvant capecitabine in patients with TNBC with no significant impact in those with HR-positive disease.[140,141] Based on these trial results, the NCCN panel has included adjuvant capecitabine as an adjuvant therapy option for those with TNBC and residual disease after preoperative therapy. For those with germline *BRCA* 1/2 mutations and TNBC, according to the NCCN panel, based on the results of the OlympiA trial (discussed in the sections on adjuvant therapy for HR-positive, HER2-negative disease) adjuvant olaparib for 1 year may be considered if tumors ≥ pT2 or ≥ pN1 disease after adjuvant chemotherapy or in those with residual disease after preoperative chemotherapy (catgeory1). Patients in the OlympiA trial did not receive capecitabine; thus, no data are available on sequencing or to guide selection of one agent over the other. (For sequencing of capecitabine or Olaparib with RT, see BINV-I, available in these guidelines at NCCN.org)

If pembrolizumab was given in combination with chemotherapy in the preoperative setting, based on the KEYNOTE-522 trial data, the panel recommends adjuvant pembrolizumab.[27]

Other Recommended Regimens

Other recommended regimens in the guidelines include: AC; epirubicin and cyclophosphamide (EC); docetaxel, doxorubicin, and cyclophosphamide (TAC); paclitaxel and carboplatin (various schedules); and docetaxel and carboplatin.

A trial compared 2 dose levels of EC chemotherapy with CMF chemotherapy in patients with node-positive breast cancer.[142] This study showed that higher-dose EC chemotherapy



PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a]

HER2-Positive

Preferred Regimens:

- **Paclitaxel + trastuzumab[f]**
- **TCH (docetaxel/carboplatin/trastuzumab)**
- **TCHP (docetaxel/carboplatin/trastuzumab/pertuzumab)**
- **If no residual disease after preoperative therapy or no preoperative therapy: Complete up to one year of HER2-targeted therapy with trastuzumab[i] (category 1) ± pertuzumab.**
- **If residual disease after preoperative therapy: Ado-trastuzumab emtansine (category 1) alone. If ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab (category 1) ± pertuzumab to complete one year of therapy.[g,h] If node positive at initial staging, trastuzumab + pertuzumab (category 1)[i]**

Useful in Certain Circumstances:

- **Docetaxel + cyclophosphamide + trastuzumab**
- **AC followed by T[b] + trastuzumab[h] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules)**
- **AC followed by T[b] + trastuzumab + pertuzumab[h] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab plus pertuzumab, various schedules)**
- **Neratinib[g] (adjuvant setting only)**
- **Paclitaxel + trastuzumab + pertuzumab[h]**
- **Ado-trastuzumab emtansine (TDM-1) (adjuvant setting only)**

Other Recommended Regimens:

- **AC followed by docetaxel[b] + trastuzumab[h] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab)**
- **AC followed by docetaxel[b] + trastuzumab + pertuzumab[h] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab + pertuzumab)**
- **Paclitaxel/carboplatin + trastuzumab + pertuzumab**

Additional Considerations for Those Receiving Preoperative/Adjuvant Therapy (BINV-L, 3)

[a] Alternative taxanes (ie, docetaxel, paclitaxel, albumin-bound paclitaxel) may be substituted for select patients due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of albumin-bound paclitaxel should not exceed 125 mg/m^2.
[b] It is acceptable to change the administration sequence to taxane (with or without HER2-targeted therapy) followed by AC.
[f] Paclitaxel + trastuzumab may be considered for patients with low-risk T1,N0,M0, HER2-positive disease, particularly those not eligible for other standard adjuvant regimens due to comorbidities.
[g] Consider extended adjuvant neratinib following adjuvant trastuzumab-containing therapy for patients with HR-positive, HER2-positive disease with a perceived high risk of recurrence. The benefit or toxicities associated with extended neratinib in patients who have received pertuzumab or ado-trastuzumab emtansine is unknown.
[h] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.
[i] Updated results from the adjuvant APHINITY trial in HER2-positive early breast cancer, with a median follow-up of 8.4 years, have confirmed the benefit of adding pertuzumab to trastuzumab plus chemotherapy in preventing recurrences in those with node positive disease.

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Figure 12. BINV-L 2 of 9. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer, Version 3.2024.

was equivalent to CMF chemotherapy and superior to moderate-dose EC in EFS and OS.

Final results from a randomized trial of TAC versus FAC chemotherapy in node-positive breast cancer demonstrated that TAC is superior to FAC.[143] Estimated 5-year DFS was 75% with TAC and 68% with FAC (HR, 0.72; 95% CI, 0.59–0.88; P=.001); survival was 87% with TAC and 81% with FAC (HR, 0.70; 95% CI, 0.53–0.91; P=.008). DFS favored TAC in both ER-positive and ER-negative tumors. At a median follow-up of 73 months, results from the 3-arm randomized NSABP B-30 trial comparing TAC versus AT versus AC followed by docetaxel (AC followed by T) demonstrated that AC followed by T had a significant advantage in DFS (HR, 0.83; P=.006) but not in OS (HR, 0.86; P=.086) when compared with TAC. In addition, both DFS (HR, 0.080; P=.001) and OS (HR, 0.83; P=.034) were significantly increased when AC followed by T was compared with AT, with AT demonstrating noninferiority compared with TAC.[144]

Useful in Certain Circumstances

Regimens in this category include dose-dense AC; AC every 3 weeks (category 2B); CMF; AC followed by weekly paclitaxel; and capecitabine as maintenance therapy for TNBC after adjuvant chemotherapy.

The phase III E1199 trial compared patients with node-positive or high-risk node-negative breast cancer who received 4 cycles of AC every 3 weeks, followed by either paclitaxel or docetaxel, either weekly or every 3 weeks. The 10-year updated results of this trial showed that incorporation of weekly paclitaxel and docetaxel every 3 weeks was associated with significant improvements in DFS and marginal improvements in OS, compared with paclitaxel given every 3 weeks. Among patients with TNBC, the 10-year DFS rate with weekly paclitaxel was 69% and the 10-year OS rate was 75%.[145]

The AC regimen for 4 cycles has been studied in randomized trials, resulting in relapse-free survival and OS equivalent to CMF chemotherapy.[146,147] No benefit from dose escalation of either doxorubicin or cyclophosphamide was shown.[134,148] Studies of CMF chemotherapy versus no chemotherapy have shown DFS and OS advantages with CMF chemotherapy.[41,149]

Results of a randomized trial in patients with TNBC (n=434) who received standard adjuvant chemotherapy demonstrated that maintenance therapy with low-dose capecitabine (dose of 650 mg/m^2 twice a day by mouth for 1 year) improved 5-year DFS and OS. The invasive DFS in those who receive adjuvant low-dose capecitabine was 85.8% compared with 75.8% in those who did not (HR for risk of distant metastasis or death, 0.60; 95% CI, 0.38–0.92; P=.02), the estimated 5-year OS with maintenance capecitabine was 85.5% versus 81.3% (HR for risk of death, 0.75; 95% CI, 0.47–1.19; P=.22).[150]

Adjuvant Therapy for HER2-Positive Tumors

Trastuzumab-containing chemotherapy regimens followed by 1 year of HER2-targeted therapy are a backbone of adjuvant therapy for patients with HER2-positive disease (Figures 1, 2, 9, 14, and 15).

The panel recommends HER2-targeted therapy in patients with HER2-positive tumors (see "Principles of HER2 Testing," available in these guidelines at NCCN.org). Preoperative systemic

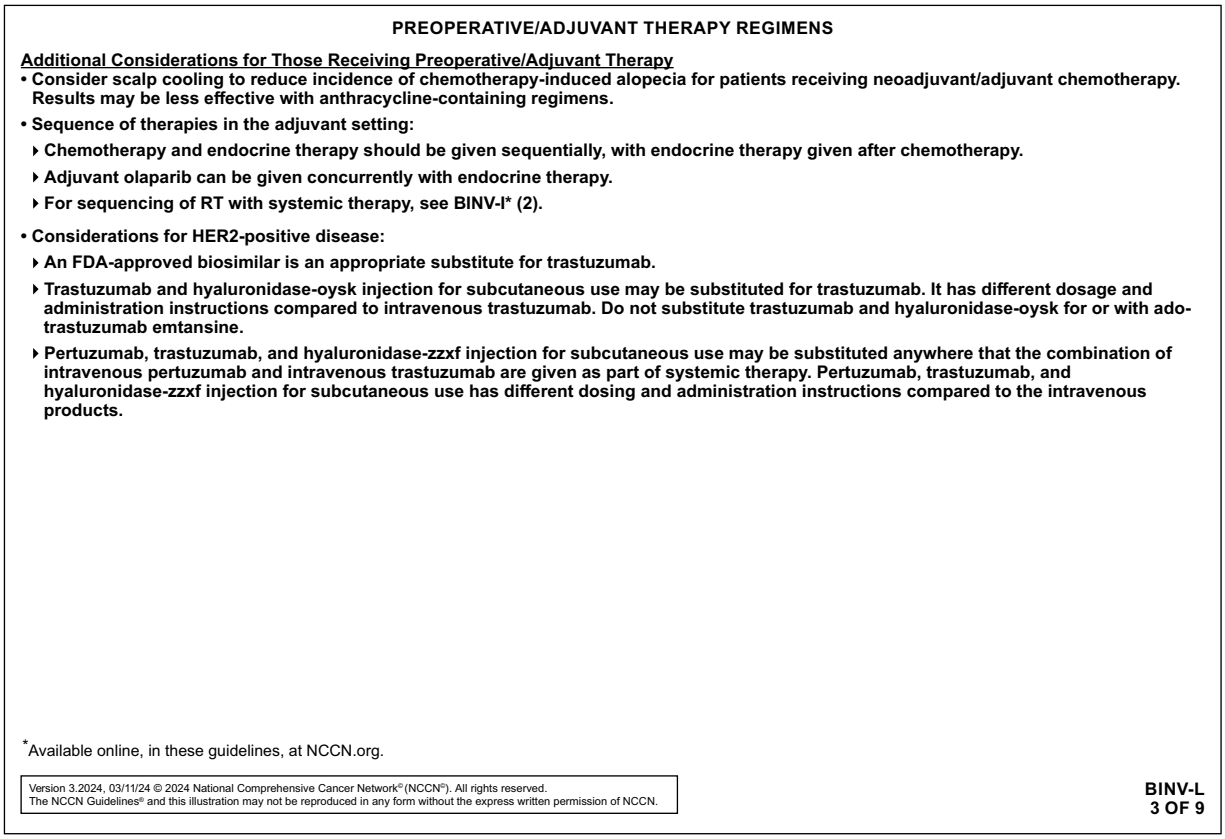

Figure 13. BINV-L 3 of 9 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer, Version 3.2024.

therapy incorporating HER2-targeted agent(s) should be considered for patients with HER2-positive disease presenting with clinical node-positive tumors or those measuring ≥2 cm (cT2) at presentation (Figures 1 and 2).

The NCCN panel suggests trastuzumab and chemotherapy be used for patients with HER2-positive, node-negative tumors measuring 0.6 to 1.0 cm (T1b) and for smaller tumors that have less than or equal to 2 mm axillary node metastases (pN1mi). Some support for this recommendation comes from studies showing a higher risk of recurrence for patients with HER2-positive, node-negative tumors less than or equal to 1 cm compared with those with HER2-negative tumors of the same size.[151]

Ten-year breast cancer-specific survival and 10-year recurrence-free survival were 85% and 75%, respectively, in patients with tumors characterized as HER2-positive, ER-positive tumors, and 70% and 61%, respectively, in patients with HER2-positive, ER-negative tumors. Two additional retrospective series report recurrence-free survival in this subpopulation of HER2-positive, node-negative tumors measuring 0.6 to 1.0 cm (T1b) and/or pN1mi. all treated without trastuzumab. In the first study, 5-year recurrence-free survival rates of 77.1% and 93.7% ($P<.001$) were observed for patients with HER2-positive and HER2-negative T1a–bN0M0 breast tumors, respectively, with no recurrence-free survival differences seen in the HER2-positive group when hormonal receptor status was considered.[152] In the other retrospective study of patients with small HER2-positive tumors, the risk of recurrence at 5 years was low (99% [95% CI, 96%–100%] for HER2-negative disease and 92% [95% CI, 86%–99%] for HER2-positive disease).[153] Subgroup analyses from several of the randomized trials have shown consistent benefit of trastuzumab irrespective of tumor size or nodal status.[154,155]

Preferred Regimens

The NCCN panel has included paclitaxel and trastuzumab as an option for patients with low-risk, HER2-positive, stage I tumors, based on a trial of 406 patients with small, node-negative, HER2-positive tumors treated with this combination. The 3-year rate of DFS was 98.7% (95% CI, 97.6–99.8) and the risk of serious toxic effects with this regimen was low (incidence of heart failure reported was 0.5%).[156] The long-term follow-up data reported 10-year invasive DFS of 91.3%, breast cancer-specific survival of 98.8% and OS rates of 94.3%.[157] Accordingly, NCCN panel has listed paclitaxel and trastuzumab as a less intensive therapeutic option, preferred for patients with low-risk T1,N0,M0, HER2-positive disease, particularly those not eligible for other standard adjuvant regimens due to comorbidities.[157]

The BCIRG 006 study randomized 3,222 patients with HER2-positive, node-positive, or high-risk node-negative breast cancer to AC followed by docetaxel; AC followed by docetaxel plus trastuzumab for 1 year; or carboplatin, docetaxel, and trastuzumab for 1 year.[155] At 65-month follow-up, patients receiving AC followed by docetaxel with trastuzumab (AC-TH) had an HR for DFS of 0.64 ($P<.001$) when compared with the group of patients in the control arm receiving the same chemotherapy regimen without trastuzumab (AC-T). The HR for DFS was 0.75 ($P=.04$) when patients in the carboplatin/docetaxel/trastuzumab (TCH)-containing arm were compared with patients in the control arm. No statistically significant difference in the HR for DFS

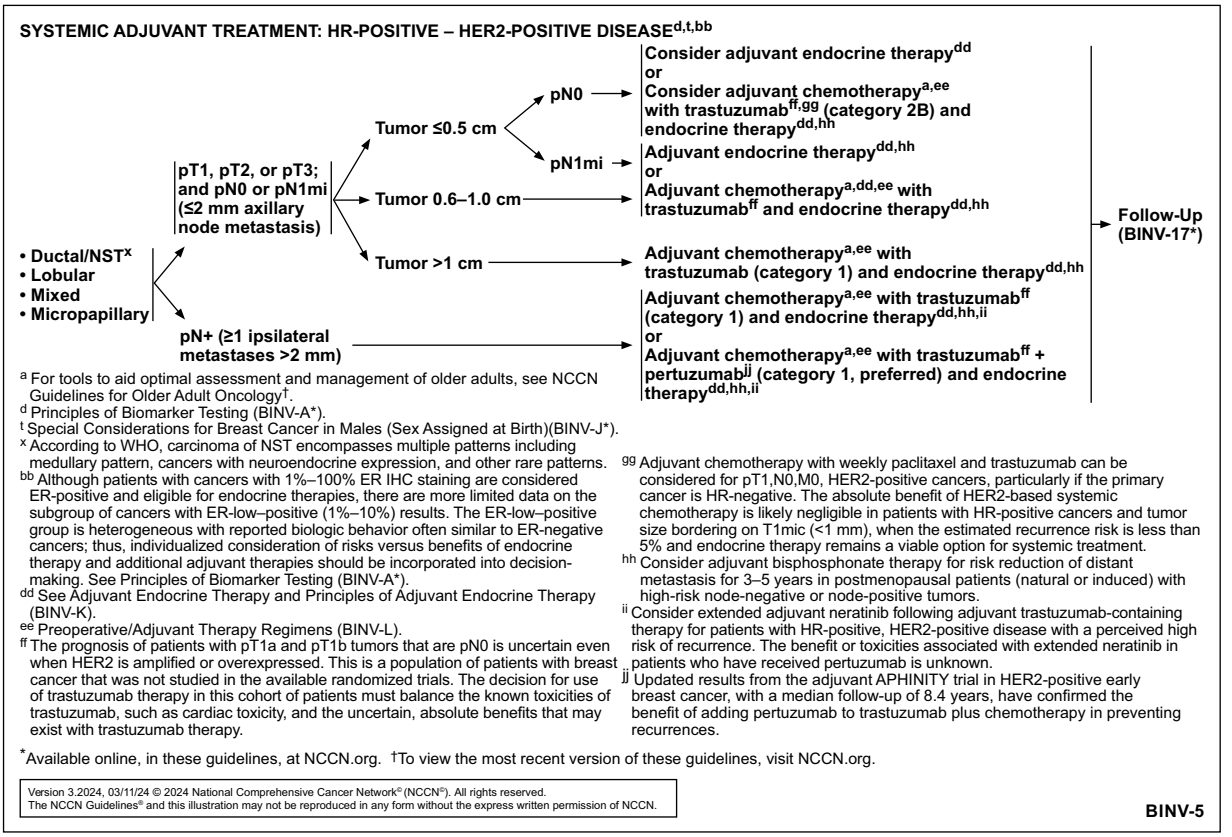

Figure 14. BINV-5. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer, Version 3.2024.

was observed between the 2 trastuzumab-containing arms. An OS advantage was reported for patients in both trastuzumab-containing arms relative to the control arm (HR for AC-TH vs AC-T, 0.63; P=.001; HR for TCH vs AC-T, 0.77; P=.04). Cardiac toxicity was significantly lower in the TCH arm (9.4% patients with >10% relative decline in left ventricular ejection fraction) compared with the AC-TH arm (18.6%; P<.0001). CHF was also more frequent with AC-TH than TCH (2% vs 0.4%; P<.001). Analysis of this trial by critical clinical event revealed more distant breast cancer recurrences with TCH (144 vs 124) but fewer cardiac events with TCH compared with AC-TH (4 vs 21).[155] In the FinHer trial, 1,010 patients were randomized to 9 weeks of vinorelbine followed by 3 cycles of FEC chemotherapy versus docetaxel for 3 cycles followed by 3 cycles of FEC chemotherapy.[158] Patients (n=232) with HER2-positive cancers that were either node-positive or node-negative and greater than or equal to 2 cm and PR-negative were further randomized to receive or not receive trastuzumab for 9 weeks during the vinorelbine or docetaxel portions of the chemotherapy only. With a median follow-up of 3 years, the addition of trastuzumab was associated with a reduction in risk of recurrence (HR, 0.42; 95% CI, 0.21–0.83; P=.01). No statistically significant differences in OS (HR, 0.41; 95% CI, 0.16–1.08; P=.07) or cardiac toxicity were observed with the addition of trastuzumab.[158] At 5-year follow-up, a comparison of the 2 arms (ie, chemotherapy with and without trastuzumab) demonstrated that the HRs for distant DFS (HR, 0.65; 95% CI, 0.38–1.12; P=.12) and OS (HR, 0.55; 95% CI, 0.27–1.11; P=.094) were higher relative to those reported at 3 years.[159] The TCH regimen is a preferred regimen, especially for those with risk factors for cardiac toxicity, based on the results of the BCIRG 006 study.

The APHINITY trial compared adjuvant trastuzumab plus pertuzumab with trastuzumab–placebo, both in combination with standard adjuvant chemotherapy in patients with node-positive or high-risk node-negative HER2-positive, operable tumors. The study demonstrated that trastuzumab plus pertuzumab significantly improved 3-year invasive DFS (HR, 0.81; 95% CI, 0.66–1.00; P=.045).[160] With long-term (8-year) follow-up, the node-positive subgroup maintained a clear invasive DFS benefit favoring the dual HER2 agent arm demonstrating 8-year invasive DFS of 86% versus 81% (HR, 0.72; 95% CI, 0.60–0.87) with no OS difference; no benefit was seen in the node-negative subgroup.[161] These updated results from the adjuvant APHINITY trial confirm the long-term benefit of adding pertuzumab to trastuzumab plus chemotherapy for node-positive disease. The panel has designated use of trastuzumab with chemotherapy as a category 1 recommendation for all HER2-positive tumors >1 cm, and based on the data above, chemotherapy plus trastuzumab and pertuzumab as a category 1, preferred regimen for HER2-positive, node-positive disease.

The data from the phase III KATHERINE trial reported improved outcomes in patients who had residual invasive cancer and received adjuvant trastuzumab emtansine (T-DM1). Invasive DFS at 3 years was 88.3% with T-DM1 versus 77.0% with trastuzumab.[162] T-DM1 significantly decreased the invasive breast cancer recurrence risk or death (HR, 0.50; 95% CI, 0.39–0.64; P<.001).[162]

The ATEMPT trial was designed to determine whether T-DM1 was more toxic than paclitaxel/trastuzumab. The long-term

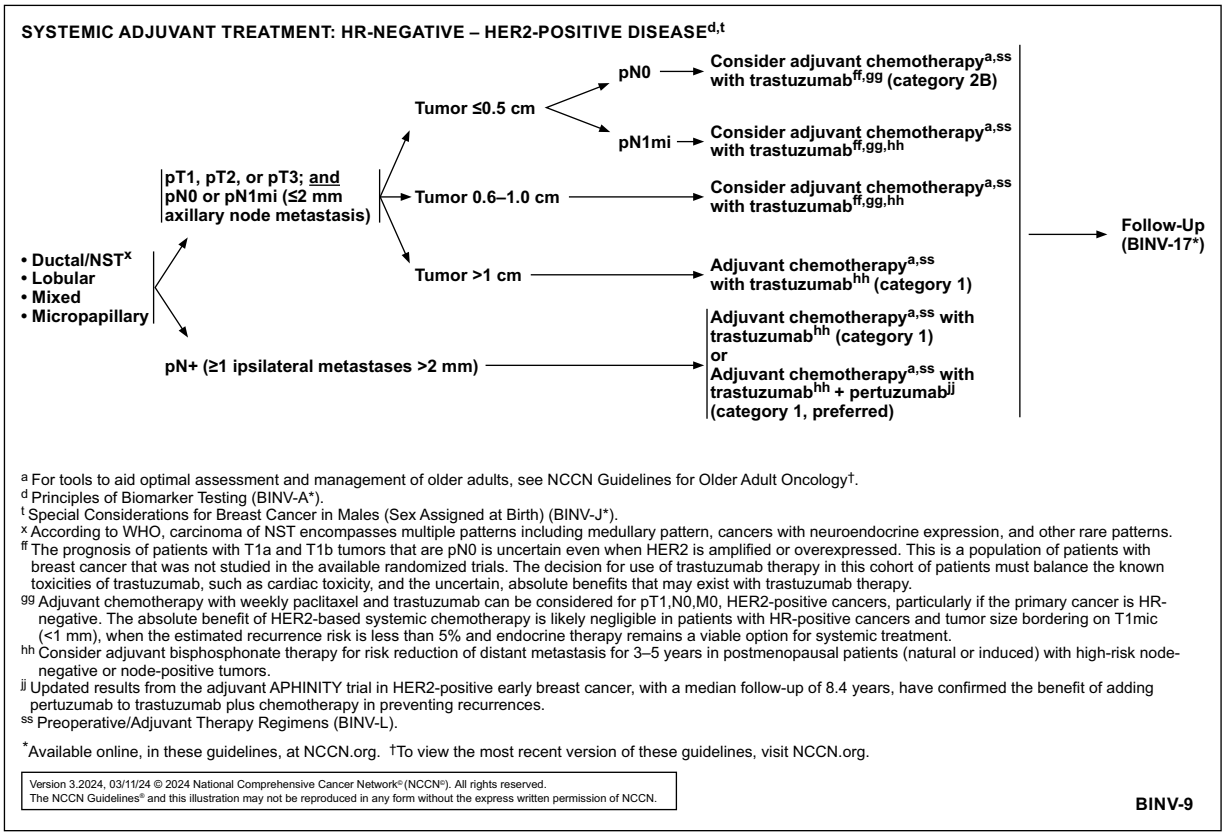

Figure 15. BINV-9. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer, Version 3.2024.

follow-up data of patients who received 1 year of adjuvant T-DM1 (n=383) or trastuzumab/paclitaxel (n=114) reported the 5-year invasive DFS rate with T-DM1 of 97.0% (95% CI, 95.2%–98.7%), the 5-year recurrence-free interval of 98.3% (95% CI, 96.3%–99.0%), and the 5-year OS rate of 97.8% (95% CI, 96.3%–99.3%).[163] The study was not powered to evaluate the efficacy of paclitaxel/trastuzumab; among those who received it, the reported 5-year invasive DFS with this combination was 91.3% (95% CI, 86.0%–96.9%), 5-year recurrence free interval was 93.3% (95% CI, 88.6%–98.2%), and 5-year OS was 97.9% (95% CI, 95.2%–100%).[163] Based on these data, T-DM1 may be considered an alternative for these patients ineligible for paclitaxel/trastuzumab.

Other Recommended Regimens

Anthracycline followed by taxane-containing chemotherapy regimens were used in the NSABP trial B-31,[164] NCCTG trial,[165] and BCIRG 006 trial.[155]

In the NOAH trial, patients were given concurrent taxane and anthracycline, then taxane alone followed by cyclophosphamide–methotrexate–fluorouracil.[166] In the FinHER study, patients were randomized to docetaxel or vinorelbine before anthracyclines,[158] and PACS 04 randomized patients to fluorouracil/epirubicin/cyclophosphamide or to epirubicin plus docetaxel.[167] The HERA trial did not mandate the choice of chemotherapy, 94% receiving anthracyclines and 26% receiving a taxane in addition to an anthracycline.

All of the previously noted adjuvant trials of trastuzumab have demonstrated clinically significant improvements in DFS. Furthermore, the HERA trial[168] and the combined analysis of the NSABP B31 and NCCTG N9831 trials[169] showed significant improvement in OS with the use of trastuzumab. A more recent meta-analysis of all the previously noted studies (excluding the BCIRG 006 trial) showed that addition of trastuzumab resulted in an average absolute reduction in 10-year risk of recurrence of 9.0% (95% CI, 7.4–10.7; $P<.0001$), a reduction in 10-year breast cancer mortality by 6.4% (4.9–7.8; $P<.0001$), and a reduction in mortality (all causes) by 6.5% (5.0–8.0; $P<.0001$).[170] The benefits of trastuzumab are independent of ER status.[164,171]

The NCCN panel considers it reasonable to incorporate pertuzumab into these adjuvant regimens.[25,172,173]

The results of the TRAIN-2 trial showed high pCR rates after treatment regimens with anthracycline plus trastuzumab and pertuzumab (67%) and also without anthracycline plus trastuzumab and pertuzumab (68%).[172] Patients who received anthracycline-containing regimen experienced more febrile neutropenia, hypokalemia, and left ventricular ejection fraction decline to grade 2 or worse (≥10% or to <50%).[172]

A follow-up analysis of the TRAIN-2 study showed similar 3-year EFS and OS with or without anthracyclines in patients with stage II and III HER2-positive breast cancer. Based on these results, considering the added toxicity of anthracycline-containing regimens, the panel has added nonanthracycline-containing regimens with trastuzumab and pertuzumab as treatment options.[174]

The NCCN panel has included the following regimen as other recommended regimens for HER2-positive disease: doxorubicin/cyclophosphamide (AC) followed by docetaxel plus trastuzumab

(followed by docetaxel plus trastuzumab); AC followed by docetaxel and trastuzumab and pertuzumab and paclitaxel/carboplatin and trastuzumab and pertuzumab.

Regimens Useful in Certain Circumstances

One year of extended therapy with neratinib after completion of 1 year of adjuvant trastuzumab without pertuzumab was evaluated in the phase III ExteNET trial. Neratinib improved invasive DFS (HR, 0.73; 95% CI, 0.57–0.92; $P=.0083$) primarily in the subgroup of HR-positive tumors (HR, 0.60; 95% CI, 0.43–0.83; $P=.063$). Neratinib is associated with moderate to severe diarrhea.

Based on the trials listed in the section for "other recommended regimen and the above data from ExteNET, the NCCN panel has included following regimens have been included as useful in certain circumstances: Docetaxel and cyclophosphamide and trastuzumab; AC followed by paclitaxel and trastuzumab followed by paclitaxel plus trastuzumab, various schedules); AC followed by paclitaxel and trastuzumab and pertuzumab, various schedules); paclitaxel and trastuzumab and pertuzumab; adjuvant neratinib and adjuvant T-DM1.

Therapeutic Duration and Other Considerations in Those Receiving HER2-Targeted Therapy

The length of trastuzumab administration in the adjuvant setting trials listed above is 12 months. The HERA trial demonstrated no additional benefit extending trastuzumab to 2 years compared with 1 year.

With respect to a duration less than 12 months, the results of the PERSEPHONE trial showed noninferiority for 6 months versus 12 months of trastuzumab treatment,[175] However, the PHARE study observed more events in the 6 month cohort compared with the 12 month cohort, and noninferiority was not established.[176] Furthermore, adverse events over time remained similar in both arms, and comparable to data reported in other trials.

Considering the conflicting results between PERSEPHONE and PHARE, in addition to the protocol design of the majority of the randomized trials establishing the benefits of trastuzumab which used 12 months of therapy, the NCCN panel recommends up to 1 year of HER2-targeted therapy with trastuzumab. Based on the updated APHINITY trial data, the addition of pertuzumab may be considered with trastuzumab in those with node-positive disease.

Increased cardiac toxicity has been observed in patients treated with trastuzumab.[164,177,178] In addition, anthracycline and taxane-based regimens in combination with HER2-targeted agents are associated with further increased risk of cardiac toxicity.[179] The panel recommends evaluation of left ventricular ejection fraction prior to and during treatment. The optimal frequency of left ventricular ejection fraction assessment during adjuvant trastuzumab therapy is not known. The FDA label recommends left ventricular ejection fraction measurements prior to initiation of trastuzumab and every 3 months during therapy.

According to the panel, use of an FDA-approved biosimilar is an appropriate substitute for trastuzumab. Trastuzumab and hyaluronidase-oysk injection approved for subcutaneous use

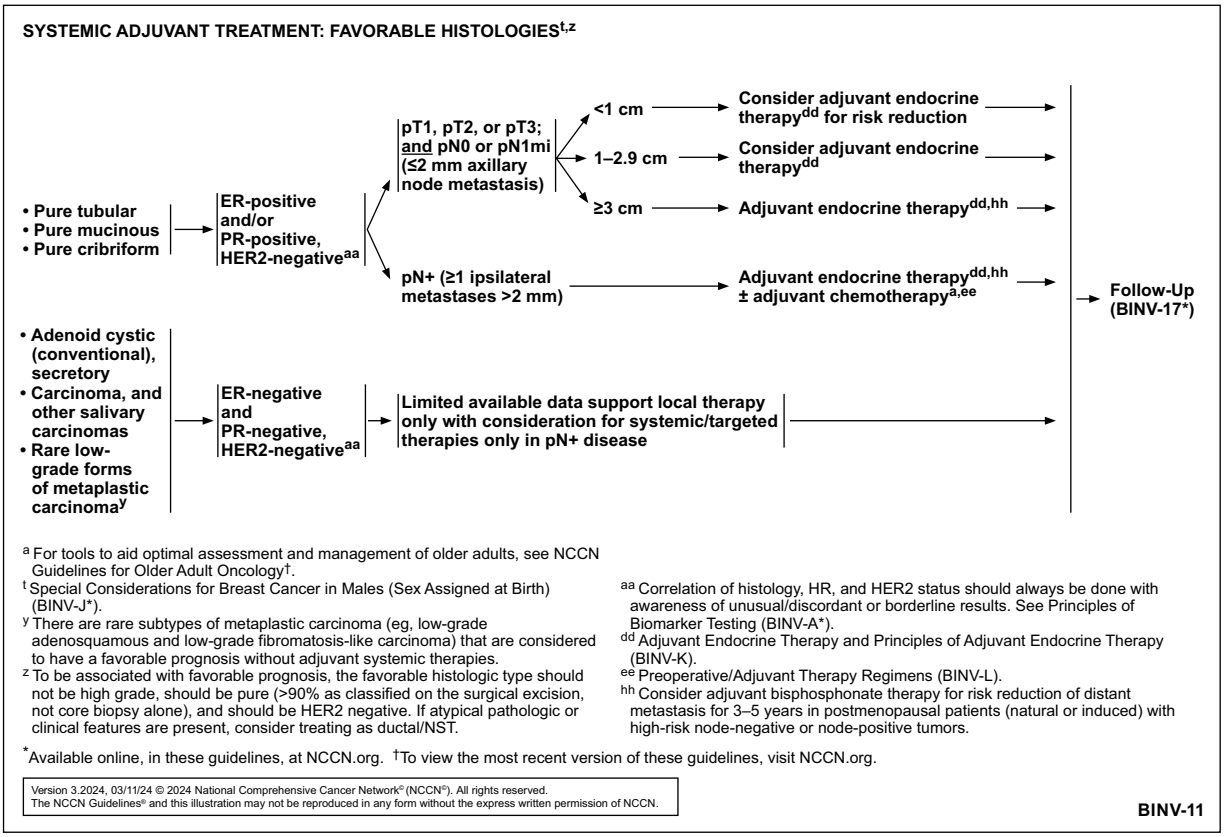

Figure 16. BINV-11. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer, Version 3.2024.

may be substituted for intravenous trastuzumab. It is important to note that it has a different dosage and administration compared with intravenous trastuzumab.

Adjuvant Therapy for Tumors of Favorable Histologies

The guidelines provide systemic treatment recommendations for the favorable histology of invasive breast cancers (including pure tubular and pure mucinous cancers, pure cribriform, adenoid cystic secretory carcinoma and other salivary carcinoma, rare low-grade forms of metaplastic carcinoma) based on ER/PR status, tumor size and ALN status (Figure 16). If used, the treatment options for endocrine therapy, chemotherapy, and sequencing of treatment with other modalities are similar to those of the usual histology of breast cancers. There are rare subtypes of metaplastic carcinoma (eg, low-grade adenosquamous and low-grade fibromatosis-like carcinoma) that have a favorable prognosis even without administration of adjuvant systemic therapies.

The vast majority of pure tubular, pure mucinous, and pure cribriform breast cancers are both ER-positive and HER2-negative. To be associated with favorable prognosis, the favorable histologic type should not be high grade, should be pure (>90% as classified on the surgical excision, not core biopsy alone), and should be HER2-negative. If atypical pathologic or clinical features are present, consider treating as ductal/no special type.

The pathology evaluation and accuracy of the ER and/or HER2 determination should be reviewed if these are ER-negative and/or HER2-positive, or if a tumor with an ER- and PR-negative status is grade 1.[29] Should a breast cancer be histologically identified as a pure tubular or mucinous breast cancer and be confirmed as ER-negative, then the tumor should be treated according to the guideline for the usual histology, ER-negative breast cancers. The panel acknowledges that prospective data regarding systemic adjuvant therapy of pure tubular and mucinous histologies are lacking.

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