National Comprehensive Cancer Network®

NCCN

Breast Cancer Version 3.2014

Clinical Practice Guidelines in Oncology

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Overview

Breast cancer is the most common malignancy in women in the United States. The American Cancer Society estimates that 235,030 Americans will be diagnosed with invasive breast cancer and 40,430 will die of the disease in the United States in 2014.[1] The incidence of breast cancer has increased steadily in the United States in the past few decades, but breast cancer–related mortality seems to be declining,[2,3] suggesting a benefit from the combination of early detection and more effective treatment.[4]

Abstract

Breast cancer is the most common malignancy in women in the United States and is second only to lung cancer as a cause of cancer death. The overall management of breast cancer includes the treatment of local disease with surgery, radiation therapy, or both, and the treatment of systemic disease with cytotoxic chemotherapy, endocrine therapy, biologic therapy, or combinations of these. The NCCN Guidelines specific to management of large clinical stage II and III tumors are discussed in this article. These guidelines are the work of the members of the NCCN Breast Cancer Panel. Expert medical clinical judgment is required to apply these guidelines in the context of an individual patient to provide optimal care. Although not stated at every decision point of the guidelines, patient participation in prospective clinical trials is the preferred option of treatment for all stages of breast cancer. (*J Natl Compr Canc Netw* 2014;12:542–590)

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Breast Cancer are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.**

Disclosures for the NCCN Breast Cancer Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Breast Cancer Panel members can be found on page 590. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

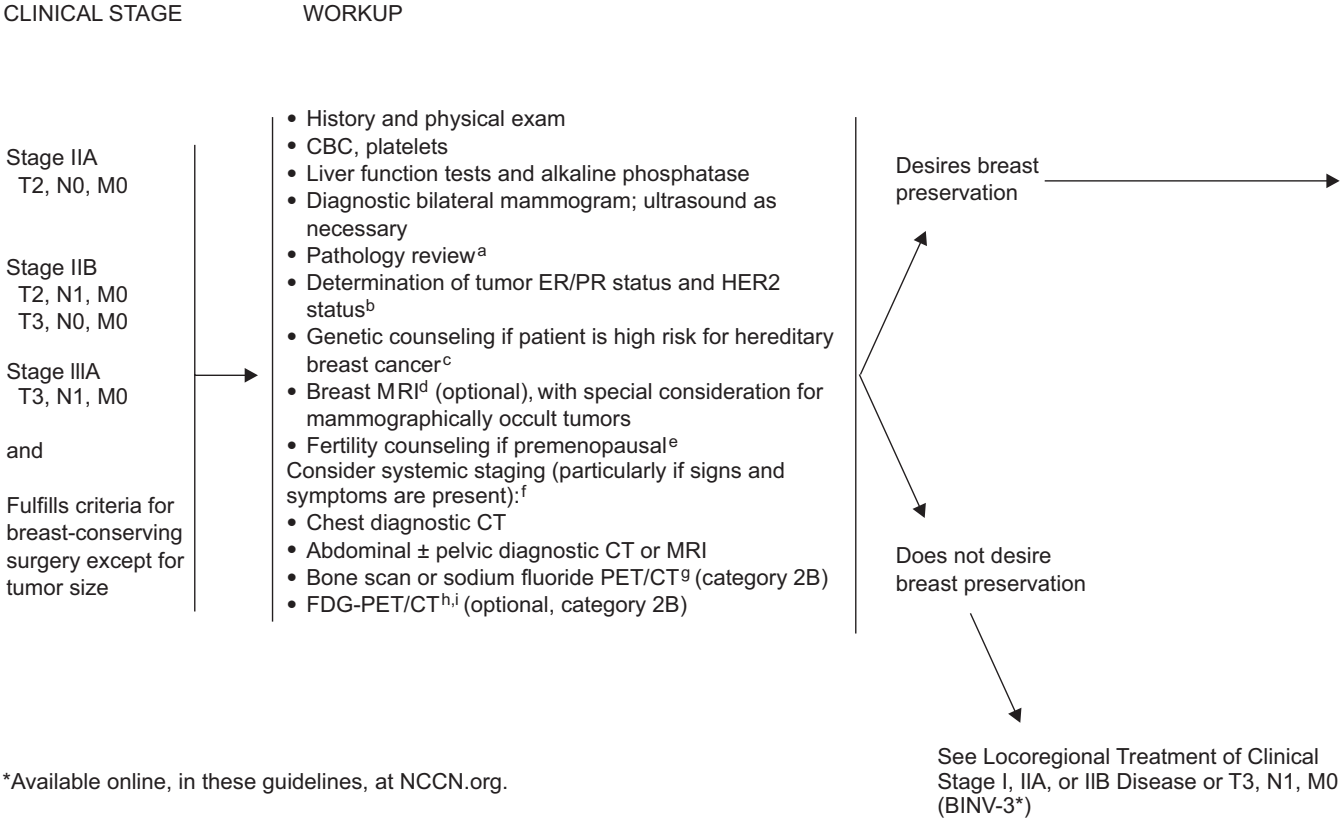
These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

Pathology Assessment

A central component of breast cancer treatment is full knowledge of disease extent and biologic features. These factors contribute to the determination of disease stage, assist in estimating the risk of cancer recurrence, and provide information that predicts response to therapy (eg, estrogen receptor [ER], progesterone receptor [PR], and HER2). These factors are determined through examination of excised tissue and provided in a written pathology report. Accurate pathology reporting requires communication between the clinician and the pathologist regarding relevant patient history, prior breast biopsies, prior irradiation to the chest, pregnancy status, characteristics of the abnormality biopsied (eg, palpable, mammographically detected microcalcifications), clinical state of lymph nodes, presence of inflammatory change or other skin abnormality, and any prior treatment administered (eg, chemotherapy, radiation therapy). The specimens should be oriented for the pathologist, and specific requests for determination of biomarkers should be stated (eg, ER, PR, and HER2 status). Data from both national and local surveys show that as many as 50% of pathology reports for breast cancer are missing some elements critical to patient management.[5,6] Significant omissions include failure to orient and report surgical margins and failure to report tumor grade consistently. The College of American Pathologists (CAP) has developed pathology reporting protocols to promote complete and standardized reporting of malignant specimens (www.cap.org). The NCCN Breast

Text cont. on page 556.

PREOPERATIVE SYSTEMIC THERAPY GUIDELINE



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

[a] The panel endorses the College of American Pathologists Protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast (http://www.cap.org).
[b] See Principles of HER2 Testing (BINV-A).
[c] See NCCN Guidelines for Genetics/Familial High-Risk Assessment: Breast and Ovarian (to view the most recent version of these guidelines, visit NCCN.org).
[d] See Principles of Dedicated Breast MRI Testing (BINV-B).
[e] See Fertility and Birth Control (BINV-C*).
[f] Routine systemic staging is not indicated for early breast cancer in the absence of symptoms.
[g] If FDG-PET/CT is performed and clearly indicates bone metastasis, on both the PET and CT component, bone scan or sodium fluoride PET/CT may not be needed.
[h] FD-PET/CT can be performed at the same time as diagnostic CT. The use of PET or PET/CT scanning is not indicated in the staging of clinical stage I, II, or operable III breast cancer. FDG-PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease.
[i] FDG-PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases in locally advanced breast cancer when used in addition to standard staging studies.

PREOPERATIVE SYSTEMIC THERAPY BREAST AND AXILLARY EVALUATION

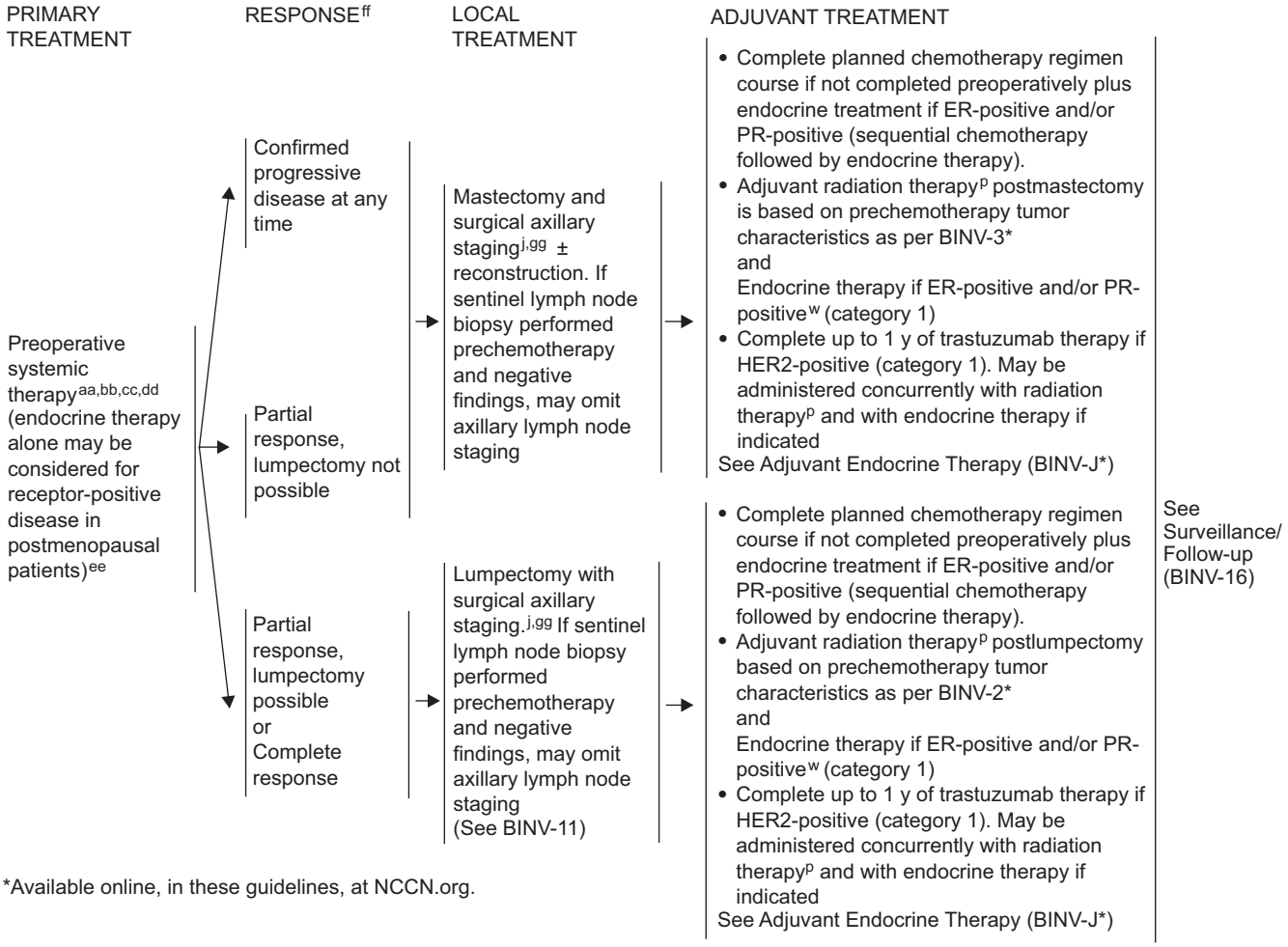
Core biopsy with placement of image-detectable marker(s), if not previously performed, must be done to demarcate the tumor bed for postchemotherapy surgical management

Clinically negative axillary lymph node(s) should have axillary ultrasound; suspicious nodes should be sampled by FNA or core biopsy and clipped with image-detectable marker; positive clipped lymph nodes must be removed if FNA or core biopsy was positive before neoadjuvant therapy.

Clinically positive axillary lymph node(s) should be sampled by FNA or core biopsy and clipped with image-detectable marker; positive clipped lymph nodes must be removed if FNA or core biopsy was positive before neoadjuvant therapy.

See Preoperative Systemic Therapy - Primary Treatment (BINV-12)

PREOPERATIVE SYSTEMIC THERAPY GUIDELINE

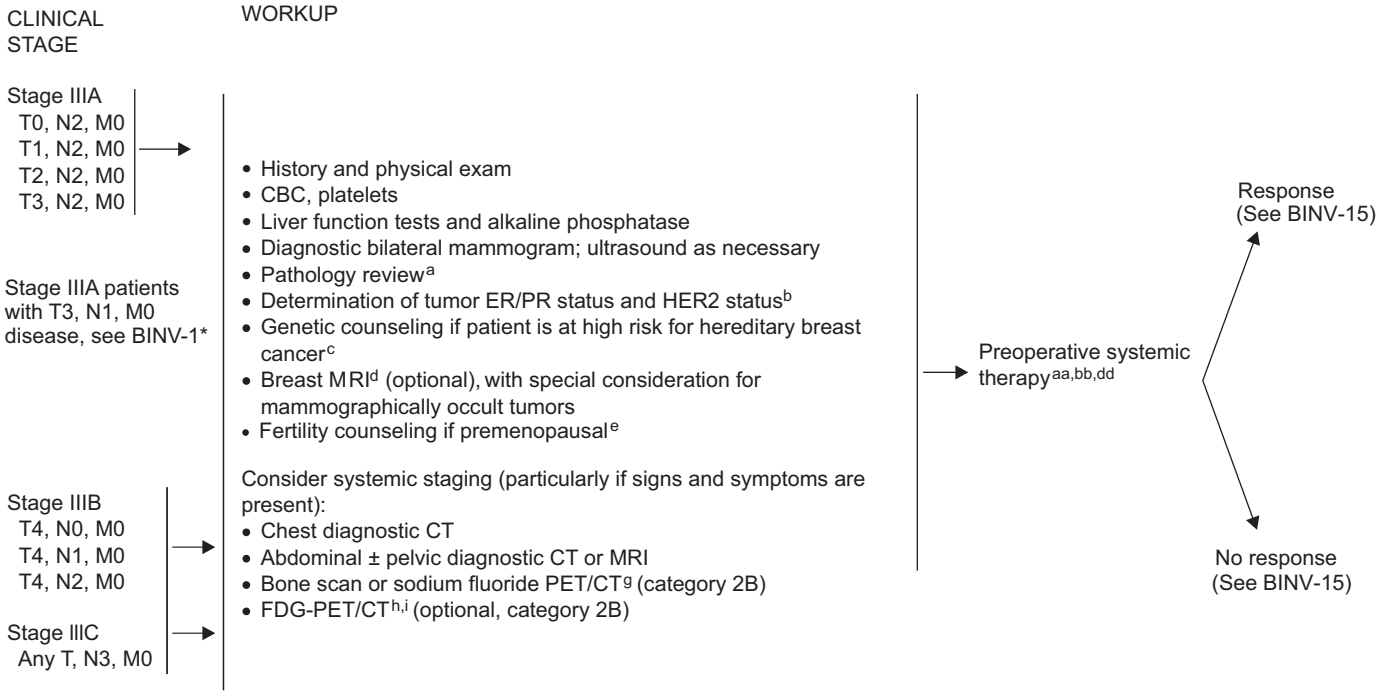


*Available online, in these guidelines, at NCCN.org.

[j] See Surgical Axillary Staging (BINV-D).
[p] See Principles of Radiation Therapy (BINV-I).
[w] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable
[aa] Several 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 Neoadjuvant/Adjuvant Chemotherapy (BINV-K). If treated with endocrine therapy, an aromatase inhibitor is preferred for postmenopausal women.
[bb] Patients with HER2-positive tumors should be treated with preoperative systemic therapy incorporating trastuzumab for at least 9 weeks of preoperative therapy. See Neoadjuvant/Adjuvant Chemotherapy (BINV-K).
[cc] Administration of all chemotherapy prior to surgery is preferred.
[dd] A pertuzumab-containing regimen may be administered preoperatively to patients with ≥T2 or ≥N1, HER2-positive, early-stage breast cancer. See Neoadjuvant/Adjuvant Chemotherapy (BINV-K).
[ee] See Definition of Menopause (BINV-L*).
[ff] The accurate assessment of in-breast tumor or regional lymph node response to preoperative chemotherapy is difficult, and should include physical examination and performance of imaging studies that were abnormal at the time of initial tumor staging. Selection of imaging methods prior to surgery should be determined by the multidisciplinary team.
[gg] Axillary staging following preoperative systemic therapy may include sentinel node biopsy or level I/II dissection. Level I/II dissection should be done for when patients were proven node-positive before neoadjuvant therapy (category 2B).
Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol 2013;14:609-618.
Boughey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA 2013;310:1455-1461.

BINV-12, -13

LOCALLY ADVANCED INVASIVE BREAST CANCER (NONINFLAMMATORY)



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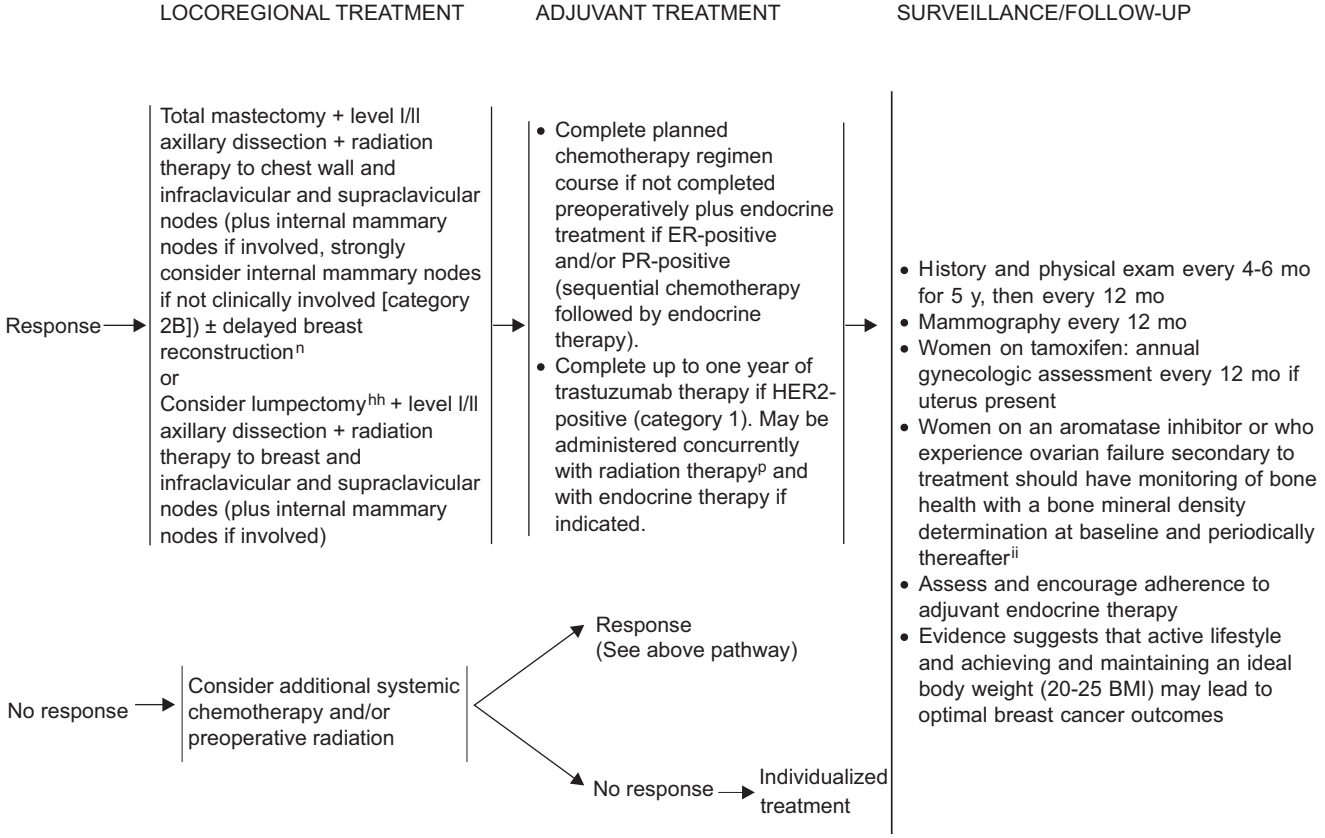
[a] The panel endorses the College of American Pathologists Protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast (http://www.cap.org).
[b] See Principles of HER2 Testing (BINV-A).
[c] See NCCN Guidelines for Genetics/Familial High-Risk Assessment: Breast and Ovarian (to view the most recent version of these guidelines, visit NCCN.org).
[d] See Principles of Dedicated Breast MRI Testing (BINV-B).
[e] See Fertility and Birth Control (BINV-C*).
[g] If FDG-PET/CT is performed and clearly indicates bone metastasis, on both the PET and CT component, bone scan or sodium fluoride PET/CT may not be needed.
[h] FDG-PET/CT can be performed at the same time as diagnostic CT. The use of PET or PET/CT scanning is not indicated in the staging of clinical stage I, II, or operable III breast cancer. FDG-PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease.
[i] FDG-PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases in locally advanced breast cancer when used in addition to standard staging studies.

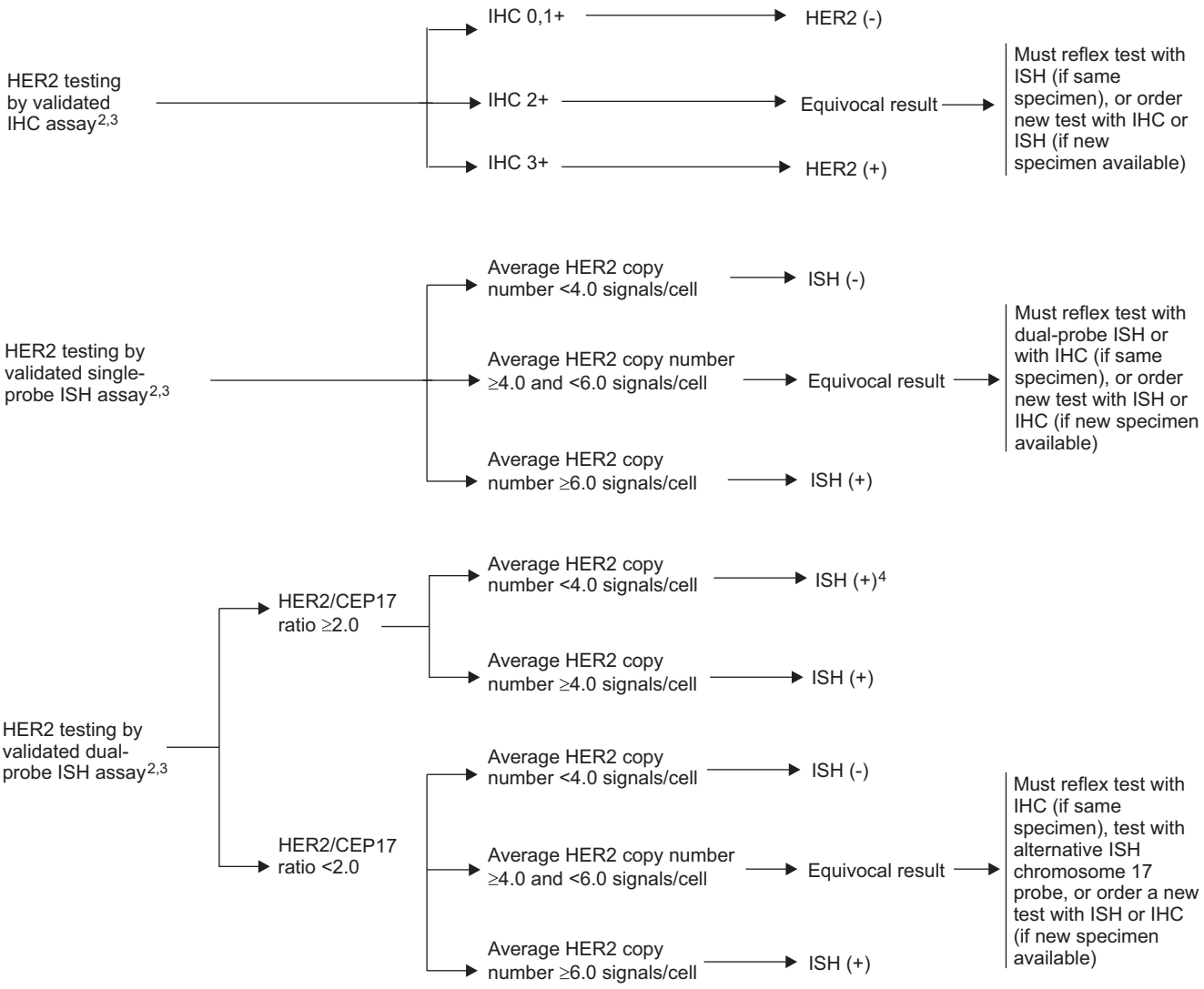
PREOPERATIVE SYSTEMIC THERAPY FOR LOCALLY ADVANCED INVASIVE BREAST CANCER (NONINFLAMMATORY)



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

[n] See Principles of Breast Reconstruction Following Surgery (BINV-H).
[p] See Principles of Radiation Therapy (BINV-I).
[aa] Several 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 Neoadjuvant/Adjuvant Chemotherapy (BINV-K). If treated with endocrine therapy, an aromatase inhibitor is preferred for postmenopausal women.
[bb] Patients with HER2-positive tumors should be treated with preoperative systemic incorporating trastuzumab for at least 9 weeks of preoperative therapy See Neoadjuvant/Adjuvant Chemotherapy (BINV-K).
[dd] A pertuzumab-containing regimen may be administered preoperatively to patients with ≥T2 or ≥N1, HER2-positive, early-stage breast cancer. See Neoadjuvant/Adjuvant Chemotherapy (BINV-K).
[hh] For patients with skin and/or chest wall involvement (T4 non-inflammatory) before neoadjuvant therapy, breast conservation may be performed in carefully selected patients based upon a multidisciplinary assessment of local recurrence risk. In addition to standard contraindications to breast conservation (see BINV-G*), exclusion criteria for breast conservation include inflammatory (T4d) disease before neoadjuvant therapy and incomplete resolution of skin involvement after neoadjuvant therapy.
[ii] The use of estrogen, progesterone, or selective estrogen receptor modulators to treat osteoporosis or osteopenia in women with breast cancer is discouraged. The use of a bisphosphonate is generally the preferred intervention to improve bone mineral density. Optimal duration of bisphosphonate therapy has not been established. Factors to consider for duration of antiosteoporosis therapy include bone mineral density, response to therapy, and risk factors for continued bone loss or fracture. Women treated with a bisphosphonate should undergo a dental examination with preventive dentistry before the initiation of therapy, and should take supplemental calcium and vitamin D.

PRINCIPLES OF HER2 TESTING[1,2]



[1]NCCN endorses the ASCO/CAP HER2 testing guideline. For additional information, see http://bit.ly/ASCO-HER2GuidelineResources.
[2]Laboratory must participate in a quality assurance accreditation program for HER2 testing. Otherwise, tissue specimen should be sent to an accredited laboratory for testing. Health care systems and providers must cooperate to ensure the highest quality testing.
[3]Evidence from trastuzumab adjuvant trials show that HER2 testing by ISH or IHC have similar utility to predict clinical benefit from HER2-targeted therapy.
[4]See ASCO/CAP HER2 Guideline Data Supplement 2E (available at http://www.asco.org/sites/www.asco.org/files/final_her2_testing_ds_10-3-13.pdf) for more information on these rare scenarios.

BINV-A

PRINCIPLES OF DEDICATED BREAST MRI TESTING

See NCCN Guidelines for Breast Cancer Screening and Diagnosis for indications for screening MRI in women at increased breast cancer risk (to view the most recent version of these guidelines, visit NCCN.org).

Personnel, Facility, and Equipment

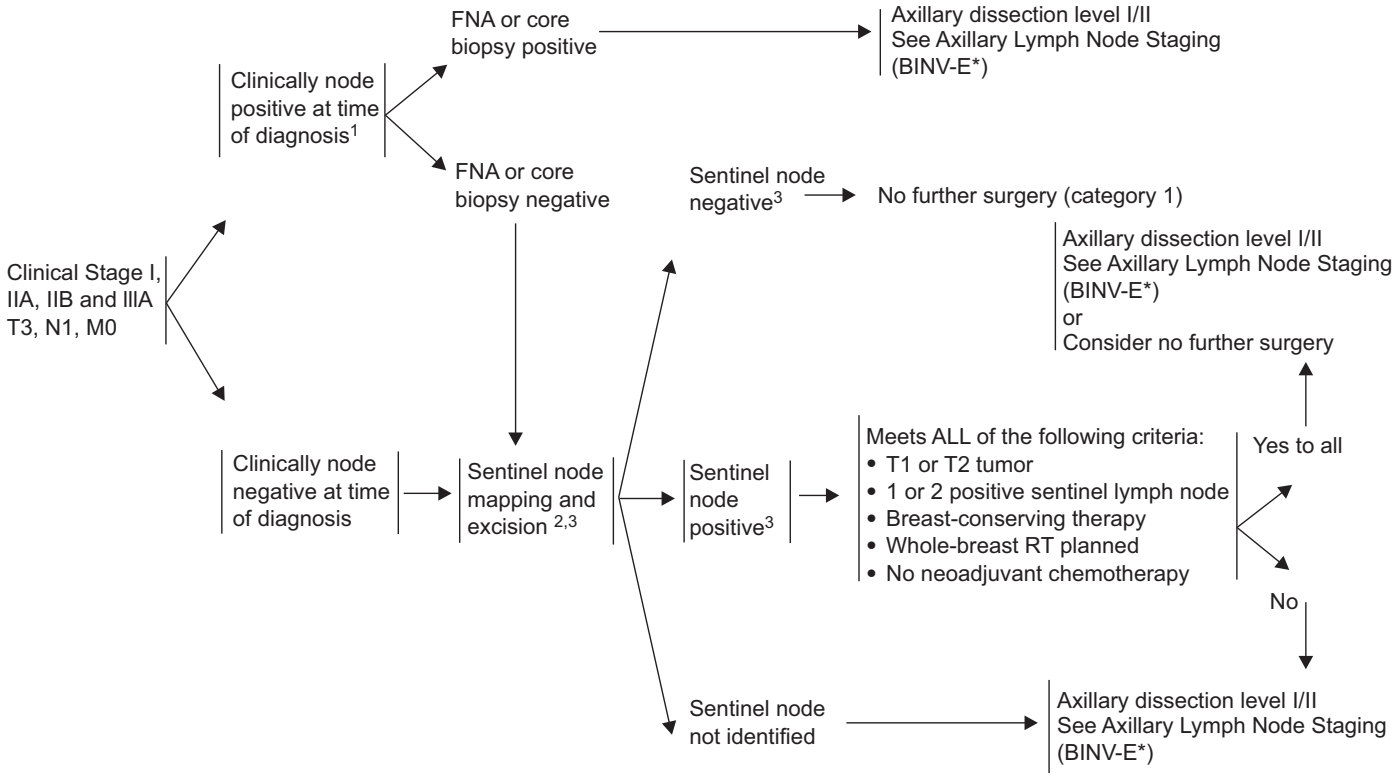
- Breast MRI examinations should be performed and interpreted by an expert breast imaging team working in concert with the multidisciplinary treatment team.
- Breast MRI examinations require a dedicated breast coil and breast imaging radiologists familiar with the optimal timing sequences and other technical details for image interpretation. The imaging center should have the ability to perform MRI-guided needle sampling and/or wire localization of MRI-detected findings.

Clinical Indications and Applications

- May be used for staging evaluation to define extent of cancer or presence of multifocal or multicentric cancer in the ipsilateral breast, or as screening of the contralateral breast cancer at time of initial diagnosis (category 2B). No high-level data demonstrate that the use of MRI to facilitate local therapy decision-making improves local recurrence or survival.[1]
- May be helpful for breast cancer evaluation before and after neoadjuvant therapy to define extent of disease, response to treatment, and potential for breast-conserving therapy.
- May be useful to detect additional disease in women with mammographically dense breast, but available data do not show differential detection rates by any subset by breast pattern (breast density) or disease type (eg, DCIS, invasive ductal cancer, invasive lobular cancer).
- May be useful for identifying primary cancer in women with axillary nodal adenocarcinoma or with Paget disease of the nipple with breast primary not identified on mammography, ultrasound, or physical examination.
- False-positive findings on breast MRI are common. Surgical decisions should not be based solely on the MRI findings. Additional tissue sampling of areas of concern identified by breast MRI is recommended.
- The utility of MRI in follow-up screening of women with prior breast cancer is undefined. It should generally be considered only in those whose lifetime risk of a second primary breast cancer is >20% based on models largely dependent on family history, such as in those with the risk associated with inherited susceptibility to breast cancer.

[1]Houssami N, Ciatto S, Macaskill P, et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol 2008;26:3248-3258.

SURGICAL AXILLARY STAGING - STAGE I, IIA, IIB and IIIA T3, N1, M0



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

[1]Consider pathologic confirmation of malignancy in clinically positive nodes using ultrasound-guided FNA or core biopsy in determining if a patient needs axillary lymph node dissection.
[2]Sentinel lymph node mapping injections may be peritumoral, subareolar, or subdermal. However, only peritumoral injections map to the internal mammary lymph node(s).
[3]Sentinel node involvement is defined by multilevel node sectioning with hematoxylin and eosin (H&E) staining. Cytokeratin immunohistochemistry (IHC) may be used for equivocal cases on H&E. Routine cytokeratin IHC to define node involvement is not recommended in clinical decision making.

PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY

- Breast reconstruction may be an option for any woman receiving surgical treatment for breast cancer. All women undergoing breast cancer treatment should be educated about breast reconstructive options as adapted to their individual clinical situation. However, breast reconstruction should not interfere with the appropriate surgical management of the cancer. The process of breast reconstruction should not govern the timing or the scope of appropriate surgical treatment for this disease. The availability of or the practicality of breast reconstruction should not result in the delay or refusal of appropriate surgical intervention.

- An evaluation of the likely cosmetic outcome of lumpectomy should be performed prior to surgery. Oncoplastic techniques for breast conservation can extend breast-conserving surgical options in situations where the resection itself would likely yield an unacceptable cosmetic outcome. Application of these procedures may reduce the need for mastectomy and reduce the chances of secondary surgery for re-excision while minimizing breast deformity. Patients should be informed of the possibility of positive margins and potential need for secondary surgery, which could include re-excision segmental resection, or could require mastectomy with or without loss of the nipple. Oncoplastic procedures can be combined with surgery on the contralateral unaffected breast to minimize long-term asymmetry.

- For mastectomy, the possibility of reconstruction should be discussed and a preoperative evaluation of reconstructive options should be considered. Surgical options for breast reconstruction following mastectomy include:
  - Procedures that incorporate breast implants (ie, tissue expander placement followed by implant placement, immediate implant placement)
  - Procedures that incorporate autologous tissue transplantation (ie, pedicled TRAM flap, fat grafting, various microsurgical flaps from the abdomen, back, buttocks, and thigh)
  - Procedures that incorporate both breast implants and autologous tissue transplantation (eg, latissimus dorsi flaps)

- Breast reconstruction following mastectomy can commence at the same time as mastectomy (“immediate”) or at some time after the completion of cancer treatment (“delayed”). In many cases, breast reconstruction involves a staged approach requiring more than one procedure, such as:
  - Surgery on the contralateral breast to improve symmetry
  - Revision surgery involving the breast and/or donor site
  - Nipple and areola reconstruction and tattoo pigmentation

- As with any mastectomy, there is a risk of local and regional cancer recurrence, and evidence suggests skin-sparing mastectomy is probably equivalent to standard mastectomy in this regard. Skin-sparing mastectomy should be performed by an experienced breast surgery team that works in a coordinated, multidisciplinary fashion to guide proper patient selection for skin-sparing mastectomy, determine optimal sequencing of the reconstructive procedure(s) in relation to adjuvant therapies, and perform a resection that achieves appropriate surgical margins. Post-mastectomy radiation should still be applied in cases treated by skin-sparing mastectomy following the same selection criteria as for standard mastectomy.

- Immediate reconstruction is contraindicated in the setting of mastectomy for inflammatory breast cancer (IBC) because of the high risk of recurrence, aggressive nature of the disease, and consequent need to proceed expeditiously to postoperative radiotherapy for local control without any potential delay. Because skin-sparing mastectomy has not yet been shown to be safe for IBC, there is also a need to resect currently or previously involved skin at the time of mastectomy, and thus no advantage to immediate reconstruction in this setting.

- In general, the nipple-areolar complex (NAC) is sacrificed with skin-sparing mastectomy for cancer therapy. However, NAC-sparing procedures may be an option in cancer patients who are carefully selected by experienced multidisciplinary teams. Retrospective data support the use of NAC-sparing procedures for breast cancer therapy with low nipple-involvement rates and low local-recurrence rates for early-stage, biologically favorable (eg, Nottingham grade 1 or 2, node-negative, HER2/neu negative, no lymphovascular invasion), invasive cancers and/or DCIS that are peripherally located in the breast (>2 cm from nipple). Nipple margin assessment is mandatory. Evidence of nipple involvement such as Paget disease or bloody nipple discharge contraindicates nipple preservation.

PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY

- Although noninflammatory, locally advanced breast cancer is not an absolute contraindication to immediate reconstruction, postmastectomy radiation should still be applied regardless of the reconstruction approach:
  - When postmastectomy radiation is required and autologous tissue reconstruction is planned, reconstruction is either delayed until after the completion of radiation therapy, or can be initiated at the time of mastectomy with tissue expander placement followed by autologous tissue reconstruction. Although some experienced breast cancer teams have used protocols in which immediate tissue reconstructions are followed by radiation therapy, it is generally preferred that the radiation therapy precede the placement of the autologous tissue, because of reported loss in reconstruction cosmesis (category 2B).
  - When implant reconstruction is planned in a patient requiring radiation therapy, a staged approach with immediate tissue expander placement followed by implant placement is preferred. Surgery to exchange the tissue expanders with permanent implants can be performed before radiation or after completion of radiation therapy. Tissue expansion of irradiated skin can result in a significantly increased risk of capsular contracture, malposition, poor cosmesis, and implant exposure. In the previously radiated patient the use of tissue expanders/implants is relatively contraindicated. Immediate placement of an implant in patients requiring postoperative radiation has an increased rate of capsular contracture, malposition, poor cosmesis, and implant exposure.

- Reconstruction selection is based on an assessment of cancer treatment, patient body habitus, obesity, smoking history, comorbidities, and patient concerns. Smoking and obesity increase the risk of complications for all types of breast reconstruction, whether with implant or flap. Smoking and obesity are therefore considered a relative contraindication to breast reconstruction and patients should be made aware of increased rates of wound healing complications and partial or complete flap failure among smokers and obese patients.

- Women who are not satisfied with the cosmetic outcome after completion of breast cancer treatment should be offered a plastic surgery consultation.

PRINCIPLES OF RADIATION THERAPY

Whole-Breast Radiation:
Target definition includes most of the breast tissue, and is best performed through both clinical assessment and CT-based treatment planning. A uniform dose distribution and minimal normal tissue toxicity are the goals, and can be accomplished using compensators such as wedges, forward planning using segments, intensity-modulated radiation therapy (IMRT), respiratory gating, or prone positioning. The breast should receive a dose of 45 to 50 Gy in 1.8 to 2.0 Gy per fraction, or 42.50 Gy at 2.66 Gy per fraction. A boost to the tumor bed is recommended in patients at higher risk (those aged <50 y and high-grade disease). This can be achieved with brachytherapy or electron beam or photon fields. Typical doses are 10 to 16 Gy at 2 Gy per fraction. All dose schedules are given 5 days per week.

Chest Wall Radiation (including breast reconstruction):
The target includes the ipsilateral chest wall, mastectomy scar, and drain sites where possible. Depending on whether the patient has been reconstructed, several techniques using photons and/or electrons are appropriate. CT-based treatment planning is encouraged to identify lung and heart volumes, and minimize exposure of these organs. Special consideration should be given to the use of bolus material when photon fields are used to ensure the skin dose is adequate.

Regional Nodal Radiation:
Target delineation is best achieved through CT-based treatment planning. For the paraclavicular and axillary nodes, prescription depth varies based on the size of the patient. For internal mammary node identification, the internal mammary artery and vein location can be used as a surrogate for the nodal locations, which usually are not visible on imaging. Dose is 50.0 to 50.4 Gy, given in 1.8 to 2.0 Gy fraction (± scar boost at 2 Gy per fraction to a total dose of approximately 60 Gy); all dose schedules are given 5 days per week. If internal mammary lymph nodes are clinically or pathologically positive, radiation therapy should be given to the internal mammary nodes.

Otherwise, the treatment to the internal mammary nodes is at the discretion of the treating radiation oncologist. CT treatment planning should be used in all cases where radiation therapy is delivered to the internal mammary lymph node field.

Accelerated Partial Breast Irradiation (APBI):
Preliminary studies of APBI suggest that rates of local control in selected patients with early-stage breast cancer may be comparable to those treated with standard whole-breast RT. However, compared with standard whole-breast radiation, several recent studies document an inferior cosmetic outcome with APBI. Follow-up is limited and studies are ongoing. Patients are encouraged to participate in clinical trials. If not trial eligible, per the consensus statement from the American Society for Radiation Oncology (ASTRO), patients who may be suitable for APBI are women aged 60 y and older who are not carriers of the BRCA1/2 mutation and are treated with primary surgery for a unifocal T1N0 ER-positive cancer. Histology should be infiltrating ductal or a favorable ductal subtype and not associated with EIC or LCIS, and margins should be negative. Thirty-four Gy in 10 fractions delivered twice per day with brachytherapy or 38.5 Gy in 10 fractions delivered twice per day with external-beam photon therapy is prescribed to the tumor bed. Other fractionation schemes are currently under investigation.

Optimizing Delivery of Individual Therapy:
It is important to individualize delivery of radiation therapy and considerations such as patient positioning (ie, prone vs supine) during administration of radiation therapy.

Neoadjuvant Chemotherapy:
Indications for radiation therapy and fields of treatment should be based on the worst stage pretreatment or posttreatment tumor characteristics in patients treated with neoadjuvant chemotherapy.

NEOADJUVANT/ADJUVANT CHEMOTHERAPY[1,2,3,4]

Regimens for HER2-negative disease (all category 1)[5]

Preferred regimens:

- Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks
- Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel
- TC (docetaxel and cyclophosphamide)

Other regimens:

- Dose-dense AC (doxorubicin/cyclophosphamide)
- FAC/CAF (fluorouracil/doxorubicin/cyclophosphamide)
- FEC/CEF (cyclophosphamide/epirubicin/fluorouracil)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- AC followed by docetaxel every 3 weeks
- AC followed by weekly paclitaxel
- EC (epirubicin/cyclophosphamide)
- FEC/CEF followed by T (fluorouracil/epirubicin/cyclophosphamide followed by docetaxel) or (fluorouracil/epirubicin/cyclophosphamide followed by weekly paclitaxel)
- FAC followed by T (fluorouracil/doxorubicin/cyclophosphamide followed by weekly paclitaxel)
- TAC (docetaxel/doxorubicin/cyclophosphamide)

Regimens for HER2-positive disease[6,7,8]

Preferred regimens:

- AC followed by T + trastuzumab ± pertuzumab[9] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab ± pertuzumab, various schedules)
- TCH (docetaxel/carboplatin/trastuzumab) ± pertuzumab

Other regimens:

- AC followed by docetaxel + trastuzumab ± pertuzumab[9]
- FEC followed by docetaxel + trastuzumab + pertuzumab[9]
- FEC followed by paclitaxel + trastuzumab + pertuzumab[9]
- Paclitaxel + trastuzumab[10]
- Pertuzumab + trastuzumab + docetaxel followed by FEC[9]
- Pertuzumab + trastuzumab + paclitaxel followed by FEC[9]

[1] Retrospective evidence suggests that anthracycline-based chemotherapy regimens may be superior to non-anthracycline-based regimens in patients with HER2-positive tumors.
[2] Randomized clinical trials demonstrate that the addition of a taxane to anthracycline-based chemotherapy provides an improved outcome.
[3] CMF and radiation therapy may be given concurrently, or the CMF may be given first. All other chemotherapy regimens should be given before radiotherapy.
[4] Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy after chemotherapy.
[5] The regimens listed for HER2-negative disease are all category 1 when used in the adjuvant setting.
[6] In patients with HER2-positive and axillary node-positive breast cancer, trastuzumab should be incorporated into the adjuvant therapy (category 1). Trastuzumab should also be considered for patients with HER2-positive node-negative tumors ≥1 cm (category 1).
[7] Trastuzumab should optimally be given concurrently with paclitaxel as part of the AC followed by paclitaxel regimen, and should be given for 1 y total duration.
[8] A pertuzumab-containing regimen can be administered to patients with ≥T2 or ≥N1, HER2-positive, early-stage breast cancer. Patients who have not received a neoadjuvant pertuzumab-containing regimen can receive adjuvant pertuzumab.
[9] 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.
[10] Paclitaxel + trastuzumab may be considered for patients with low-risk stage I, HER2-positive disease, particularly those not eligible for other standard adjuvant regimens because of comorbidities.

BINV-K

Text cont. from page 543.

Cancer Panel endorses the use of the CAP protocols for reporting the pathologic analysis of all breast cancer specimens.

ER/PR Testing

ER and PR tumor status is normally determined through immunohistochemistry (IHC) testing. Although this method is considered reliable when performed by experienced pathology personnel, several reports have indicated that the reliability of ER and PR determinations can vary widely among laboratories.[7–9] These interlaboratory differences may be attributable to the diverse methodologies and interpretation schema used to evaluate tumor hormonal status. An NCCN Task Force and a panel of ASCO and CAP members have reviewed this topic and issued recommendations on ER and PR testing in breast cancer.[10,11] Breast cancers that have at least 1% of cells staining positive for ER should be considered ER-positive.[10–12]

HER2 Testing

The determination of HER2 tumor status is also recommended for all newly diagnosed invasive breast cancers and for first recurrences of breast cancer whenever possible. The NCCN Breast Cancer Panel endorses CAP accreditation for anatomic pathology laboratories performing HER2 testing.

HER2 status can be assessed through measuring the number of HER2 gene copies using in situ hybridization (ISH) techniques or a complementary method in which the quantity of HER2 cell surface receptors is assessed with IHC.[13] Assignment of HER2 status based on mRNA assays or multigene arrays is not recommended. The accuracy of HER2 assays used in clinical practice is a major concern, and results from several studies have shown that false-positive[14–18] as well as false-negative[14,19] HER2 test results are common. A joint panel from ASCO and CAP issued updated HER2 testing guidelines to avoid these false-positive or false-negative results. These updated guidelines have been published in the *Archives of Pathology & Laboratory Medicine* and the *Journal of Clinical Oncology*.[20,21] The NCCN Panel endorses these updated ASCO/CAP recommendations for quality HER2 testing, and has outlined them in the algorithm.

Treatment Approach

Conceptually, the treatment of breast cancer includes the treatment of local disease with surgery, radiation therapy, or both, and the treatment of systemic disease with cytotoxic chemotherapy, endocrine therapy, biologic therapy, or combinations of these. The need for and selection of various local or systemic therapies are based on several prognostic and predictive factors. These factors include tumor histology, clinical and pathologic characteristics of the primary tumor, axillary lymph node (ALN) status, tumor hormone receptor content, tumor HER2 status, multigene testing, presence or absence of detectable metastatic disease, patient comorbid conditions, patient age, and menopausal status. Breast cancer does occur in men, and men with breast cancer should be treated similarly to postmenopausal women, except that the use of aromatase inhibitors is ineffective without concomitant suppression of testicular steroidogenesis.[22,23] Patient preference is a major component of the decision-making process, especially when survival rates are equivalent among the available treatment options. Although not explicitly stated at every decision point of the guidelines, patient participation in prospective clinical trials is the preferred treatment option for all stages of breast cancer.

The management specific to large clinical stage II tumors and stage III tumors is discussed herein.

Invasive Breast Cancer Stages II and III

Staging and Workup

The recommended workup and staging of invasive breast cancer includes a history and physical examination; a CBC count; liver function tests; bilateral diagnostic mammography; breast ultrasonography, if necessary; determination of tumor ER and PR status; determination of tumor HER2 status; and pathology review. Genetic counseling is recommended if the patient is considered to be at high risk for hereditary breast cancer, as defined by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Genetic/Familial High-Risk Assessment: Breast and Ovarian (to view the most recent version of these guidelines, visit NCCN.org).

Use of MRI during initial workup is optional and may be specially considered for mammographically

occult tumors. MRI may be used to define the extent of cancer or presence of multifocal or multicentric cancer in the ipsilateral breast, or for screening of the contralateral breast (category 2B). It may be helpful for breast cancer evaluation before and after neoadjuvant therapy to define extent of disease, response to treatment, and potential for breast-conserving therapy. MRI of the breast should be performed using a dedicated breast coil, with consultation with the multidisciplinary treatment team, and by a breast imaging team capable of performing MRI-guided biopsy. The limitations of breast MRI include a high percentage of false-positive findings.[24–26] Therefore, MRI should generally be considered for staging breast cancer in patients whose breasts cannot be imaged adequately with mammography and ultrasound (eg, women with very dense breast tissue; women with positive axillary nodal status and occult primary tumor presumed to originate in the breast; to evaluate the chest wall).[27] No randomized, prospective assessment of the utility of MRI in staging of or treatment decision-making in breast cancer is available. One retrospective study suggested an outcome benefit,[28] whereas another did not.[29] One systematic review reported that breast MRI staging altered surgical treatment in 7.8% to 33.3% of women.[26] However, no differences in outcome, if any, can be demonstrated in that analysis. Patients should not be denied the option of breast-conservation therapy based on MRI findings alone without tissue sampling.

Optional Studies as Directed by Signs and Symptoms for All Stages: Additional tests may be considered based on the signs and symptoms. A bone scan is indicated for patients presenting with localized bone pain or elevated alkaline phosphatase. If pulmonary symptoms are present, chest diagnostic CT is indicated. Abdominal imaging using diagnostic CT or MRI is indicated if the patient has elevated alkaline phosphatase, abnormal results on liver function tests, abdominal symptoms, or abnormal physical examination of the abdomen or pelvis. These studies are not indicated in patients with stage I disease without signs/symptoms of metastatic disease, nor are they needed in many other patients with early-stage breast cancer.[30] These recommendations are supported by a study evaluating patients with newly diagnosed breast cancer by bone scan, liver ultrasonography, and chest radiography.[31] Metastases were identified by bone scan in 5.1%, 5.6%, and 14.0% of patients with stage I, II, and III disease, respectively, and no evidence of metastasis was detected by liver ultrasonography or chest radiography in patients with stage I or II disease.[31]

Additional Workup for Patients With Locally Advanced Disease: *Locally advanced breast cancer* describes a subset of invasive breast cancer for which the initial clinical and radiographic evaluation documents advanced disease confined to the breast and regional lymph nodes. The AJCC clinical staging system used in these guidelines and for the determination of operability is recommended, and locally advanced disease is represented by the stage III category. Patients with stage III disease may be further divided into those for whom the initial surgical approach is unlikely to successfully remove all disease or to provide long-term local control, and those for whom a reasonable initial surgical approach is likely to achieve pathologically negative margins and provide long-term local control. Thus, patients with stage IIIA disease are divided into those who have clinical T3N1M0 disease versus those who have clinical TanyN2M0 disease, based on evaluation by a multidisciplinary team. For patients diagnosed with clinical stage III disease, systemic staging should be considered with tests such as a bone scan or sodium fluoride PET/CT (category 2B), and abdominal imaging with diagnostic CT (with or without pelvic CT) or MRI.

Fluorodeoxyglucose (FDG)/PET scan is optional (category 2B). FDG-PET scan can be considered at the same time as diagnostic CT. If FDG-PET and diagnostic CT are performed and both clearly indicate bone metastases, bone scan or sodium fluoride PET/CT may not be needed. The consensus of the panel is that FDG-PET/CT is most helpful when standard imaging results are equivocal or suspicious. However, limited studies[32–38] support a potential role for FDG-PET/CT to detect regional node involvement and distant metastases in locally advanced breast cancer, including T3N1M0 disease. A retrospective study comparing bone scan with integrated FDG-PET/CT in women with stages I–III breast cancer with suspected metastasis observed a high concordance (81%) between the studies for reporting osseous metastases.[39] The panel suggests that bone scan may be omitted if FDG-PET/CT results are positive for bone metastases.

Equivocal or suspicious sites identified by PET/CT scanning should be biopsied for confirmation when-

ever possible and if the disease site would impact the course of treatment. In the past decade, the advent of PET/CT scanners has significantly changed the approach to PET imaging.[40] However, the terminology has also created confusion regarding the nature of the scans obtained from a PET/CT device. PET/CT scanners have both a PET and CT scanner in the same gantry that allows precise coregistration of molecular (PET) and anatomic (CT) imaging. Almost all current clinical PET imaging is performed using combined PET/CT devices.

In PET/CT tomographs, the CT scanner has a second important role beyond diagnostic CT scanning.[40] For PET applications, the CT scan is also used for photon attenuation correction and for anatomic localization of the PET imaging findings. For these tasks, the CT scan is usually taken without breathholding, to match PET image acquisition, and typically uses low-dose (nondiagnostic) CT. Radiation exposure for these nondiagnostic CT scans is lower than for diagnostic CT. Intravenous contrast is not needed for this task.

PET/CT scanners typically include a high-quality CT device that can also be used for stand-alone, optimized, and fully diagnostic CT. Diagnostic CT scans are acquired using breathholding for optimal chest imaging and are often performed with intravenous contrast. For fully diagnostic CT, the CT beam current, and therefore patient radiation exposure, is considerably higher than for the low-dose CT needed for PET requirements. Radiation exposures associated with fully diagnostic CT are often greater than for the emission (PET) component of the study.

Currently, the approach to clinical PET/CT imaging varies widely across centers.[41] Many centers perform low-dose CT as part of a PET/CT scan, and perform optimized, fully diagnostic CT only when diagnostic CT has also been requested in addition to PET/CT. Other centers combine diagnostic CT scans with PET on all of their PET/CT images. The CT scans described in the workup section of the guidelines refer to fully optimized diagnostic CT scans, whereas the PET or PET/CT scans refer to scans primarily directed toward the PET component, not necessarily using diagnostic-quality CT. Referring physicians must understand the differences between PET/CT performed primarily for PET imaging and fully optimized CT performed as a stand-alone diagnostic CT examination.[41] It may be convenient to perform PET/CT and diagnostic CT at the same time.

Fertility Counselling

Numerous epidemiologic studies have shown that childbearing after treatment of invasive breast cancer does not increase rates of recurrence or death from breast cancer.[42] The offspring of pregnancies after treatment of breast cancer do not have an increased rate of birth defects or other serious childhood illness. However, treatment of breast cancer, especially with cytotoxic agents, may impair fertility. Therefore, it is reasonable and appropriate to consider fertility preservation before breast cancer treatment in young women who desire to bear children.[43–47] No high-level evidence shows that ovarian suppression or other interventions decrease the toxicity of cytotoxic chemotherapy on the premenopausal ovary.[48] However, many women, especially those younger than 35 years, regain menstrual function within 2 years of completing chemotherapy.[49] Resumption of menses does not necessarily correlate with fertility, and fertility may be preserved without menses.

All premenopausal patients should be informed about the potential impact of chemotherapy on fertility and asked about their desire for potential future pregnancies. Premenopausal women with newly diagnosed breast cancer who desire to bear children after breast cancer treatment should undergo consultation with a physician with expertise in fertility before initiation of chemotherapy.[47,50] Multiple factors must be considered when making a decision about fertility preservation, including patient preference, patient age, risk of premature ovarian failure based on anticipated chemotherapy, and length of optimal endocrine therapy. It is important for fetal safety that women do not become pregnant during breast cancer treatment. Also see NCCN Guidelines for Adolescent and Young Adult Oncology (to view the most recent version of these guidelines, visit NCCN.org).

Preoperative Systemic Therapy

Preoperative chemotherapy should be considered for women with locally advanced invasive breast cancer (stage III) and those with large clinical stage IIA, stage IIB, and T3N1M0 tumors who meet the criteria for breast-conserving therapy except for tumor size and wish to undergo breast-conserving therapy. In the available data from clinical trials of preoperative systemic therapy, pretreatment biopsies have

been limited to core needle biopsy or fine-needle aspiration (FNA) cytology. Therefore, according to the NCCN panel, in patients anticipated to receive preoperative systemic therapy, core biopsy of the breast tumor and placement of image-detectable markers should be considered to demarcate the tumor bed for any future (postchemotherapy) surgical management. Clinically positive ALNs should be sampled through FNA or core biopsy, and the positive nodes must be removed after preoperative systemic therapy at the time of definitive surgery. Patients with clinically negative ALNs should undergo axillary ultrasound before neoadjuvant treatment. For those with clinically suspicious ALNs, the panel recommends consideration of either a core biopsy or FNA of these nodes.[51] If FNA or core biopsy indicates any positive nodes, these should be removed after neoadjuvant therapy at the time of definitive surgery.

According to the panel, axillary staging after preoperative systemic therapy may include sentinel node biopsy or level I/II dissection. Level I/II dissection should be performed when patients are proven node-positive before neoadjuvant therapy (category 2B). The false-negative rate of sentinel lymph node (SLN) biopsy in either the pre- or postchemotherapy setting is low.[52–54] Nevertheless, the possibility remains that a pathologic complete response after chemotherapy may occur in lymph node metastases previously undetected in the clinical examination. SLN excision can be considered before preoperative systemic therapy is administered, because it provides additional information to guide local and systemic treatment decisions.[55,56] If SLN resection is performed after administration of preoperative systemic therapy, both the prechemotherapy clinical and the postchemotherapy pathologic nodal stages must be used to determine the risk of local recurrence. Close communication between members of the multidisciplinary team, including the pathologist, is particularly important when any treatment strategy involving preoperative systemic therapy is planned.

In some patients, preoperative systemic therapy results in sufficient tumor response to make breast-conserving therapy possible. Because complete or near-complete clinical responses are common, the use of percutaneously placed clips into the breast under mammographic or ultrasound guidance or other method of localizing prechemotherapy tumor volume aids in the postchemotherapy resection of the original area of tumor and is encouraged. The results of the NSABP B-18 trial show that breast conservation rates are higher after preoperative systemic therapy.[57] However, preoperative systemic therapy has no demonstrated disease-specific survival advantage over postoperative adjuvant chemotherapy in patients with stage II tumors. NSABP B-27 was a 3-arm, randomized, phase III trial of women with invasive breast cancer treated with preoperative systemic therapy with AC (doxorubicin/cyclophosphamide) for 4 cycles followed by local therapy alone, preoperative AC followed by preoperative docetaxel for 4 cycles followed by local therapy, or AC followed by local therapy followed by 4 cycles of postoperative docetaxel.[58] Results from this study, which involved 2411 women, documented a higher rate of complete pathologic response at the time of local therapy in patients treated preoperatively with 4 cycles of AC followed by 4 cycles of docetaxel versus 4 cycles of preoperative AC. This trial did not show disease-free and overall survivals to be superior with the addition of docetaxel treatment.[58] A disease-free survival advantage was observed (hazard ratio [HR], 0.71; 95% CI, 0.55–0.91; P=.007) favoring preoperative versus postoperative docetaxel in the subset of patients experiencing a clinical partial response to AC. For patients with inoperable, noninflammatory, locally advanced disease at presentation (clinical stages IIIA [except for T3N1M0], IIIB, or IIIC), the initial use of anthracycline-based preoperative systemic therapy with or without a taxane is standard therapy.[59]

Several chemotherapy regimens have been studied as preoperative systemic therapy. The panel believes that the regimens recommended in the adjuvant setting are appropriate to consider in the preoperative systemic therapy setting. The benefits of "tailoring" preoperative systemic therapy (ie, switching following limited response) or using preoperative systemic therapy to evaluate disease responsiveness have not been well studied.[60]

Preoperative Systemic Therapy in Patients With HER2$^+$ Tumors: In women with HER2$^+$ tumors treated with neoadjuvant chemotherapy, the addition of neoadjuvant trastuzumab to paclitaxel followed by chemotherapy with FEC (fluorouracil/epirubicin/cyclophosphamide) was associated with

an increase in the pathologic complete response rate from 26.0% to 65.2% (P=.016).[61] Thus, the incorporation of trastuzumab into neoadjuvant chemotherapy regimens seems to be important in HER2$^+$ tumors.[62]

The GeparQuinto phase III trial led by the German Breast Group studied 620 women with untreated, HER2$^+$, primary invasive breast cancer.[63] Patients were randomized to receive 4 cycles of epirubicin/cyclophosphamide followed by docetaxel administered concurrently with either trastuzumab or lapatinib. The primary end point, pathologic complete response, was achieved in 30.3% of patients who received trastuzumab plus chemotherapy, compared with 22.7% of patients who received lapatinib plus chemotherapy (odds ratio, 0.68; 95% CI, 0.47–0.97; P<.04).[63] Edema and dyspnea occurred more frequently in the trastuzumab group, whereas diarrhea and skin rash occurred more frequently in the lapatinib group.

The NeoALTTO trial randomized 455 patients with HER2$^+$ primary breast cancer to receive lapatinib plus paclitaxel or trastuzumab plus paclitaxel or a combination of lapatinib and trastuzumab plus paclitaxel.[64] The results showed that the pathologic complete response rate was 51.3% (95% CI, 43.1–59.5) in the lapatinib plus trastuzumab combination arm, compared with a rate of 24.7% (95% CI, 18.1–32.3) for the lapatinib arm and 29.5% (95% CI, 22.4–37.5) for the trastuzumab arm. The difference in pathologic complete response rate between the lapatinib plus trastuzumab arm and the trastuzumab arm was statistically significant (difference, 21.1%; range, 9.1–34.2; P=.0001). The pathologic complete response rate difference between the lapatinib and trastuzumab arms was not statistically significant (difference, –4.8%; range, –17.6–8.2; P=.34).[64] Grade 3/4 liver enzyme abnormalities occurred more frequently with trastuzumab plus lapatinib or lapatinib alone compared to trastuzumab alone.[64] Updated preliminary data presented at the 2013 San Antonio Breast Cancer Symposium showed that patients who experienced a pathologic complete response had a better outcome than those who did not.[65] These studies thus confirm that the use of HER2-targeted therapy is important in the preoperative treatment of HER2$^+$ primary breast cancer. Significant uncertainty remains regarding the optimal regimen of HER2 targeting. The NeoALTTO study results confirm the potential of dual HER2-targeted therapy in the neoadjuvant setting.

Pertuzumab is a recombinant humanized monoclonal antibody that inhibits the ligand-dependent dimerization of HER2 and its downstream signaling. Pertuzumab and trastuzumab bind to different epitopes of HER2 receptor and have complementary mechanisms of action. When administered together in HER2$^+$ tumor models and in humans, they provide a greater overall antitumor effect than either alone.[66,67] Because the combination of pertuzumab and trastuzumab showed significant overall survival benefit in the metastatic setting,[68] it was also examined in the neoadjuvant setting.[69,70]

The FDA recently granted accelerated approval for pertuzumab in combination with trastuzumab and docetaxel as neoadjuvant treatment for patients with HER2$^+$ early-stage breast cancer, including those with either tumors greater than 2 cm in diameter (≥T2) or positive nodes (≥N1). The accelerated approval was based on the results of 2 phase II trials, the NeoSphere trial[70] and the TRYPHAENA study,[69] which showed significant improvement in pathologic complete response in patients receiving pertuzumab, trastuzumab, and docetaxel. Pathologic complete response is defined by the FDA as "the absence of invasive cancer in the breast and lymph nodes."

In the NeoSphere trial, 417 patients were randomized 1:1:1:1 to receive trastuzumab plus docetaxel; pertuzumab and trastuzumab plus docetaxel; pertuzumab and trastuzumab; or pertuzumab plus docetaxel. A total of 45.8% (95% CI, 36.1–55.7) of patients who received pertuzumab plus trastuzumab and docetaxel experienced a pathologic complete response, compared with only 29% (CI, 20.6–38.5) who experienced a pathologic complete response on the trastuzumab plus docetaxel regimen (P=.0063).[70] The TRYPHAENA was a phase II randomized multicenter trial designed to evaluate the safety and tolerability of trastuzumab and pertuzumab in combination with anthracycline- or carboplatin-based neoadjuvant chemotherapy. A total of 225 patients with HER2$^+$, locally advanced (T2–3, N2–3, M0; T4a–cNanyM0), inflammatory (T4dNanyM0) or early-stage breast cancer (tumors >2 cm) were enrolled and randomized 1:1:1 to receive 6 cycles of neoadjuvant therapy with FEC plus trastuzumab and pertuzumab followed by docetaxel, trastuzumab,

and pertuzumab; FEC followed docetaxel, trastuzumab, and pertuzumab; or docetaxel, carboplatin, trastuzumab along with pertuzumab. Based on the assessment of pathologic complete response, all 3 regimens seem active. The reported pathologic complete response ranged from 57.3% to 66.2%, with the highest seen in patients who received pertuzumab, trastuzumab, docetaxel, and carboplatin chemotherapy. The adverse events reported in the trial were consistent with those seen with each of the 3 agents, and low rates of symptomatic left ventricular systolic dysfunction were reported.

The panel has included pertuzumab-based regimens as neoadjuvant therapy options for patients with early-stage (≥T2 or ≥N1) $HER2^+$ tumors.

Preoperative Systemic Endocrine Therapy: Several randomized trials have assessed the value of neoadjuvant endocrine therapy in postmenopausal women with ER^+ breast cancer. These studies have generally compared the rates of objective response and breast-conserving surgery among treatment with tamoxifen, anastrozole, anastrozole plus tamoxifen, and letrozole. These studies consistently show that the use of either anastrozole or letrozole alone provides superior rates of breast-conserving surgery and usually objective response when compared with tamoxifen.[71,72] Based on these trials, the panel recommends that if preoperative endocrine therapy is to be used, an aromatase inhibitor is preferred in the treatment of postmenopausal women with hormone receptor-positive disease.

Locoregional Treatment After Preoperative Systemic Therapy

For large stage II tumors and IIIA (T3N1M0), local therapy after a complete or partial response to preoperative systemic therapy is usually lumpectomy, if possible, along with surgical axillary staging. If lumpectomy is not possible or progressive disease is confirmed, mastectomy is performed along with surgical axillary staging with or without breast reconstruction. Surgical axillary staging may include SLN biopsy or level I/II dissection. If SLN biopsy was performed before administering preoperative systemic therapy and the findings were negative, then further ALN staging is not necessary. If an SLN procedure was performed before administering preoperative systemic therapy and the findings were positive, then a level I/II ALN dissection should be performed. Local therapy for clinical stages IIIA (except for T3N1M0), IIIB, or IIIC after a clinical response to preoperative systemic therapy usually consists of total mastectomy with level I/II ALN dissection, with or without delayed breast reconstruction or lumpectomy and level I/II axillary dissection.

If an inoperable tumor fails to respond, or the response is minimal, after several cycles of preoperative systemic therapy, or the disease progresses at any point, an alternative chemotherapy agent and/or preoperative radiation therapy could be considered followed by local therapy, usually a mastectomy plus axillary dissection, with or without breast reconstruction. Postsurgical adjuvant treatment for these patients consists of completion of planned chemotherapy if not completed preoperatively, followed by endocrine therapy (category 1) in women with ER^- and/or PR^+ tumors. Up to 1 year of trastuzumab therapy should be completed if the tumor is $HER2^+$ (category 1).

Radiation therapy is recommended based on prechemotherapy characteristics to the chest wall and supraclavicular lymph nodes (see "Principles of Radiation Therapy" [available online, in these guidelines, at NCCN.org] and "Radiation After Mastectomy" on page 562). The panel recommends strong consideration of including the internal mammary lymph nodes in the radiation therapy field (category 2B). Endocrine therapy and trastuzumab can be administered concurrently with radiation therapy if indicated.

Surgical Axillary Staging

Pathologic confirmation of malignancy using ultrasound-guided FNA or core biopsy must be considered in patients with clinically positive nodes to determine whether axillary lymph node dissection is needed.

Performance of SLN mapping and resection in the surgical staging of the clinically negative axilla is recommended by the panel for assessment of the pathologic status of the ALNs in patients with clinical stage I or II breast cancer.[54,73–81] This recommendation is supported by results of randomized clinical trials showing decreased arm and shoulder morbidity (eg, pain, lymphedema, sensory loss) in patients with breast cancer undergoing SLN biopsy compared with patients undergoing standard ALN dissection.[81,82] No significant differences in the effectiveness of the SLN procedure or level I and II dissection in deter-

mining the presence or absence of metastases in axillary nodes were seen in these studies. However, not all women are candidates for SLN resection. An experienced SLN team is mandatory for the use of SLN mapping and excision.[83,84] Women who have clinical stage I or II disease and do not have immediate access to an experienced SLN team should be referred to an experienced SLN team for the definitive surgical treatment of the breast and surgical ALN staging. In addition, potential candidates for SLN mapping and excision should have clinically negative ALNs at the time of diagnosis, or a negative core or FNA biopsy of any clinically suspicious ALNs.

In many institutions, SLNs are assessed for the presence of metastases using both hematoxylin-eosin (H&E) staining and cytokeratin IHC. The clinical significance of a lymph node that is negative on H&E staining but positive on cytokeratin IHC is not clear. Because the historical and clinical trial data on which treatment decisions are based have relied on H&E staining, the panel does not recommend routine cytokeratin IHC to define node involvement and believes that current treatment decisions should be made based solely on H&E staining. This recommendation is further supported by a randomized clinical trial (ACOSOG Z0010) of patients with H&E-negative nodes, in which further examination by cytokeratin IHC was not associated with improved overall survival over a median of 6.3 years.[85] In the uncommon situation in which H&E staining is equivocal, reliance on the results of cytokeratin IHC is appropriate.

Multiple attempts have been made to identify cohorts of women with involved SLNs who have a low enough risk for non-SLN involvement that complete axillary dissection might be avoided if the SLN is positive. None of the early studies identified a low risk group of patients with positive SLN biopsies but consistently negative nonsentinel nodes.[86–92] Nonetheless, a randomized trial (ACOSOG Z0011) compared SLN resection alone with ALN dissection in women aged 18 years or older with T1/T2 tumors, fewer than 3 positive SLNs, and undergoing breast-conserving surgery and whole-breast irradiation, and found no difference in local recurrence, disease-free survival, or overall survival between the treatment groups. Only ER^- status, age younger than 50 years, and lack of adjuvant systemic therapy were associated with decreased overall survival.[93] At a median follow-up of 6.3 years, locoregional recurrences were noted in 4.1% of the ALN dissection patients (n=420) and 2.8% of the SLN dissection patients (n=436; *P*=.11). Median overall survival was approximately 92% in each group.[94] Therefore, based on these results after SLN mapping and excision, if a patient has a T1 or T2 tumor with 1 to 2 positive SLNs, did not receive neoadjuvant therapy, and is treated with lumpectomy and whole breast radiation, the panel recommends considering either level I and II axillary dissection or no further axillary surgery.

The panel recommends level I or II axillary dissection when patients have clinically positive nodes at the time of diagnosis, which is confirmed by FNA or core biopsy, and when sentinel nodes are not identified. Traditional level I and II evaluation of ALN requires that at least 10 lymph nodes should be provided for pathologic evaluation to accurately stage the axilla.[95,96] ALN should be extended to include level III nodes only if gross disease is apparent in the level II nodes. In the absence of gross disease in level II nodes, lymph node dissection should include tissue inferior to the axillary vein from the latissimus dorsi muscle laterally to the medial border of the pectoralis minor muscle (level I/II). Furthermore, according to the panel, without definitive data demonstrating superior survival with ALN dissection or SLN resection, these procedures may be considered optional in patients who have particularly favorable tumors, those for whom the selection of adjuvant systemic therapy will not be affected by the results of the procedure, those who are elderly, and those with serious comorbid conditions. Women who do not undergo ALN dissection or ALN irradiation are at increased risk for ipsilateral lymph node recurrence.[97] Women who undergo mastectomy are appropriate candidates for breast reconstruction (see next section).

Radiation Therapy After Mastectomy

Node-Positive Disease: Three randomized clinical trials have shown that a disease-free and overall survival advantage is conferred by irradiation of the chest wall and regional lymph nodes in women with positive ALNs after mastectomy and ALN dissection.[98–102] In these trials, the ipsilateral chest wall and ipsilateral locoregional lymph nodes were irradiated. Based on these studies, the current guidelines recommend postmastectomy irradiation in women with 4 or more positive ALNs, and strong consideration of postmastectomy irradiation in women with 1 to 3

positive ALNs. Two retrospective analyses have provided evidence for the benefit of radiation therapy in only selected patients receiving preoperative systemic therapy before mastectomy.[103,104]

However, the panel recommends that decisions related to administration of radiation therapy for patients receiving neoadjuvant chemotherapy should be made based on prechemotherapy tumor characteristics, irrespective of tumor response to preoperative systemic therapy (ie, radiation therapy is recommended in patients with clinical stage III disease and a pathologic complete response to neoadjuvant chemotherapy).

Women with 4 or more positive ALNs are at substantially increased risk for locoregional recurrence of disease. The use of prophylactic chest wall irradiation in this setting substantially reduces the risk of local recurrence.[105] The use of postmastectomy, postchemotherapy chest wall irradiation, and regional lymph node irradiation is recommended (category 1).

The recommendation for strong consideration of chest wall and supraclavicular irradiation in women with 1 to 3 involved ALNs generated substantial controversy among panel members. The use of regional nodal irradiation is supported by a subgroup analysis of studies from the Danish Breast Cancer Cooperative Group.[106] In this analysis, a substantial survival benefit was associated with postmastectomy radiation therapy for women with 1 to 3 positive ALNs. Some panel members believe chest wall and supraclavicular irradiation should be used routinely after mastectomy and chemotherapy in this subgroup of patients. However, other panel members believe radiation should be considered in this setting but should not be mandatory, because studies do not show an advantage. This is an unusual situation in which high-level evidence exists but is contradictory.[100–102,105,106] Women with 1 to 3 involved ALNs and tumors larger than 5 cm or tumors with pathologic margins postmastectomy should receive radiation therapy to the chest wall and supraclavicular area.

The panel also recommends strong consideration of ipsilateral internal mammary field radiation therapy in women with positive ALNs (category 2B).

Results from the randomized NCIC-CTG MA.20 trial show that additional regional node irradiation reduces the risk of locoregional and distant recurrence and improves disease-free survival.[107] The study enrolled 1832 women; most (85%) had 1 to 3 positive lymph nodes, and a smaller proportion (10%) had high-risk, node-negative breast cancer. All women had been treated with breast-conserving surgery and adjuvant chemotherapy or endocrine therapy. The participants were randomized to receive either whole-breast radiation therapy alone or whole-breast radiation plus regional node radiation therapy. The interim data found that after a median follow-up of 62 months, statistically significant benefits were seen in the group receiving the added regional node radiation therapy, including improved disease-free survival (HR, 0.68; P=.003; 5-year risk, 89.7% and 84.0%) and overall survival (HR, 0.76; P=.07; 5-year risk, 92.3% and 90.7%).[107] The consensus of the panel is that radiation therapy should be given to clinically or pathologically positive ipsilateral internal mammary lymph nodes, with a strong consideration of treatment of the internal mammary lymph nodes.

Postmastectomy irradiation should be performed using CT-based treatment planning to assure reduced radiation dose to the heart and lungs. The recommended radiation dose for whole-breast radiation is 45 to 50 Gy in fractions of 1.8 to 2.0 Gy, or 42.5 Gy in fractions of 2.55 Gy to the ipsilateral chest wall, mastectomy scar, and drain sites. An additional boost dose of 10 to 16 Gy radiation in 2-Gy single doses is recommended patients who are at high risk for disease recurrence (eg, age <50 years with high-grade tumors).[108–110]

Node-Negative Disease: Features in node-negative tumors that predict a high rate of local recurrence include primary tumors greater than 5 cm and close (<1 mm) or positive pathologic margins. Chest wall irradiation is recommended for these patients.[111] Consideration should be given to radiation to the ipsilateral supraclavicular area and to the ipsilateral internal mammary lymph nodes (category 2B), especially in patients with inadequate axillary evaluation or extensive lymphovascular invasion. Postmastectomy radiation therapy is not recommended for patients with tumors 5 cm or smaller, margins greater than or equal to 1 mm, and no positive ALNs.

The panel recommends that decisions related to administration of radiation therapy for patients receiving preoperative systemic therapy should be made based on preoperative systemic therapy tumor characteristics irrespective of response to neoadju-

vant chemotherapy. Endocrine therapy and trastuzumab can be administered concurrently with radiation therapy if indicated.

Breast Reconstruction

Breast reconstruction may be an option for any woman receiving surgical treatment for breast cancer. Therefore, all women undergoing breast cancer treatment should be educated about breast reconstructive options appropriate for their individual clinical situation. However, breast reconstruction should not interfere with the appropriate surgical management of the cancer.

Factors to be considered when deciding the type of reconstruction include patient preference, body habitus, smoking history, comorbidities, plans for irradiation, and expertise and experience of the reconstruction team. Reconstruction is an optional procedure that does not impact the probability of recurrence or death, but it is associated with an improved quality of life for many patients. It is sometimes necessary to perform surgery on the contralateral breast (eg, breast reduction, implantation) to achieve optimal symmetry between the ipsilateral reconstructed breast and the contralateral breast.

Breast Reconstruction After Mastectomy: Mastectomy results in loss of the breast for breastfeeding, loss of sensation in the skin of the breast and nipple areolar complex (NAC), and loss of the breast for cosmetic, body image, and psychosocial purposes. The loss of the breast for cosmetic, body image, and psychosocial issues may be partially overcome through the performance of breast reconstruction with or without reconstruction of the NAC. Reconstruction can be performed either immediately after mastectomy and under the same anesthetic or in a delayed fashion after mastectomy. In many cases, breast reconstruction involves a staged approach requiring more than one procedure, such as surgery on the contralateral breast to improve symmetry, revision surgery involving the breast and/or donor site, and/or nipple and areola reconstruction and tattoo pigmentation.

Many factors must be considered in the decision-making about breast reconstruction after mastectomy. Several different types of breast reconstruction include the use of implants, autogenous tissues, or both.[112–114] Reconstruction with implants can be performed either through immediate placement of a permanent subpectoral implant or initial placement of a subpectoral expander implant followed by gradual expansion of the implant envelope with stretching of the pectoralis major muscle and overlying skin, followed by replacement of the expander with a permanent implant. A wide variety of implants are available that contain saline, silicone gel, or a combination of saline and silicone gel inside a solid silicone envelope. Autogenous tissue methods of reconstruction use various combinations of fat, muscle, skin, and vasculature from donor sites (eg, abdomen, buttock, back) that may be brought to the chest wall with their original blood supply (pedicle flap) or as free flaps with microvascular anastomoses to blood supply from the chest wall/thorax.[115] Several procedures using autologous tissue are available, including transverse rectus abdominis myocutaneous flap, latissimus dorsi flap, and gluteus maximus myocutaneous flap reconstruction. Composite reconstruction techniques use implants in combination with autogenous tissue reconstruction to provide volume and symmetry. Patients with underlying diabetes or who smoke tobacco have increased rates of complications after autogenous tissue breast cancer reconstruction, presumably because of underlying microvascular disease.

Skin-Sparing Mastectomy: Skin-sparing mastectomy procedures are appropriate for some patients and involve removal of the breast parenchyma, including the NAC, while preserving most of the original skin envelope and are followed by immediate reconstruction with autogenous tissue, a prosthetic implant, or a composite of autogenous tissue and an implant. Skin-sparing mastectomy involving preservation of the skin of the NAC has become the subject of increased attention. Possible advantages of this procedure include improvements in breast cosmesis, body image, and nipple sensation after mastectomy, although the impact of this procedure on these quality-of-life issues has not been well studied.[116–118] Limited data from surgical series, with short follow-up, suggest that performance of NAC-sparing mastectomy in selected patients is associated with low rates of both occult involvement of the NAC with breast cancer and local recurrence of disease.[117,119,120] NAC-sparing procedures may be an option in patients who are carefully selected by experienced multidisciplinary teams. According to the panel, assessment of nipple margins is mandatory when considering NAC-sparing procedures. Retro-

spective data support the use of NAC-sparing procedures for patients with breast cancer, with low rates of nipple involvement and local recurrence because of early-stage, biologically favorable (eg, Nottingham grade I or 2, node-negative, HER2$^-$, no lymphovascular invasion), invasive cancers and/or ductal carcinoma in situ that are peripherally located in the breast (>2 cm from nipple).[121,122] Contraindications for nipple preservation include evidence of nipple involvement, such as Paget disease or bloody nipple discharge. Several prospective trials are underway to evaluate NAC-sparing mastectomy in the setting of cancer, and enrollment in such trials is encouraged.

Advantages of a skin-sparing mastectomy procedure include an improved cosmetic outcome resulting in a reduction in the size of the mastectomy scar and a more natural breast shape, especially when autologous tissue is used in reconstruction,[123] and the ability to perform immediate reconstruction. Although no randomized studies have been performed, results of several mostly retrospective studies have indicated that the risk of local recurrence is not increased in patients undergoing skin-sparing mastectomies compared with those undergoing non–skin-sparing procedures; however, strong selection biases almost certainly exist in the identification of patients appropriate for skin-sparing procedures.[124–128] Reconstruction of the NAC may also be performed in a delayed fashion if desired by the patient. Reconstructed nipples are devoid of sensation. According to the panel, skin-sparing mastectomy should be performed by an experienced breast surgery team that works in a coordinated, multidisciplinary fashion to guide proper patient selection for skin-sparing mastectomy, determine optimal sequencing of the reconstructive procedures in relation to adjuvant therapies, and perform a resection that achieves appropriate surgical margins. Postmastectomy radiation should still be applied in patients treated with skin-sparing mastectomy based on the same selection criteria as for standard mastectomy.

Postmastectomy Radiation and Breast Reconstruction: Plans for postmastectomy radiation therapy can impact decisions related to breast reconstruction because there is a significantly increased risk of implant capsular contracture after irradiation of an implant. Furthermore, postmastectomy irradiation may have a negative impact on breast cosmesis when autologous tissue is used in immediate breast reconstruction, and may interfere with the targeted delivery of radiation when immediate reconstruction is performed using either autologous tissue or breast implants.[129,130] Some studies, however, have not found a significant compromise in reconstruction cosmesis after irradiation.[131] The preferred approach to breast reconstruction for these patients was a subject of controversy among the panel. Although some experienced breast cancer teams have used protocols in which immediate tissue reconstructions are followed by radiation therapy, it is generally preferred that the radiation therapy precede the placement of the autologous tissue, because of reported loss in reconstruction cosmesis (category 2B).

When implant reconstruction is planned in a patient requiring radiation therapy, the panel prefers a staged approach with immediate tissue expander placement, followed by implant placement. Surgery to exchange the tissue expanders with permanent implants can be performed before radiation or after completion of radiation therapy. Tissue expansion of irradiated skin can result in a significantly increased risk of capsular contracture, malposition, poor cosmesis, and implant exposure. The use of tissue expanders/implants is relatively contraindicated in patients who have been previously irradiated. Immediate placement of an implant in patients requiring postoperative radiation has an increased rate of capsular contracture, malposition, poor cosmesis, and implant exposure.

Several reconstructive approaches are summarized for these patients in "Principles of Breast Reconstruction Following Surgery," available online, in these guidelines, at NCCN.org.

Breast Reconstruction After Lumpectomy: Issues related to breast reconstruction also pertain to women who undergo or have undergone a lumpectomy, particularly when the surgical defect is large and/or expected to be cosmetically unsatisfactory. An evaluation of the likely cosmetic outcome of lumpectomy should be performed before surgery. Oncoplastic techniques for breast conservation can extend breast-conserving surgical options in situations in which the resection, itself, would likely yield an unacceptable cosmetic outcome.[132] The evolving field of oncoplastic surgery includes the use of "volume displacement" techniques performed in conjunction with a large partial mastectomy.[133] Oncoplastic volume displacement procedures combine the removal

of generous regions of breast tissue (typically designed to conform to the segmentally distributed cancer in the breast) with "mastopexy" techniques in which remaining breast tissues are shifted together within the breast envelope to fill the resulting surgical defect and thereby avoid the creation of significant breast deformity. Volume displacement techniques are generally performed during the same operative setting as the breast-conserving lumpectomy by the same surgeon who is performing the cancer resection.[133,134]

Advantages of oncoplastic volume displacement techniques are that they permit the removal of larger regions of breast tissue, thereby achieving wider surgical margins around the cancer, and at the same time better preserve the natural shape and appearance of the breast than standard breast resections.[135]

Limitations of oncoplastic volume displacement techniques include lack of standardization among centers, performance at only a limited number of sites in the United States, and the possible need for subsequent mastectomy if pathologic margins are positive when further breast-conserving attempts are deemed impractical or unrealistic. Nevertheless, panel consensus is that these issues should be considered before surgery for women who are likely to have a surgical defect that is cosmetically unsatisfactory, and that women who undergo lumpectomy and are dissatisfied with the cosmetic outcome after treatment should be offered a consultation with a plastic surgeon to address the repair of resulting breast defects. Patients should be informed of the possibility of positive margins and potential need for secondary surgery, which could include reexcision segmental resection or could require mastectomy with or without loss of the nipple. Oncoplastic procedures can be combined with surgery on the contralateral unaffected breast to minimize long-term asymmetry.

Finally, it is important to note that the primary focus should be on treatment of the tumor, and such treatment should not be compromised when decisions regarding breast reconstruction are made.

Systemic Adjuvant Therapy

After surgical treatment, adjuvant systemic therapy should be considered. The decision is often based on individual risk of relapse and predicted sensitivity to a particular treatment (eg, ER/PR and HER2 status).

The published results of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview analyses of adjuvant polychemotherapy and tamoxifen show convincing reductions in the odds of recurrence and death in all age groups for chemotherapy and for endocrine therapy.[2,136] Thus, the current guidelines recommend adjuvant therapy without regard to patient age (category 1). The decision to use systemic adjuvant therapy requires considering and balancing the risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, the toxicity of the therapy, and comorbidity.[137,138] The decision-making process requires a collaboration involving the health care team and the patient. Panel consensus is that data are insufficient to make definitive chemotherapy recommendations for patients older than 70 years. Although AC or CMF (cyclophosphamide/methotrexate/fluorouracil) was superior to capecitabine in a randomized trial of women aged 65 years or older with early-stage breast cancer, enrollment in that study was discontinued early.[139] A possibility also exists that AC/CMF is not superior to any chemotherapy in this cohort. Therefore, treatment should be individualized for women in this age group, with consideration given to comorbid conditions.

Estimating Risk of Relapse or Death and Benefits of Systemic Treatment

Several prognostic factors predict for future recurrence or death from breast cancer. The strongest prognostic factors are patient age, comorbidity, tumor size, tumor grade, number of involved ALNs, and possibly HER2 tumor status. Algorithms have been published estimating rates of recurrence,[137] and a validated computer-based model to estimate 10-year disease-free and overall survivals is available (Adjuvant! Online; www.adjuvantonline.com) that incorporates all of the above prognostic factors except for HER2 tumor status.[138,140] These tools help clinicians objectively estimate outcome with local treatment only, and also help estimate the absolute benefits expected from systemic adjuvant endocrine therapy and chemotherapy. These estimates may be used by the clinician and patient in their shared decision-making regarding the toxicities, costs, and benefits of systemic adjuvant therapy.[141]

A determination of the HER2 status of the tumor is recommended for prognostic purposes for patients with node-negative breast cancer.[142] More

importantly, HER2 tumor status also provides predictive information used in selecting optimal adjuvant/neoadjuvant therapy and in the selection of therapy for recurrent or metastatic disease (category 1). For example, retrospective analyses have shown that anthracycline-based adjuvant therapy is superior to non–anthracycline-based adjuvant chemotherapy in patients with HER2$^+$ tumors,[143–147] and that the dose of doxorubicin may be important in the treatment of tumors that are HER2$^+$.[148] Prospective evidence of the predictive utility of HER2 status in early-stage[149–154] and metastatic breast cancer[155–157] is available for trastuzumab-containing therapies.

Use of DNA microarray technologies to characterize breast cancer has allowed for the development of classification systems based on gene expression profiles.[158] Five major subtypes of breast cancer have been identified by DNA microarray gene expression profiling: ER$^+$/HER2$^-$ (luminal A and B subtypes); ER$^-$/HER2$^-$ (basal subtype); HER2$^+$; and tumors that have characteristics similar to normal breast tissue.[159–161] In retrospective analyses, these gene expression subtypes are associated with differing relapse-free survival and overall survival.

Another gene-based approach is the 21-gene assay using reverse transcription polymerase chain reaction (RT-PCR) on RNA isolated from paraffin-embedded breast cancer tissue (Oncotype Dx). On retrospective analysis of 2 trials (NSABP B-14 and B-20) performed in women with hormone receptor–positive, ALN-negative invasive breast cancer, this assay system was able to quantify risk of recurrence as a continuous variable (eg, Oncotype Dx recurrence score) and to predict responsiveness to both tamoxifen and CMF or methotrexate/5-fluorouracil/leucovorin chemotherapy.[162,163] A comparison of simultaneous analyses of breast cancer tumors using 5 different gene expression models indicated that 4 of these methods (including MammaPrint and Oncotype Dx) provided similar predictions of clinical outcome.[164]

A similar approach has been used to define more limited sets of genes for prognostic and predictive purposes.[165] For example, the MammaPrint assay uses microarray technology to analyze a 70-gene expression profile from breast tumor tissue as a means of selecting patients with early-stage breast cancer who are more likely to develop distant metastases.[166–172] MammaPrint is approved by the FDA for helping to assign women with ER$^+$ or ER$^-$ breast cancer into a high versus low risk for recurrence, but not for predicting benefit from adjuvant systemic therapy. Studies using MammaPrint as a prognostic and predictive tool are small and/or retrospective in nature.

Multiple other multigene or multigene expression assay systems have been developed. These systems are generally based on small, retrospective studies, and the panel believes that none are currently sufficiently validated to warrant inclusion in the guidelines.

Although many of the DNA microarray technologies are able to stratify patients into prognostic and/or predictive subsets on retrospective analysis, the gene subsets differ from study to study, and prospective clinical trials testing the utility of these techniques have yet to be reported. Currently, prospective randomized clinical trials are addressing the use of Oncotype DX and MammaPrint as predictive and/or prognostic tools in populations of women with early-stage, lymph node–negative breast cancer.[173,174] Pending the results of the prospective trials, the panel considers the 21-gene RT-PCR assay to be an option when evaluating patients with primary tumors characterized as 0.6 to 1.0 cm with unfavorable features or greater than 1.0 cm, and node-negative, hormone receptor–positive, and HER2$^-$ (category 2A). In this circumstance, the recurrence score may be determined to help estimate the likelihood of recurrence and benefit from chemotherapy. The panel emphasizes that the recurrence score should be used for decision-making only in the context of other elements of risk stratification for an individual patient. Unplanned, retrospective subset analysis from a single randomized clinical trial in postmenopausal, ALN-positive, ER$^+$ breast cancer found that the 21-gene RT-PCR assay may provide predictive information for chemotherapy benefit in addition to tamoxifen.[175] Patients with a high score in the study benefited from chemotherapy, whereas patients with a low score did not seem to benefit from the addition of chemotherapy, regardless of the number of positive lymph nodes.[175] Patient selection for assay use remains controversial.

The additional benefit from adjuvant chemotherapy in addition to endocrine therapy is currently unclear for intermediate-risk patients (as assessed by the gene-based assays). The TAILORx and RxPONDER trials are being conducted to help answer

this question. In the TAILORx trial, patients with node-negative, hormone receptor–positive breast cancer classified as being at low risk based on the gene signature or Adjuvant! Online estimates receive endocrine therapy alone, whereas patients deemed to be at high risk based on gene signature profiles or other characteristics receive chemotherapy in addition to endocrine therapy. Those classified as intermediate risk are randomized to receive chemotherapy or no chemotherapy.[176] The RxPONDER trial will confirm the SWOG-8814 trial data for women with ER$^+$, node-positive disease treated with endocrine therapy with or without chemotherapy based on risk scores.[173] The findings from these trials will help determine the benefit of treating patients at intermediate risk with adjuvant chemotherapy. The MINDACT trial is underway in Europe to compare the 70-gene signature with the commonly used clinicopathologic criteria in selecting patients with breast cancer with 0 to 3 positive nodes for adjuvant chemotherapy.[174] The findings from this trial will help determine the prognostic value of MammaPrint and the benefit of treating intermediate-risk patients with adjuvant chemotherapy.

Stratification for Systemic Adjuvant Therapy

The guidelines recognize subsets of patients who have early breast cancer with the usual histologies based on responsiveness to endocrine therapy and trastuzumab (ie, hormone receptor status, HER2 status). Patients are then further stratified according to risk of disease recurrence based on anatomic and pathologic characteristics (ie, tumor grade, tumor size, ALN status, angiolymphatic invasion).

Endocrine therapy may be considered to reduce the risk for a second contralateral breast cancer, especially in those with ER$^+$ disease. The NSABP database demonstrated a correlation between the ER status of a new contralateral breast tumor and the original primary tumor, which reinforced the notion that endocrine therapy is not an effective strategy to reduce the risk for contralateral breast cancer in patients diagnosed with ER$^-$ tumors.[177] Unfavorable prognostic features include intramammary angiolymphatic invasion, high nuclear grade, high histologic grade, HER2$^+$ status, or hormone receptor–negative status (category 2B).

ALN-Negative Tumors

For women with lymph node-negative, hormone receptor-negative tumors greater than 1 cm in diameter, systemic adjuvant chemotherapy is recommended (category 1). For those with lymph node–negative, hormone receptor–positive breast cancer tumors greater than 1 cm, endocrine therapy with chemotherapy is recommended (category 1). Incremental benefit of combination chemotherapy in patients with lymph node–negative, hormone receptor–positive breast cancer may be relatively small.[178] Therefore, the panel recommends that tumor hormone receptor status be included as one of the factors considered when making chemotherapy-related treatment decisions for patients with node-negative, hormone receptor–positive breast cancer. Patients for whom this evaluation may be especially important are those with tumors characterized as 0.6 to 1.0 cm and hormone receptor–positive that are grade 2 or 3 or have unfavorable features, or greater than 1 cm and hormone receptor–positive and HER2$^-$. However, chemotherapy should not be withheld from these patients solely based on ER$^+$ tumor status.[2,178,179]

The use of genomic/gene expression array data that also incorporate additional prognostic/predictive biomarkers (eg, Oncotype Dx recurrence score) may provide additional prognostic and predictive information beyond anatomic staging and determination of ER/PR and HER2 status. Assessment of the role of the genomic/gene expression array technology is difficult because of the retrospective nature of the studies, the evolution of chemotherapy and hormone therapy regimens, and the overall more favorable prognosis of the patients with lymph node–negative disease compared with those enrolled in the historically controlled clinical trials. Some NCCN Member Institutions consider performing RT-PCR analysis (eg, Oncotype DX assay) to further refine risk stratification for adjuvant chemotherapy in patients with node-negative, ER$^+$, HER2$^-$ breast cancers greater than 0.5 cm, whereas others do not.

ALN–Positive Tumors

Patients with lymph node–positive disease are candidates for chemotherapy and, if the tumor is hormone receptor–positive, for the addition of endocrine therapy (category 1). In postmenopausal women with hormone receptor–positive disease, an aromatase inhibitor should be used either as initial adjuvant therapy, sequentially with tamoxifen, or as extended therapy after tamoxifen, unless a contraindication exists or the woman declines this therapy. In premenopausal women, adjuvant tamoxifen is

recommended. If both chemotherapy and tamoxifen are administered, data from the Intergroup trial 0100 suggest that delaying initiation of tamoxifen until after completion of chemotherapy improves disease-free survival compared with concomitant administration.[179] Consequently, chemotherapy followed by endocrine therapy should be the preferred therapy sequence.

Adjuvant Endocrine Therapy

The guidelines call for the determination of ER and PR content in all primary invasive breast cancers.[10] Patients with invasive breast cancers that are ER$^+$ or PR$^+$ should be considered for adjuvant endocrine therapy regardless of patient age, lymph node status, or whether adjuvant chemotherapy is to be administered.[180] Selected studies suggest that HER2$^+$ breast cancers may be less sensitive to some endocrine therapies, although other studies have failed to confirm this finding.[145,181–188] 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.[189] However, given the favorable toxicity profile of the available endocrine therapies, the panel recommends the use of adjuvant endocrine therapy in most women with hormone receptor–positive breast cancer regardless of menopausal status, age, or HER2 status of the tumor. Possible exceptions to this recommendation are patients with lymph node–negative cancers 0.5 cm or less or 0.6 to 1.0 cm in diameter with favorable prognostic features for whom the prognosis is so favorable that the benefits of adjuvant endocrine therapy are very small.

The most firmly established adjuvant endocrine therapy is tamoxifen for both premenopausal and postmenopausal women.[2] In women with ER$^+$ breast cancer, adjuvant tamoxifen decreases the annual odds of recurrence by 39% and the annual odds of death by 31% irrespective of the use of chemotherapy, patient age, menopausal status, or ALN status.[2] In patients receiving both tamoxifen and chemotherapy, chemotherapy should be given first, followed by sequential tamoxifen.[179] Prospective, randomized trials have shown that 5 years of tamoxifen is more effective than 1 to 2 years.[190,191]

The ATLAS trial randomly allocated 12894 women who had completed 5 years of tamoxifen to either continue tamoxifen up to 10 years or discontinue at 5 years (control). The outcome analyses of 6846 women with ER$^+$ disease showed that extending adjuvant treatment up to 10 years reduced the risk of relapse and breast cancer–related mortality.[192] The risk of recurrence during years 5 to 14 was 21.4% for women receiving tamoxifen versus 25.1% for controls (absolute recurrence reduction, 3.7%). Patients receiving tamoxifen beyond 10 years of treatment had a greater reduction in risk of progression, possibly because of 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. Furthermore, reduced mortality was apparent after completion of 10 years of treatment with tamoxifen. With regard to toxicity, the most important adverse effects noted in all women in ATLAS were an increased risk of endometrial cancer after treatment with 10 years of tamoxifen and pulmonary embolism. The recurrence rate ratios for incidence of adverse events (hospitalization or death) were: pulmonary embolus, 1.87 (95% CI, 1.13–3.07; P=.01 [including 0.2% mortality in both treatment groups]); stroke, 1.06 (0.83–1.36); ischemic heart disease, 0.76 (0.60–0.95; P=.02); and endometrial cancer, 1.74 (1.30–2.34; P=.0002). The cumulative risk for endometrial cancers during 5 to 14 years was 3.1%, with a mortality of 0.4% associated with endometrial cancer, higher than what was noted in the control group of patients receiving only 5 years of therapy (cumulative risk, 1.6%; mortality, 0.2%).[192]

Results are expected in the near future of other ongoing trials of extended tamoxifen, such as the aTTom trial of 5 versus 10 years tamoxifen among approximately 7000 women. Preliminary results of this trial have shown that continuation of tamoxifen beyond 5 years resulted in a nonsignificant reduction in recurrences.[193]

The role of adjuvant ovarian ablation or suppression in premenopausal women with hormone receptor–positive breast cancer is incompletely defined.[194–196] Ovarian ablation may be accomplished through surgical oophorectomy or ovarian irradiation. Ovarian suppression uses luteinizing hormone–releasing hormone (LH-RH) agonists that cause suppression of luteinizing hormone (LH) and release of follicle stimulating hormone (FSH) from the pituitary and reduction in ovarian estrogen production. Available LH-RH agonists in the United States include goserelin and leuprolide. When used

for ovarian suppression, both agents should be given as monthly injections.

The EBCTCG performed a meta-analysis of randomized studies of ovarian ablation or suppression alone versus no adjuvant treatment in women older than 50 years, with many of the subjects in the trials unselected based on hormone receptor status. Reductions in the annual odds of recurrence and death favored ovarian ablation/suppression over no adjuvant treatment (age <40 years: 25% reduction in recurrence rate and 29% reduction in death rate; age 40–49 years: 29% reduction in recurrence rate and 29% reduction in death rate).[195] Analysis of ovarian suppression versus no adjuvant therapy did not show a significant reduction in recurrence (HR reduction, 28.4; 95% CI, 50.5–3.5; *P*=.08) or death (HR reduction, 22; 95% CI, 4.1–6.4; *P*=.11).[197]

Studies in premenopausal women of ovarian ablation or suppression alone versus CMF chemotherapy alone generally demonstrate similar antitumor efficacy in patients with hormone receptor–positive tumors, and superior outcomes with CMF in patients with hormone receptor–negative tumors.[197–205] Findings also suggest that the benefits of ovarian suppression/ablation may be greater in the younger premenopausal group. Studies of ovarian ablation/suppression plus tamoxifen versus chemotherapy alone in premenopausal women generally demonstrate no difference in rates of recurrence or survival between the treatments.[195,206,207]

A large Intergroup study in premenopausal women with hormone receptor–positive, node-positive breast cancer studied adjuvant CAF chemotherapy versus CAF plus ovarian suppression with goserelin (CAF-Z) versus CAF-Z plus tamoxifen (CAF-ZT).[198] The results showed no improvement in time to recurrence or overall survival between CAF with CAF-Z. There was improvement in time to recurrence (HR 0.73, 95% CI 0.59–0.90; *P* < .01) but not overal survival with CAF-Z compared with CAF-ZT (HR, 0.91, 95% CI, 0.71– 1.15; *P*=.21). This study did not include a CAF plus tamoxifen arm, so the contribution of the goserelin to the improved time to recurrence in the CAF-ZT arm cannot be assessed. The EBCTCG also conducted a meta-analysis examining the addition of ovarian suppression/ablation.[195] They identified no statistically significant reduction in annual rates of recurrence or death with the addition of ovarian suppression or ablation to chemotherapy in women younger than 40 years or aged 40 to 49 years.

Thus, selected studies currently suggest benefit from the use of ovarian ablation or suppression in the adjuvant treatment of premenopausal women with hormone receptor–positive breast cancer. However, the benefit of ovarian suppression or ablation when added to combination chemotherapy or tamoxifen, as would be widely used in the United States, is uncertain.

Several studies have evaluated aromatase inhibitors in the treatment of postmenopausal women with early-stage breast cancer. These studies have used aromatase inhibitors as initial adjuvant therapy, as sequential therapy after 2.0 to 3.0 years of tamoxifen, or as extended therapy after 4.5 to 6.0 years of tamoxifen. The aromatase inhibitors are not active in the treatment of women with functioning ovaries and should not be used in women whose ovarian function cannot be assessed reliably because of treatment-induced amenorrhea. The results from 2 prospective randomized clinical trials have provided evidence of an overall survival 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^- disease]) when compared with tamoxifen as the only endocrine therapy.[208,209] In addition, the NCIC-CTG MA-17 trial showed a survival advantage for extended therapy with letrozole compared with placebo in women with ALN-positive (but not lymph node–negative), ER^+ breast cancer.[210] However, no survival differences have been reported for patients receiving initial adjuvant therapy with an aromatase inhibitor versus first-line tamoxifen.[211,212]

Tamoxifen and aromatase inhibitors have different side effect profiles. Both contribute to hot flashes and night sweats and may cause vaginal dryness. Aromatase inhibitors are more commonly associated with musculoskeletal symptoms, osteoporosis, and increased rate of bone fracture, whereas 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 aromatase inhibitor. The ATAC trial showed that anastrozole is superior to tamoxifen or the combination of

tamoxifen and anastrozole in the adjuvant endocrine therapy of postmenopausal women with hormone receptor–positive breast cancer.[213,214] With a median of 100 months follow-up, results in 5216 postmenopausal women with hormone receptor–positive, early-stage breast cancer enrolled in the ATAC trial demonstrated fewer recurrences (HR for disease-free survival, 0.85; 95% CI, 0.76–0.94; *P*=.003) with anastrozole compared with tamoxifen.[211] 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.[214] ATAC trial subprotocols show that anastrozole has a lesser effect on endometrial tissue than tamoxifen[215]; anastrozole and tamoxifen have similar effects on quality of life, with most patients reporting no significant impairment of overall quality of life[216]; anastrozole is associated with a greater loss of bone mineral density[217]; anastrozole shows a small pharmacokinetic interference of unclear significance in the presence of tamoxifen[218]; and no evidence supports an interaction between prior chemotherapy and anastrozole.[219]

BIG 1-98 is a randomized trial testing the use of tamoxifen alone for 5 years, letrozole alone for 5 years, 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 in patients in the sequential arms during their first 2 years of treatment only.[212] With 8010 women included in the analysis, disease-free survival was superior in the women treated with letrozole (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 overall survival has been 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.[220] In addition, a higher incidence of bone fracture was observed for women in the letrozole arm compared with those in the tamoxifen arm (9.5% vs 6.5%).[221] After a longer follow-up (median, 71 months), no significant improvement in disease-free survival was noted with either tamoxifen followed by letrozole or the reverse sequence 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).[222]

Five trials have studied the use of tamoxifen for 2 to 3 years followed sequentially by a third-generation aromatase inhibitor versus continued tamoxifen. The Italian Tamoxifen Anastrozole (ITA) trial randomized 426 postmenopausal women 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.[223] 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).[223] Updated results from this study show the HR for relapse-free survival as 0.56 (95% CI, 0.35–0.89; *P*=.01); the *P* value for overall survival analysis remained at 0.1.[224] The IES trial randomized 4742 postmenopausal women with breast cancer who had completed a total of 2 to 3 years of tamoxifen to either continue tamoxifen or switch to exemestane to complete a total of 5 years of endocrine therapy.[225] The results at a median of 55.7 months of follow-up demonstrated the superiority of sequential exemestane in terms of disease-free survival (HR, 0.76; 95% CI, 0.66–0.88; *P*=.0001), with a significant difference in overall survival in only patients with ER^+ tumors (HR, 0.83; 95% CI 0.69–1.00; log rank *P*=.05). A prospectively planned, combined analysis of 3224 patients enrolled in the ABCSG trial 8 and the Arimidex Nolvadex (ARNO 95) trial has also been reported.[226] Patients in this combined analysis had been randomized after 2 years of tamoxifen to complete 5 years of adjuvant tamoxifen or 3 years of anastrozole. With 28 months of median follow-up available, event-free survival 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 showed that switching from tamoxifen to anastrozole was associated with significant increases in both disease-free survival (HR, 0.66; 95% CI,

0.44–1.00; *P*=.049) and overall survival (HR, 0.0.53; 95% CI, 0.28–0.99; *P*=.045).[209] A meta-analysis of the ABCSG 8, ARNO 95, and ITA studies showed significant improvement in overall survival (HR, 0.71; 95% CI, 0.52–0.98; *P*=.04) with a switch to anastrozole.[227]

The TEAM trial compared sequential 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.[228] 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 finding is consistent with the data from the BIG 1-98 trial,[222] 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.

Results of the MA-17 trial in 5187 women who had completed 4.5 to 6.0 years of adjuvant tamoxifen showed that extended therapy with letrozole provides benefit in postmenopausal women with hormone receptor–positive, early-stage breast cancer.[210,229] At a median follow-up of 2.5 years, the results showed fewer recurrences or new contralateral breast cancers with extended letrozole (HR, 0.58; 95% CI, 0.45– 0.76; *P*<.001). No difference in overall survival was observed (HR, 0.82; 95% CI, 0.57–1.19; *P*=.3), although a survival advantage was seen in the subset of patients with ALN-positive disease (HR 0.61; 95% CI, 0.38–0.98; *P*=.04). 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 1579 women who had been randomly assigned to placebo after 4.5 to 6.0 years of tamoxifen.[230,231] The median time since completion of tamoxifen was 2.8 years. Both disease-free survival and distant disease-free survival 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 6.0 years of tamoxifen therapy followed by no endocrine therapy for an extended period. A formal quality-of-life analysis showed reasonable preservation of quality of life during extended endocrine therapy, although women may experience ongoing menopausal symptoms and loss of bone mineral density.[232,233] 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 a clear direction regarding treatment of postmenopausal women.[192] No available data suggest that an aromatase inhibitor for 5 years provides a better long-term benefit than 10 years of tamoxifen.

In the extension study of ABCSG trial 6, postmenopausal patients with hormone receptor–positive breast cancer received 5 years of adjuvant tamoxifen and were randomized to 3 years of anastrozole or no further therapy.[234] At a median follow-up of 62.3 months, women who received anastrozole (n=387) were reported to have a statistically significantly reduced risk of recurrence compared with women who received no further treatment (n=469; HR, 0.62; 95% CI, 0.40–0.96; *P*=.031).[234]

The differences in design and patient populations among the studies of aromatase inhibitors do not allow for the direct comparison of the results of these studies. A meta-analysis of adjuvant trials of aromatase inhibitors versus tamoxifen alone versus after 2 or 3 years of tamoxifen documented lower recurrence rates with the aromatase inhibitor–containing regimen, with no clear impact on overall survival.[235] Whether initial, sequential, or extended use of adjuvant aromatase inhibitors is the optimal strategy is unknown.

The optimal duration of aromatase inhibitor treatment is also not known, nor is the optimal use vis-à-vis chemotherapy established. Furthermore, the long-term (>5-year) safety and efficacy of these agents are still under investigation. The various studies are consistent in demonstrating that the use of a third-generation aromatase inhibitor in postmenopausal women with hormone receptor–positive breast cancer lowers the risk of recurrence, including ipsilateral breast tumor recurrence, contralateral breast cancer, and distant metastatic disease, when used as initial adjuvant therapy, sequential therapy, or extended therapy. The panel finds no compelling evidence of meaningful efficacy or toxicity differences between the aromatase inhibitors anastrozole, letrozole, and exemestane. All 3 have shown similar antitumor efficacy and toxicity profiles in randomized studies in the adjuvant settings. These guidelines recommend the following adjuvant endocrine therapy options for women with early-stage breast cancer who are postmenopausal at diagnosis: an

aromatase inhibitor as initial adjuvant therapy for 5 years (category 1); tamoxifen for 2 to 3 years followed by one of the following options: an aromatase inhibitor to complete 5 years of adjuvant endocrine therapy (category 1) or 5 years of aromatase inhibitor therapy (category 2B); or tamoxifen for 4.5 to 6.0 years followed by 5 years of an aromatase inhibitor (category 1) or consideration of tamoxifen for up to 10 years. In postmenopausal women, 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 aromatase inhibitors.

In premenopausal women, aromatase inhibitors are associated with the development of benign ovarian pathology and do not adequately suppress ovarian estrogen synthesis. Premenopausal women should not be given adjuvant initial therapy with an aromatase inhibitor outside the confines of a clinical trial. Women who are premenopausal at diagnosis and who become amenorrheic with chemotherapy may have continued estrogen production from the ovaries without menses. Serial assessment of circulating LH, FSH, and estradiol to assure a true postmenopausal status is mandatory if this subset of women is to be considered for therapy with an aromatase inhibitor.[236,237] After 5 years of tamoxifen (category 1), for women postmenopausal at that time (including those who have become postmenopausal during the 5 years of tamoxifen therapy), the panel recommends considering extended therapy with an aromatase inhibitor 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 continuation of tamoxifen therapy for up to 10 years.

Measurement of the nuclear antigen Ki67 using IHC gives an estimate of the tumor cells in the proliferative phase (G1, G2, and M phases) of the cell cycle. Studies have shown the prognostic value of Ki67 as a biomarker and its usefulness in predicting response and clinical outcome.[238] One small study suggests that measurement of Ki67 after short-term exposure to endocrine treatment may be useful in selecting patients resistant to endocrine therapy and those who may benefit from additional interventions.[239] However, these data require larger analytic and clinical validation. In addition, standardization of tissue handling and processing is required to improve the reliability and value of Ki67 testing. No conclusive evidence currently shows that Ki67 alone, especially baseline Ki67 as an individual biomarker, helps in selecting the type of endocrine therapy for an individual patient. Therefore, the panel does not currently recommend assessment of Ki67.

The cytochrome P-450 (CYP) enzyme, CYP2D6, is involved in the conversion of tamoxifen to endoxifen. More than 100 allelic variants of *CYP2D6* have been reported in the literature.[240] Individuals with wild-type *CYP2D6* alleles are classified as extensive metabolizers of tamoxifen. Those with 1 or 2 variant alleles with either reduced or no activity are designated as intermediate metabolizers and poor metabolizers, respectively. A large retrospective study of 1325 patients found that time to disease recurrence was significantly shortened in poor metabolizers of tamoxifen.[241] However, the BIG 1-98 trial reported on the outcome based on CYP2D6 genotype in a subset of postmenopausal patients with endocrine-responsive early-stage invasive breast cancer.[242] The study found no correlation between CYP2D6 allelic status and disease outcome or between CYP2D6 allelic status and tamoxifen-related adverse effects.[242] A genetic analysis of the ATAC trial found no association between CYP2D6 genotype and clinical outcomes.[243] Given the limited and conflicting evidence at this time,[244] the panel does not recommend CYP2D6 testing as a tool to determine the optimal adjuvant endocrine strategy. This recommendation is consistent with the ASCO guidelines.[245] When prescribing a selective serotonin reuptake inhibitor (SSRI), it is reasonable to avoid potent and intermediate CYP2D6 inhibiting agents, particularly paroxetine and fluoxetine, if an appropriate alternative exists.

Adjuvant Cytotoxic Chemotherapy

Several combination chemotherapy regimens are appropriate to consider when adjuvant cytotoxic chemotherapy is used. All adjuvant chemotherapy regimens listed in these guidelines have been evaluated in phase III clinical trials, and the current version of the adjuvant chemotherapy guideline does not distinguish between options for chemotherapy regimens by ALN status.

The adjuvant chemotherapy guidelines also include specific representative doses and schedules for the recommended adjuvant chemotherapy regimens. The regimens have been categorized as "preferred" or "other."

The purpose of distinguishing the adjuvant chemotherapy regimens as preferred and other adjuvant chemotherapy regimens is to convey the sense of the panel regarding the relative efficacy and toxicity of the regimens.[246] Factors considered by the panel include the efficacy, toxicity, and treatment schedules of the regimens. The following sections summarize clinical trial results focusing on treatment efficacy.

Preferred Regimens

Regimens listed as preferred include dose-dense AC with dose-dense sequential paclitaxel; dose-dense AC followed by sequential weekly paclitaxel; and docetaxel plus cyclophosphamide (TC).

The results of 2 randomized trials comparing AC chemotherapy with or without sequential paclitaxel chemotherapy in women with axillary node-positive breast cancer suggest improved disease-free survival rates, and 1 showed improved overall survival, with the addition of paclitaxel.[247,248] On retrospective analysis, the apparent advantage of the paclitaxel-containing regimen seems to be greater in women with ER^- breast cancers.

A randomized trial evaluated the use of concurrent versus sequential chemotherapy (doxorubicin followed by paclitaxel followed by cyclophosphamide versus 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.[249]

The ECOG E1199 study was a 4-arm trial that randomized 4950 women to receive AC chemotherapy followed by either paclitaxel or docetaxel on an every-3-week schedule or a weekly schedule.[250–252] At a median 63.8 months of follow-up, no statistically significant differences in disease-free or overall survivals were observed when comparing paclitaxel with docetaxel or weekly versus every-3-week administration. In a secondary series of comparisons, weekly paclitaxel was superior to every-3-week paclitaxel in disease-free survival (HR, 1.27; 95% CI, 1.03–1.57; P=.006) and overall survival (HR, 1.32; 95% CI, 1.02–1.72; P=.01), and every-3-week docetaxel was superior to every-3-week paclitaxel in disease-free survival (HR, 1.23; 95% CI, 1.00–1.52; P=.02) but not overall survival.[252] Based on these results and the findings from the CALGB 9741 trial that showed that dose-dense AC followed by paclitaxel every 2 weeks had a survival benefit compared with AC followed by paclitaxel every 3 weeks,[249] the every-3-week paclitaxel regimen was removed from the guidelines.

Combination TC was compared with AC chemotherapy in a trial that randomized 1016 women with stage I–III breast cancer.[253] At a median follow-up of 7 years, overall disease-free survival (81% vs 75%; HR, 0.74; 95% CI, 0.56–0.98; P=.033) and overall survival (87% vs 82%; HR, 0.69; 95% CI, 0.50–0.97; P=.032) were significantly improved with TC compared with AC.

Other Regimens

Other regimens included in the guidelines are AC; fluorouracil, doxorubicin, and cyclophosphamide (FAC/CAF); cyclophosphamide, epirubicin, and fluorouracil (FEC/CEF); epirubicin and cyclophosphamide (EC); cyclophosphamide, methotrexate, and fluorouracil (CMF); AC with sequential docetaxel administered every 3 weeks; AC with sequential weekly paclitaxel; FEC/CEF followed by docetaxel or weekly paclitaxel; FAC followed by weekly paclitaxel; and docetaxel, doxorubicin, and cyclophosphamide (TAC).

The AC regimen for 4 cycles has been studied in randomized trials, resulting in relapse-free and overall survivals equivalent to those seen with CMF chemotherapy.[254–256] No benefit from dose escalation of either doxorubicin or cyclophosphamide was shown.[247,257]

Studies of CMF chemotherapy versus no chemotherapy have shown disease-free and overall survival advantages with CMF chemotherapy.[2,258] Studies using FAC/CAF chemotherapy have shown that the use of full-dose chemotherapy regimens is important.[259] In the EBCTCG overview of polychemotherapy, comparison of anthracycline-containing regimens with CMF showed a 12% further reduction in the annual odds of recurrence (P=.006) and an 11% further reduction in the annual odds of death (P=.02) with anthracycline-containing regimens.[258] Based on these data, the panel qualified the appropriate chemotherapy regimens by the statement that anthracycline-containing regimens are preferred for node-positive patients.

The EBCTCG analysis, however, did not consider the potential interaction between HER2 tu-

mor status and efficacy of anthracycline-containing versus CMF chemotherapy regimens. Retrospective analysis has suggested that the superiority of anthracycline-containing chemotherapy may be limited to the treatment of breast cancers that are $HER2^+$.[142,144,147,186,260–262] The retrospective finding across several clinical trials that anthracycline-based chemotherapy may be more efficacious in patients whose tumors are $HER2^+$ has led to a footnote stating that anthracycline-based chemotherapy may be superior to non–anthracycline-containing regimens in the adjuvant treatment of these patients.

Two randomized prospective trials of CEF chemotherapy in ALN-positive breast cancer are available. In one trial, premenopausal women with node-positive breast cancer were randomized to receive classic CMF therapy versus CEF chemotherapy using high-dose epirubicin. Both 10-year relapse-free survival (52% vs 45%; *P*=.007) and overall survival (62% vs 58%; *P*=.085) favored the CEF arm.[263] The second trial compared CEF given intravenously every 3 weeks at 2 dose levels of epirubicin (50 vs 100 mg/m^2) in premenopausal and postmenopausal women with node-positive breast cancer. Five-year disease-free survival (55% vs 66%; *P*=.03) and overall survival (65% vs 76%; *P*=.007) both favored the epirubicin 100 mg/m^2 arm.[264]

Another trial compared 2 dose levels of EC chemotherapy with CMF chemotherapy in women with node-positive breast cancer.[265] This study showed that higher-dose EC chemotherapy was equivalent to CMF chemotherapy and superior to moderate-dose EC in event-free survival and overall survival. Another randomized trial in women with ALN-positive breast cancer compared 6 cycles of FEC with 3 cycles of FEC followed by 3 cycles of docetaxel.[206] Five-year disease-free survival (78.4% vs 73.2%; adjusted *P*=.012) and overall survival (90.7% vs 86.7%; *P*=.017) were superior with sequential FEC followed by docetaxel. However, no significant disease-free survival differences were seen in a large randomized study comparing adjuvant chemotherapy with 4 cycles of every-3-week FEC followed by 4 cycles of every-3-week docetaxel with standard anthracycline chemotherapy regimens (eg, FEC or epirubicin followed by CMF) in women with node-positive or high-risk node-negative operable breast cancer.[266]

The addition of weekly paclitaxel following FEC was shown to be superior to FEC alone in a randomized study of 1246 women with early-stage breast cancer.[267] The former regimen was associated with a 23% reduction in the risk of relapse compared with FEC (HR, 0.77; 95% CI, 0.62–0.95; *P*=.022), although no significant difference in overall survival was seen when the 2 arms were compared at a median follow-up of 66 months.

Final results from a randomized trial of TAC versus FAC chemotherapy in ALN-positive breast cancer demonstrated that TAC is superior to FAC.[268] Estimated 5-year disease-free survival rates were 75% with TAC and 68% with FAC (HR, 0.72; 95% CI, 0.59–0.88; *P*=.001), and overall survival rates were 87% and 81%, respectively (HR, 0.70; 95% CI, 0.53–0.91; *P*=.008). Disease-free survival favored TAC in both ER^+ and ER^- 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) showed that AC followed by T had a significant advantage in disease-free survival (HR, 0.83; *P*=.006) but not in overall survival (HR, 0.86; *P*=.086) compared with TAC. In addition, both disease-free survival (HR, 0.080; *P*=.001) and overall survival (HR, 0.83; *P*=.034) were significantly increased when AC followed by T was compared with AT, with AT showing noninferiority compared with TAC.[269]

Several retrospective studies have evaluated the potential interaction of chemotherapy benefit and ER status.[2,178] These studies assessed the effect of chemotherapy on the risk of breast cancer recurrence in patients with ER^+ tumors receiving adjuvant endocrine therapy when compared with patients with ER^- tumor status not undergoing adjuvant endocrine therapy. These analyses suggest that the benefits of chemotherapy are significantly greater in patients with ER^- disease. For example, the results of Berry et al[178] showed that 22.8% more patients with ER^- tumors survived without disease for 5 years if they received chemotherapy; this benefit was only 7% for patients with ER^+ tumors receiving chemotherapy. The guidelines therefore include a recommendation for endocrine therapy and consideration of chemotherapy for patients with node-negative disease and either ER^+ tumors that are greater than 1 cm and $HER2^-$ or tumors 0.6 to 1.0 cm that are grade 2 or 3 or with unfavorable features.

Adjuvant HER2-Targeted Therapy

The panel recommends HER2-targeted therapy in

patients with HER+ tumors. Trastuzumab is a humanized monoclonal antibody with specificity for the extracellular domain of HER2.[270] Results of several randomized trials testing trastuzumab as adjuvant therapy have been reported.[149–154,271–273]

NSABP B-31 patients with HER2+, node-positive breast cancer were randomly assigned to 4 cycles of AC every 3 weeks followed by paclitaxel for 4 cycles every 3 weeks or the same regimen with 52 weeks of trastuzumab commencing with paclitaxel. In the NCCTG N9831 trial, patients with HER2+ breast cancer that was node-positive, or, if node-negative, with primary tumors greater than 1 cm if ER– and PR– or greater than 2 cm if ER+ or PR+, were similarly randomized except that paclitaxel was given on a low-dose weekly schedule for 12 weeks and a third arm delayed trastuzumab until the completion of paclitaxel.

The NSABP B-31 and NCCTG N9831 trials have been jointly analyzed with the merged control arms for both trials compared with the merged arms using trastuzumab begun concurrently with paclitaxel. A total of 4045 patients were included in the joint analysis performed at 3.9 years median follow-up. A 48% reduction in the risk of recurrence (HR, 0.52; 95% CI, 0.45–0.60; *P*<.001) and a 39% reduction in the risk of death (HR, 0.61; 95% CI, 0.50–0.75; log-rank *P*=.001) were documented.[272] Similar significant effects on disease-free survival were observed when results of the NSABP B-31 and NCCTG N9831 trials were analyzed separately. Cardiac toxicity was increased in patients treated with trastuzumab.[152,274,275] In the adjuvant trastuzumab trials, the rates of grade III/IV congestive heart failure (CHF) or cardiac-related death in patients receiving treatment regimens containing trastuzumab ranged from 0% (FinHer trial) to 4.1% (NSABP B-31 trial).[149,150,152,154,274,275] The frequency of cardiac dysfunction seems to be related to both age and baseline left ventricular ejection fraction. An analysis of data from N9831 showed the 3-year cumulative incidence of CHF or cardiac death to be 0.3%, 2.8%, and 3.3% in the trial arms without trastuzumab, with trastuzumab following chemotherapy, and with trastuzumab initially combined with paclitaxel, respectively.[274] The acceptable rate of significant cardiac toxicity observed in the trastuzumab adjuvant trials partly reflects rigorous monitoring for cardiac dysfunction. Furthermore, concerns have been raised regarding the long-term cardiac risks associated with trastuzumab therapy based on follow-up evaluations of cardiac function in patients enrolled in some of these trials.[276,277]

A third trial (HERA) (N=5081) tested trastuzumab for 1 or 2 years compared with none in patients with HER2+ and either node-positive disease or node-negative disease with tumors 1 cm or greater who had completed all local therapy and a variety of standard chemotherapy regimens.[150] At a median follow-up of 1 year, a 46% reduction in the risk of recurrence in those who received trastuzumab compared with those who did not (HR 0.54; 95%, CI 0.43–0.67; *P*<.0001), no difference in overall survival, and acceptable cardiac toxicity were reported. The 2-year data indicate that 1 year of trastuzumab therapy is associated with an overall survival benefit when compared with observation (HR for risk of death, 0.66; 95% CI, 0.47–0.91; *P*=.0115).[278] After this initial analysis, patients randomized to chemotherapy alone were allowed to crossover to trastuzumab. Intention-to-treat analysis including crossover patients was reported at 4-year median follow-up.[273] The primary end point of disease-free survival continued to be significantly higher in the trastuzumab-treated group (78.6%) versus the observation group (72.2; HR, 0.76; 95%, CI 0.66–0.87; *P*<.0001). At a median follow-up of 8 years, the study reported no significant difference in the secondary end point of disease-free survival in patients treated with trastuzumab for 2 years compared with 1 year.[151] Therefore, 1 year of adjuvant trastuzumab remains the current standard of treatment.

The BCIRG 006 study randomized 3222 women with HER2+, 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 and docetaxel plus trastuzumab for 1 year.[154] At 65-month follow-up, patients receiving AC followed by docetaxel with trastuzumab (AC-TH) had an HR for disease-free survival 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 disease-free survival was 0.75 (*P*=.04) when patients in the carboplatin/docetaxel/trastuzumab (TCH)-arm were compared with patients in the control arm. No statistically significant difference in the HR for disease-free survival was observed between

the 2 trastuzumab-containing arms. An overall survival 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 (2.0% 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).[154]

In the FinHer trial, 1010 women 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.[149] Patients (n=232) with HER2$^+$ cancers that were either node-positive or were node-negative, 2 cm or greater, and PR$^-$ were further randomized to treatment with or without 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 overall survival (HR, 0.41; 95% CI, 0.16–1.08; *P*=.07) or cardiac toxicity were observed with the addition of trastuzumab.[149] At 5-year follow-up, a comparison of the arms (ie, chemotherapy with and without trastuzumab) showed that the HRs for distant disease-free survival (HR, 0.65; 95% CI, 0.38–1.12; *P*=.12) and overall survival (HR, 0.55; 95% CI, 0.27–1.11; *P*=.094) were higher relative to those reported at 3 years.[271]

All of the adjuvant trials of trastuzumab have demonstrated clinically significant improvements in disease-free survival, and the combined analysis from the NSABP B31 and NCCTG N9831 trials,[272] and the HERA trial,[150] showed significant improvement in overall survival with the use of trastuzumab in patients with high-risk HER2$^+$ breast cancer. Therefore, regimens from each of these trials are included as trastuzumab-containing adjuvant regimen choices in the guidelines. The benefits of trastuzumab are independent of ER status.[152,153] In the FNCLCC-PACS-04 trial, 528 women with HER2$^+$, node-positive breast cancer were randomly assigned to receive trastuzumab or observation after completion of adjuvant anthracycline-based chemotherapy with or without docetaxel.[279] No statistically significant disease-free survival or overall survival benefit was observed with the addition of trastuzumab. These results suggest that the sequential administration of trastuzumab after chemotherapy is not as efficacious as a schedule involving concomitant chemotherapy and trastuzumab.

Retrospective analyses of low-risk patients with small tumors show that in T1a–b,N0 breast cancers, HER2 overexpression added a 15% to 30% risk for recurrence.[280–283] These risks rates are substantially higher than those seen among similarly sized HER2$^-$ tumors.

A recent single-arm, multicenter trial studied the benefit of trastuzumab-based chemotherapy in patients with HER2$^+$ node-negative tumors 3 cm or less. All patients received trastuzumab and weekly paclitaxel for 12 weeks, followed by completion of a year of trastuzumab monotherapy.[284] Among patients enrolled, 50% had tumors 1.0 cm or less and 9% of patients had tumors between 2 and 3 cm. The end point of the study was disease-free survival. The results presented at the 2013 San Antonio Breast Cancer Symposium showed that the 3-year disease-free survival rate in the overall population was 98.7% (95% CI, 97.6–99.8; *P*<.0001).

Dual anti-HER2 blockade associated with trastuzumab plus lapatinib, trastuzumab plus pertuzumab has shown significant improvements in the pathologic complete response rate when compared with chemotherapy associated with one anti-HER2 agent in the neoadjuvant setting. The results of the ongoing ALTTO trial are expected to provide additional data on the long-term outcome in the adjuvant setting with dual HER2 blockade (lapatinib plus trastuzumab).

NCCN Recommendation for Adjuvant HER2-Targted Therapy: Based on these studies, the panel has designated the use of trastuzumab with chemotherapy as a category 1 recommendation in patients with HER2$^+$ tumors greater than 1 cm.

The panel suggests that trastuzumab and chemotherapy be used for women with HER2$^+$ node-negative tumors measuring 0.6 to 1.0 cm (ie, T1b) and for smaller tumors that have 2 mm or less axillary node metastases (pN1mi). Some support for this recommendation comes from studies showing a higher risk of recurrence for patients with HER2$^+$ node-negative tumors 1 cm or less compared with those with HER2$^-$

tumors of the same size. Results of a retrospective study of 1245 women with early-stage breast cancer tumors characterized as T1pN0.[285] Rates of 10-year breast cancer–specific and recurrence-free survivals were 85% and 75%, respectively, in women with tumors characterized as $HER2^+/ER^+$, and 70% and 61%, respectively, in women with $HER2^+/ER^-$ tumors.

Two additionals retrospective studies have also investigated recurrence-free survival in this patient population. In one large study, 5-year recurrence-free survival rates of 77.1% and 93.7% ($P<.001$) were observed for patients with $HER2^+$ and $HER2^-$ T1a–bN0M0 breast tumors, respectively, with no recurrence-free survival differences seen in the $HER2^+$ group when hormonal receptor status was considered.[281] In another retrospective study of women with small $HER2^+$ tumors, the risk of recurrence at 5 years was low, although disease-free survival was inferior in the group with $HER2^+$, hormone receptor–positive disease.[286] None of the patients in these 2 retrospective studies had received trastuzumab. Subgroup analyses from several of the randomized trials have shown a consistent benefit with trastuzumab irrespective of tumor size or nodal status.[154,287,288]

The panel recommends AC followed by paclitaxel with trastuzumab, commencing with the first dose of paclitaxel, for 1 year as a preferred HER2-targeting adjuvant regimen. The TCH regimen is also a preferred regimen, especially in those with risk factors for cardiac toxicity, given the results of the BCIRG 006 study that showed superior disease-free survival in patients receiving either TCH or AC followed by docetaxel plus trastuzumab both compared with AC followed by docetaxel alone.

Other trastuzumab-containing regimens included in these guidelines are AC followed by docetaxel and trastuzumab,[154] and docetaxel plus trastuzumab followed by FEC.[149]

Based on the recent data presented at the 2013 San Antonio Breast Cancer Symposium,[284] the panel has included paclitaxel and trastuzumab as an option for patients with low-risk $HER2^+$ stage 1 tumors.

Considering the unprecedented improvement in overall survival in the metastatic setting[68] and the significant improvement in pathologic complete response seen in the neoadjuvant setting,[69,70] the panel considers it reasonable to incorporate pertuzumab to the above adjuvant regimens, if the patient has not received pertuzumab as a part of their neoadjuvant therapy An ongoing study is evaluating pertuzumab and trastuzumab with standard chemotherapy regimens in the adjuvant setting.[289,290]

Posttherapy Surveillance and Follow-up

Posttherapy follow-up is optimally performed by members of the treatment team and includes the performance of regular history/physical examinations every 4 to 6 months for the first 5 years after primary therapy and annually thereafter. Mammography should be performed annually.

The routine performance of alkaline phosphatase and liver function tests are not included in the guidelines.[291–293] In addition, the Panel notes no evidence to support the use of "tumor markers" for breast cancer, and routine bone scans, CT scans, MRI scans, PET scans, or ultrasound examinations in the asymptomatic patient provide no advantage in survival or ability to palliate recurrent disease and are, therefore, not recommended.[35,294]

The use of dedicated breast MRI may be considered an option for posttherapy surveillance and follow-up in women at high risk for bilateral disease, such as carriers of *BRCA1/2* mutations. Rates of contralateral breast cancer after either breast-conserving therapy or mastectomy have been reported to be increased in women with *BRCA1/2* mutations compared with patients with sporadic breast cancer.[295–297] (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian and NCCN Guidelines for Breast Cancer Screening and Diagnosis; to view the most recent version of these guidelines, visit NCCN.org).

The panel recommends that women with an intact uterus who are taking adjuvant tamoxifen should have yearly gynecologic assessments and rapid evaluation of any vaginal spotting that might occur, because of the risk of tamoxifen-associated endometrial carcinoma in postmenopausal women.[298] The performance of routine endometrial biopsy or ultrasonography in the asymptomatic woman is not recommended. Neither test has demonstrated utility as a screening test in any population of women. Most women with tamoxifen-associated uterine carcinoma have early vaginal spotting.

If an adjuvant aromatase inhibitor is considered in women with amenorrhea after treatment, baseline levels of estradiol and gonadotropin followed by serial monitoring of these hormones should be

performed if endocrine therapy with an aromatase inhibitor is initiated.[236] Bilateral oophorectomy assures postmenopausal status in young women with therapy-induced amenorrhea and may be considered before initiating therapy with an aromatase inhibitor in a young woman.

Symptom management for women on adjuvant endocrine therapies often requires treatment of hot flashes and the treatment of concurrent depression. Venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), has been studied and is an effective intervention in decreasing hot flashes.[299–302] Evidence suggests that concomitant use of tamoxifen with certain SSRIs (eg, paroxetine, fluoxetine) may decrease plasma levels of endoxifen, an active metabolite of tamoxifen.[303,304] These SSRIs/SNRIs may interfere with the enzymatic conversion of tamoxifen to endoxifen by inhibiting a particular isoform of CYP2D6. However, the mild CYP2D6 inhibitors, such as citalopram, escitalopram, sertraline, and venlafaxine, seem to have no or only minimal effect on tamoxifen metabolism.[236,305,306]

Follow-up also includes assessment of patient adherence to ongoing medication regimens, such as endocrine therapies. Predictors of poor adherence to medication include the presence of side effects associated with the medication, and incomplete understanding by the patient of the benefits associated with regular administration of the medication.[307] The panel recommends the implementation of simple strategies to enhance patient adherence to endocrine therapy, such as direct questioning of the patient during office visits and brief, clear explanations on the value of taking the medication regularly and the therapeutic importance of longer durations of endocrine therapy.

Evidence suggests that a healthy lifestyle may lead to better breast cancer outcomes. A nested case control study of 369 women with ER^+ tumors who developed a second primary breast cancer compared with 734 matched control patients who did not develop a second primary tumor showed an association between obesity (body mass index [BMI] ≥30), smoking, and alcohol consumption and contralateral breast cancer.[308] A prospective study of 1490 women diagnosed with stage I–III breast cancer showed an association among high fruit and vegetable consumption and physical activity and improved survivorship, regardless of obesity.[309] Thus, the panel recommends an active lifestyle and ideal body weight (BMI, 20–25) for optimal overall health and breast cancer outcomes.

Many young women treated for breast cancer remain or regain premenopausal status after treatment for breast cancer. For these women, the panel discourages the use of hormonal birth control methods, regardless of the hormone receptor status of the tumor.[310] Alternative birth control methods are recommended, including intrauterine devices, barrier methods, and, for those with no intent of future pregnancy, tubal ligation or vasectomy for the partner. Breastfeeding during endocrine or chemotherapy treatment is not recommended by the panel because of risks to the infant. Breastfeeding after breast-conserving treatment for breast cancer is not contraindicated. However, lactation from an irradiated breast may not be possible, or may occur only with a diminished capacity.[310,311]

The panel recommends that women on an adjuvant aromatase inhibitor 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 use of estrogen, progesterone, or selective ER modulators to treat osteoporosis or osteopenia in women with breast cancer is discouraged. The use of a bisphosphonate is generally the preferred intervention to improve bone mineral density. Optimal duration of bisphosphonate therapy has not been established. Factors to consider for duration of antiosteoporosis therapy include bone mineral density, response to therapy, and risk factors for continued bone loss or fracture. Women treated with a bisphosphonate should undergo a dental examination with preventive dentistry before the initiation of therapy, and should take supplemental calcium and vitamin D.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9–29.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687–1717.
3. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011;61:212–236.
4. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 2005;353:1784–1792.

5. White J, Morrow M, Moughan J, et al. Compliance with breast-conservation standards for patients with early-stage breast carcinoma. Cancer 2003;97:893–904.
6. Wilkinson NW, Shahryarinejad A, Winston JS, et al. Concordance with breast cancer pathology reporting practice guidelines. J Am Coll Surg 2003;196:38–43.
7. Allred DC, Harvey JM, Berardo M, Clark GM. Prognostic and predictive factors in breast cancer by immunohistochemical analysis. Mod Pathol 1998;11:155–168.
8. Rhodes A, Jasani B, Barnes DM, et al. Reliability of immunohistochemical demonstration of oestrogen receptors in routine practice: interlaboratory variance in the sensitivity of detection and evaluation of scoring systems. J Clin Pathol 2000;53:125–130.
9. Rudiger T, Hofler H, Kreipe HH, et al. Quality assurance in immunohistochemistry: results of an interlaboratory trial involving 172 pathologists. Am J Surg Pathol 2002;26:873–882.
10. Allred DC, Carlson RW, Berry DA, et al. NCCN Task Force Report: estrogen receptor and progesterone receptor testing in breast cancer by immunohistochemistry. J Natl Compr Canc Netw 2009;7(Suppl 6):S1–21; quiz S22–23.
11. Hammond MEH, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 2010;28:2784–2795.
12. Hammond ME. ASCO-CAP guidelines for breast predictive factor testing: an update. Appl Immunohistochem Mol Morphol 2011;19:499–500.
13. Wang S, Saboorian MH, Frenkel E, et al. Laboratory assessment of the status of Her-2/neu protein and oncogene in breast cancer specimens: comparison of immunohistochemistry assay with fluorescence in situ hybridisation assays. J Clin Pathol 2000;53:374–381.
14. Dybdal N, Leiberman G, Anderson S, et al. Determination of HER2 gene amplification by fluorescence in situ hybridization and concordance with the clinical trials immunohistochemical assay in women with metastatic breast cancer evaluated for treatment with trastuzumab. Breast Cancer Res Treat 2005;93:3–11.
15. Paik S, Bryant J, Tan-Chiu E, et al. Real-world performance of HER2 testing—National Surgical Adjuvant Breast and Bowel Project experience. J Natl Cancer Inst 2002;94:852–854.
16. Paik S, Tan-Chiu E, Bryant J, et al. Successful quality assurance program for HER2 testing in the NSABP trial for Herceptin [abstract]. Breast Cancer Res Treat 2002;76(Suppl):Abstract S31.
17. Perez EA, Suman VJ, Davidson NE, et al. HER2 testing by local, central, and reference laboratories in specimens from the North Central Cancer Treatment Group N9831 Intergroup adjuvant trial. J Clin Oncol 2006;24:3032–3038.
18. Tubbs RR, Pettay JD, Roche PC, et al. Discrepancies in clinical laboratory testing of eligibility for trastuzumab therapy: apparent immunohistochemical false-positives do not get the message. J Clin Oncol 2001;19:2714–2721.
19. Press MF, Sauter G, Bernstein L, et al. Diagnostic evaluation of HER-2 as a molecular target: an assessment of accuracy and reproducibility of laboratory testing in large, prospective, randomized clinical trials. Clin Cancer Res 2005;11:6598–6607.
20. Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol 2013;31:3997–4013.
21. Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline update. Arch Pathol Lab Med 2014;138:241–256.
22. Giordano SH, Buzdar AU, Hortobagyi GN. Breast cancer in men. Ann Intern Med 2002;137:678–687.
23. Giordano SH, Valero V, Buzdar AU, Hortobagyi GN. Efficacy of anastrozole in male breast cancer. Am J Clin Oncol 2002;25:235–237.
24. Esserman L. Integration of imaging in the management of breast cancer. J Clin Oncol 2005;23:1601–1602.
25. Gundry KR. The application of breast MRI in staging and screening for breast cancer. Oncology (Williston Park) 2005;19:159–169.
26. Houssami N, Ciatto S, Macaskill P, et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol 2008;26:3248–3258.
27. Lehman CD, DeMartini W, Anderson BO, Edge SB. Indications for breast MRI in the patient with newly diagnosed breast cancer. J Natl Compr Canc Netw 2009;7:193–201.
28. Fischer U, Zachariae O, Baum F, et al. The influence of preoperative MRI of the breasts on recurrence rate in patients with breast cancer. Eur Radiol 2004;14:1725–1731.
29. Solin LJ, Orel SG, Hwang WT, et al. Relationship of breast magnetic resonance imaging to outcome after breast-conservation treatment with radiation for women with early-stage invasive breast carcinoma or ductal carcinoma in situ. J Clin Oncol 2008;26:386–391.
30. Members of the Breast Cancer Disease Site Group. Baseline staging tests in primary breast cancer. Hamm C, Tey R, reviewers. Toronto (ON): Cancer Care Ontario; 2011 Nov 1 [Endorsed 2011 Oct 11]. Program in Evidence-based Care Evidence-Based Series No.: 1-14 Version 2.
31. Puglisi F, Follador A, Minisini AM, et al. Baseline staging tests after a new diagnosis of breast cancer: further evidence of their limited indications. Ann Oncol 2005;16:263–266.
32. Aukema TS, Straver ME, Peeters MJ, et al. Detection of extra-axillary lymph node involvement with FDG PET/CT in patients with stage II-III breast cancer. Eur J Cancer 2010;46:3205–3210.
33. Fuster D, Duch J, Paredes P, et al. Preoperative staging of large primary breast cancer with [^{18}F]fluorodeoxyglucose positron emission tomography/computed tomography compared with conventional imaging procedures. J Clin Oncol 2008;26:4746–4751.
34. Groheux D, Moretti JL, Baillet G, et al. Effect of (^{18})F-FDG PET/CT imaging in patients with clinical stage II and III breast cancer. Int J Radiat Oncol Biol Phys 2008;71:695–704.
35. Podoloff DA, Advani RH, Allred C, et al. NCCN task force report: positron emission tomography (PET)/computed tomography (CT) scanning in cancer. J Natl Compr Canc Netw 2007;5(Suppl 1):S1–22; quiz 23–24.
36. Rosen EL, Eubank WB, Mankoff DA. FDG PET, PET/CT, and breast cancer imaging. Radiographics 2007;27(Suppl 1):S215–229.

37. van der Hoeven JJM, Krak NC, Hoekstra OS, et al. ^{18}F(2-fluoro-2-deoxy-d-glucose positron emission tomography in staging of locally advanced breast cancer. J Clin Oncol 2004;22:1253–1259.
38. Niikura N, Costelloe CM, Madewell JE, et al. FDG-PET/CT compared with conventional imaging in the detection of distant metastases of primary breast cancer. Oncologist 2011;16:1111–1119.
39. Morris PG, Lynch C, Feeney JN, et al. Integrated positron emission tomography/computed tomography may render bone scintigraphy unnecessary to investigate suspected metastatic breast cancer. J Clin Oncol 2010;28:3154–3159.
40. Alessio AM, Kinahan PE, Cheng PM, et al. PET/CT scanner instrumentation, challenges, and solutions. Radiol Clin North Am 2004;42:1017–1032.
41. Wong TZ, Paulson EK, Nelson RC, et al. Practical approach to diagnostic CT combined with PET. AJR Am J Roentgenol 2007;188:622–629.
42. Kranick JA, Schaefer C, Rowell S, et al. Is pregnancy after breast cancer safe? Breast J 2010;16:404–411.
43. Cruz MR, Prestes JC, Gimenes DL, Fanelli MF. Fertility preservation in women with breast cancer undergoing adjuvant chemotherapy: a systematic review. Fertil Steril 2010;94:138–143.
44. Dunn L, Fox KR. Techniques for fertility preservation in patients with breast cancer. Curr Opin Obstet Gynecol 2009;21:68–73.
45. Oktem O, Oktay K. Fertility preservation for breast cancer patients. Semin Reprod Med 2009;27:486–492.
46. Redig AJ, Brannigan R, Stryker SJ, et al. Incorporating fertility preservation into the care of young oncology patients. Cancer 2011;117:4–10.
47. Lee S, Ozkavukcu S, Heytens E, et al. Value of early referral to fertility preservation in young women with breast cancer. J Clin Oncol 2010;28:4683–4686.
48. Lobo RA. Potential options for preservation of fertility in women. N Engl J Med 2005;353:64–73.
49. Sukumvanich P, Case LD, Van Zee K, et al. Incidence and time course of bleeding after long-term amenorrhea after breast cancer treatment: a prospective study. Cancer 2010;116:3102–3111.
50. Peate M, Meiser B, Friedlander M, et al. It's now or never: fertility-related knowledge, decision-making preferences, and treatment intentions in young women with breast cancer—an Australian fertility decision aid collaborative group study. J Clin Oncol 2011;29:1670–1677.
51. Alkuwari E, Auger M. Accuracy of fine-needle aspiration cytology of axillary lymph nodes in breast cancer patients: a study of 115 cases with cytologic-histologic correlation. Cancer 2008;114:89–93.
52. Classe JM, Bordes V, Campion L, et al. Sentinel lymph node biopsy after neoadjuvant chemotherapy for advanced breast cancer: results of Ganglion Sentinelle et Chimiotherapie Neoadjuvante, a French prospective multicentric study. J Clin Oncol 2009;27:726–732.
53. Hunt KK, Yi M, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy is accurate and reduces the need for axillary dissection in breast cancer patients. Ann Surg 2009;250:558–566.
54. Kuehn T, Vogl FD, Helms G, et al. Sentinel-node biopsy for axillary staging in breast cancer: results from a large prospective German multi-institutional trial. Eur J Surg Oncol 2004;30:252–259.
55. Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol 2013;14:609–618.
56. Boughey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA 2013;310:1455–1461.
57. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998;16:2672–2685.
58. Bear HD, Anderson S, Smith RE, et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 2006;24:2019–2027.
59. Hortobagyi GN, Singletary SE, Strom EA. Treatment of locally advanced and inflammatory breast cancer. In: Harris JR, Lippman ME, Morrow M, Osborne CK, eds. Diseases of the Breast. Philadelphia: Lippincott Williams & Wilkins; 2004:645–660.
60. Hudis C, Modi S. Preoperative chemotherapy for breast cancer: miracle or mirage? JAMA 2007;298:2665–2667.
61. Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol 2005;23:3676–3685.
62. Buzdar AU, Valero V, Ibrahim NK, et al. Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: an update of the initial randomized study population and data of additional patients treated with the same regimen. Clin Cancer Res 2007;13:228–233.
63. Untch M, Loibl S, Bischoff J, et al. Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy (GeparQuinto, GBG 44): a randomised phase 3 trial. Lancet Oncol 2012;13:135–144.
64. Baselga J, Bradbury I, Eidtmann H, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. Lancet 2012;379:633–640.
65. Piccart-Gebhart M, Holmes A, de Azambuja E, et al. The association between event-free survival and pathological complete response to neoadjuvant lapatinib, trastuzumab or their combination in HER2-positive breast cancer. Survival follow-up analysis of the NeoALTTO study (BIG 1-06). [abstract]. Presented at the 2013 San Antonio Breast Cancer Symposium; December 10–14, 2013; San Antonio, Texas. Abstract S1-01.
66. Scheuer W, Friess T, Burtscher H, et al. Strongly enhanced antitumor activity of trastuzumab and pertuzumab combination treatment on HER2-positive human xenograft tumor models. Cancer Res 2009;69:9330–9336.
67. Baselga J, Cortes J, Im SA, et al. Biomarker analyses in CLEOPATRA: a phase III, placebo-controlled study of pertuzumab in HER2-positive, first-line metastatic breast cancer (MBC) [abstract]. Cancer Res 2012;72(24 Suppl):Abstract S5-1.
68. Swain S, Kim S-B, Cortes J, et al. Confirmatory overall survival (OS) analysis of CLEOPATRA: a randomized, double-blind, placebo-controlled phase III study with pertuzumab (P),

trastuzumab (T), and docetaxel (D) in patients (pts) with HER2-positive first-line (1L) metastatic breast cancer (MBC) [abstract]. Cancer Res 2012;72(24 Suppl):Abstract P5-18-26.

69. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol 2013;24:2278–2284.
70. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13:25–32.
71. Ellis MJ, Coop A, Singh B, et al. Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. J Clin Oncol 2001;19:3808–3816.
72. Smith IE, Dowsett M, Ebbs SR, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. J Clin Oncol 2005;23:5108–5116.
73. Bass SS, Lyman GH, McCann CR, et al. Lymphatic mapping and sentinel lymph node biopsy. Breast J 1999;5:288–295.
74. Cox CE. Lymphatic mapping in breast cancer: combination technique. Ann Surg Oncol 2001;8:67S–70S.
75. Cox CE, Nguyen K, Gray RJ, et al. Importance of lymphatic mapping in ductal carcinoma in situ (DCIS): why map DCIS? Am Surg 2001;67:513–519.
76. Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer—a multicenter validation study. N Engl J Med 1998;339:941–946.
77. Krag DN, Anderson SJ, Julian TB, et al. Primary outcome results of NSABP B-32, a randomized phase III clinical trial to compare sentinel node resection (SNR) to conventional axillary dissection (AD) in clinically node-negative breast cancer patients [abstract]. J Clin Oncol 2010;28(Suppl 18):Abstract LBA505.
78. Lyman GH, Giuliano AE, Somerfield MR, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol 2005;23:7703–7720.
79. McMasters KM, Giuliano AE, Ross MI, et al. Sentinel-lymph-node biopsy for breast cancer—not yet the standard of care. N Engl J Med 1998;339:990–995.
80. O'Hea BJ, Hill AD, El-Shirbiny AM, et al. Sentinel lymph node biopsy in breast cancer: initial experience at Memorial Sloan-Kettering Cancer Center. J Am Coll Surg 1998;186:423–427.
81. Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med 2003;349:546–553.
82. Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. J Natl Cancer Inst 2006;98:599–609.
83. Cox CE, Salud CJ, Cantor A, et al. Learning curves for breast cancer sentinel lymph node mapping based on surgical volume analysis. J Am Coll Surg 2001;193:593–600.
84. Dupont E, Cox C, Shivers S, et al. Learning curves and breast cancer lymphatic mapping: institutional volume index. J Surg Res 2001;97:92–96.
85. Giuliano AE, Hawes D, Ballman KV, et al. Association of occult metastases in sentinel lymph nodes and bone marrow with survival among women with early-stage invasive breast cancer. JAMA 2011;306:385–393.
86. Degnim AC, Reynolds C, Pantvaidya G, et al. Nonsentinel node metastasis in breast cancer patients: assessment of an existing and a new predictive nomogram. Am J Surg 2005;190:543–550.
87. Houvenaeghel G, Nos C, Giard S, et al. A nomogram predictive of non-sentinel lymph node involvement in breast cancer patients with a sentinel lymph node micrometastasis. Eur J Surg Oncol 2009;35:690–695.
88. Katz A, Smith BL, Golshan M, et al. Nomogram for the prediction of having four or more involved nodes for sentinel lymph node-positive breast cancer. J Clin Oncol 2008;26:2093–2098.
89. Kohrt HE, Olshen RA, Bermas HR, et al. New models and online calculator for predicting non-sentinel lymph node status in sentinel lymph node positive breast cancer patients. BMC Cancer 2008;8:66.
90. Scow JS, Degnim AC, Hoskin TL, et al. Assessment of the performance of the Stanford Online Calculator for the prediction of nonsentinel lymph node metastasis in sentinel lymph node-positive breast cancer patients. Cancer 2009;115:4064–4070.
91. van la Parra RF, Ernst MF, Bevilacqua JL, et al. Validation of a nomogram to predict the risk of nonsentinel lymph node metastases in breast cancer patients with a positive sentinel node biopsy: validation of the MSKCC breast nomogram. Ann Surg Oncol 2009;16:1128–1135.
92. Werkoff G, Lambaudie E, Fondrinier E, et al. Prospective multicenter comparison of models to predict four or more involved axillary lymph nodes in patients with breast cancer with one to three metastatic sentinel lymph nodes. J Clin Oncol 2009;27:5707–5712.
93. Giuliano AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. Ann Surg 2010;252:426–432; discussion 432–423.
94. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011;305:569–575.
95. Axelsson CK, Mouridsen HT, Zedeler K. Axillary dissection of level I and II lymph nodes is important in breast cancer classification. The Danish Breast Cancer Cooperative Group (DBCG). Eur J Cancer 1992;28A:1415–1418.
96. Kiricuta CI, Tausch J. A mathematical model of axillary lymph node involvement based on 1446 complete axillary dissections in patients with breast carcinoma. Cancer 1992;69:2496–2501.
97. Fisher B, Redmond C, Fisher ER, et al. Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. N Engl J Med 1985;312:674–681.
98. Hellman S. Stopping metastases at their source. N Engl J Med 1997;337:996–997.
99. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast

cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med 1997;337:949–955.

100. Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet 1999;353:1641–1648.

101. Ragaz J, Olivotto IA, Spinelli JJ, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst 2005;97:116–126.

102. Recht A, Edge SB, Solin LJ, et al. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001;19:1539–1569.

103. Huang EH, Tucker SL, Strom EA, et al. Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy. J Clin Oncol 2004;22:4691–4699.

104. McGuire SE, Gonzalez-Angulo AM, Huang EH, et al. Postmastectomy radiation improves the outcome of patients with locally advanced breast cancer who achieve a pathologic complete response to neoadjuvant chemotherapy. Int J Radiat Oncol Biol Phys 2007;68:1004–1009.

105. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;366:2087–2106.

106. Overgaard M, Nielsen HM, Overgaard J. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. Radiother Oncol 2007;82:247–253.

107. Whelan TJ, Olivotto I, Ackerman I, et al. NCIC-CTG MA.20: an intergroup trial of regional nodal irradiation in early breast cancer [abstract]. J Clin Oncol 2011;29 (18 Suppl):Abstract LBA1003.

108. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010;362:513–520.

109. Group ST, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet 2008;371:1098–1107.

110. Group ST, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol 2008;9:331–341.

111. Nielsen HM, Overgaard M, Grau C, et al. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. J Clin Oncol 2006;24:2268–2275.

112. Ahmed S, Snelling A, Bains M, Whitworth IH. Breast reconstruction. BMJ 2005;330:943–948.

113. Edlich RF, Winters KL, Faulkner BC, et al. Advances in breast reconstruction after mastectomy. J Long Term Eff Med Implants 2005;15:197–207.

114. Pennington DG. Breast reconstruction after mastectomy: current state of the art. ANZ J Surg 2005;75:454–458.

115. Chang DW. Breast Reconstruction with Microvascular MS-TRAM and DIEP Flaps. Arch Plast Surg 2012;39:3–10.

116. Garcia-Etienne CA, Cody Iii HS 3rd, Disa JJ, et al. Nipple-sparing mastectomy: initial experience at the Memorial Sloan-Kettering Cancer Center and a comprehensive review of literature. Breast J 2009;15:440–449.

117. Petit JY, Veronesi U, Orecchia R, et al. Nipple sparing mastectomy with nipple areola intraoperative radiotherapy: one thousand and one cases of a five years experience at the European institute of oncology of Milan (EIO). Breast Cancer Res Treat 2009;117:333–338.

118. Yueh JH, Houlihan MJ, Slavin SA, et al. Nipple-sparing mastectomy: evaluation of patient satisfaction, aesthetic results, and sensation. Ann Plast Surg 2009;62:586–590.

119. Chung AP, Sacchini V. Nipple-sparing mastectomy: where are we now? Surg Oncol 2008;17:261–266.

120. Gerber B, Krause A, Dieterich M, et al. The oncological safety of skin sparing mastectomy with conservation of the nipple-areola complex and autologous reconstruction: an extended follow-up study. Ann Surg 2009;249:461–468.

121. Mallon P, Feron JG, Couturaud B, et al. The role of nipple-sparing mastectomy in breast cancer: a comprehensive review of the literature. Plast Reconstr Surg 2013;131:969–984.

122. Piper M, Peled AW, Foster RD, et al. Total skin-sparing mastectomy: a systematic review of oncologic outcomes and postoperative complications. Ann Plast Surg, in press.

123. Toth BA, Forley BG, Calabria R. Retrospective study of the skin-sparing mastectomy in breast reconstruction. Plast Reconstr Surg 1999;104:77–84.

124. Carlson GW, Styblo TM, Lyles RH, et al. The use of skin sparing mastectomy in the treatment of breast cancer: the Emory experience. Surg Oncol 2003;12:265–269.

125. Downes KJ, Glatt BS, Kanchwala SK, et al. Skin-sparing mastectomy and immediate reconstruction is an acceptable treatment option for patients with high-risk breast carcinoma. Cancer 2005;103:906–913.

126. Foster RD, Esserman LJ, Anthony JP, et al. Skin-sparing mastectomy and immediate breast reconstruction: a prospective cohort study for the treatment of advanced stages of breast carcinoma. Ann Surg Oncol 2002;9:462–466.

127. Medina-Franco H, Vasconez LO, Fix RJ, et al. Factors associated with local recurrence after skin-sparing mastectomy and immediate breast reconstruction for invasive breast cancer. Ann Surg 2002;235:814–819.

128. Newman LA, Kuerer HM, Hunt KK, et al. Presentation, treatment, and outcome of local recurrence afterskin-sparing mastectomy and immediate breast reconstruction. Ann Surg Oncol 1998;5:620–626.

129. Kronowitz SJ, Robb GL. Radiation therapy and breast reconstruction: a critical review of the literature. Plast Reconstr Surg 2009;124:395–408.

130. Tran NV, Chang DW, Gupta A, et al. Comparison of immediate and delayed free TRAM flap breast reconstruction in patients receiving postmastectomy radiation therapy. Plast Reconstr Surg 2001;108:78–82.

131. Mehta VK, Goffinet D. Postmastectomy radiation therapy after TRAM flap breast reconstruction. Breast J 2004;10:118–122.

132. Clough KB, Kaufman GJ, Nos C, et al. Improving breast cancer surgery: a classification and quadrant per quadrant atlas for oncoplastic surgery. Ann Surg Oncol 2010;17:1375–1391.

133. Anderson BO, Masetti R, Silverstein MJ. Oncoplastic approaches to partial mastectomy: an overview of volume-displacement techniques. Lancet Oncol 2005;6:145–157.
134. Huemer GM, Schrenk P, Moser F, et al. Oncoplastic techniques allow breast-conserving treatment in centrally located breast cancers. Plast Reconstr Surg 2007;120:390–398.
135. Kaur N, Petit JY, Rietjens M, et al. Comparative study of surgical margins in oncoplastic surgery and quadrantectomy in breast cancer. Ann Surg Oncol 2005;12:539–545.
136. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Peto R, Davies C, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet 2012;379:432–444.
137. Loprinzi CL, Thome SD. Understanding the utility of adjuvant systemic therapy for primary breast cancer. J Clin Oncol 2001;19:972–979.
138. Ravdin PM, Siminoff LA, Davis GJ, et al. Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. J Clin Oncol 2001;19:980–991.
139. Muss HB, Berry DA, Cirrincione CT, et al. Adjuvant chemotherapy in older women with early-stage breast cancer. N Engl J Med 2009;360:2055–2065.
140. Olivotto IA, Bajdik CD, Ravdin PM, et al. Population-based validation of the prognostic model ADJUVANT! for early breast cancer. J Clin Oncol 2005;23:2716–2725.
141. Loprinzi CL, Ravdin PM. Decision-making for patients with resectable breast cancer: individualized decisions for and by patients and their physicians. J Natl Compr Canc Netw 2003;1:189–196.
142. Cooke T, Reeves J, Lanigan A, Stanton P. HER2 as a prognostic and predictive marker for breast cancer. Ann Oncol 2001;12(Suppl 1):23–28.
143. Paik S, Bryant J, Park C, et al. erbB-2 and response to doxorubicin in patients with axillary lymph node-positive, hormone receptor-negative breast cancer. J Natl Cancer Inst 1998;90:1361–1370.
144. Paik S, Bryant J, Tan-Chiu E, et al. HER2 and choice of adjuvant chemotherapy for invasive breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-15. J Natl Cancer Inst 2000;92:1991–1998.
145. Piccart MJ, Di Leo A, Hamilton A. HER2. a 'predictive factor' ready to use in the daily management of breast cancer patients? Eur J Cancer 2000;36:1755–1761.
146. Pritchard KI, Shepherd LE, O'Malley FP, et al. HER2 and responsiveness of breast cancer to adjuvant chemotherapy. N Engl J Med 2006;354:2103–2111.
147. Thor AD, Berry DA, Budman DR, et al. erbB-2, p53, and efficacy of adjuvant therapy in lymph node-positive breast cancer. J Natl Cancer Inst 1998;90:1346–1360.
148. Dressler LG, Berry DA, Broadwater G, et al. Comparison of HER2 status by fluorescence in situ hybridization and immunohistochemistry to predict benefit from dose escalation of adjuvant doxorubicin-based therapy in node-positive breast cancer patients. J Clin Oncol 2005;23:4287–4297.
149. Joensuu H, Kellokumpu-Lehtinen Pl, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 2006;354:809–820.
150. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005;353:1659–1672.
151. Goldhirsch A, Piccart-Gebhart M, Procter M, et al. HERA TRIAL: 2 years versus 1 year of trastuzumab after adjuvant chemotherapy in women with HER2-positive early breast cancer at 8 years of median follow up. Cancer Res 2012;72:S5–2.
152. Romond E, Perez E, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353:1673–1684.
153. Romond E, Suman V, Jeong JH, et al. Trastuzumab plus adjuvant chemotherapy for HER2-positive breast cancer: final planned joint analysis of overall survival (OS) from NSABP B-31 and NCCTG N9831. Cancer Res 2012;72(24 Suppl):S5.
154. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011;365:1273–1283.
155. Cobleigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol 1999;17:2639–2648.
156. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783–792.
157. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 2002;20:719–726.
158. Jeffrey SS, Lonning PE, Hillner BE. Genomics-based prognosis and therapeutic prediction in breast cancer. J Natl Compr Canc Netw 2005;3:291–300.
159. Perou CM, Jeffrey SS, van de Rijn M, et al. Distinctive gene expression patterns in human mammary epithelial cells and breast cancers. Proc Natl Acad Sci U S A 1999;96:9212–9217.
160. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 2001;98:10869–10874.
161. Sorlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci U S A 2003;100:8418–8423.
162. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004;351:2817–2826.
163. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. J Clin Oncol 2006;24:3726–3734.
164. Fan C, Oh DS, Wessels L, et al. Concordance among gene-expression-based predictors for breast cancer. N Engl J Med 2006;355:560–569.
165. Wang Y, Klijn JG, Zhang Y, et al. Gene-expression profiles to predict distant metastasis of lymph-node-negative primary breast cancer. Lancet 2005;365:671–679.
166. Glas AM, Floore A, Delahaye LJ, et al. Converting a breast cancer microarray signature into a high-throughput diagnostic test. BMC Genomics 2006;7:278.
167. van de Vijver MJ, He YD, van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 2002;347:1999–2009.
168. van 't Veer LJ, Dai H, van de Vijver MJ, et al. Gene expression profiling predicts clinical outcome of breast cancer. Nature 2002;415:530–536.

169. Knauer M, Mook S, Rutgers EJ, et al. The predictive value of the 70-gene signature for adjuvant chemotherapy in early breast cancer. Breast Cancer Res Treat 2010;120:655–661.

170. Kunz G. Use of a genomic test (MammaPrint) in daily clinical practice to assist in risk stratification of young breast cancer patients. Arch Gynecol Obstet 2011;283:597–602.

171. Ishitobi M, Goranova TE, Komoike Y, et al. Clinical utility of the 70-gene MammaPrint profile in a Japanese population. Jpn J Clin Oncol 2010;40:508–512.

172. Mook S, Knauer M, Bueno-de-Mesquita JM, et al. Metastatic potential of T1 breast cancer can be predicted by the 70-gene MammaPrint signature. Ann Surg Oncol 2010;17:1406–1413.

173. A phase III, randomized clinical trial of standard adjuvant endocrine therapy +/-chemotherapy in patients with 1-3 positive nodes, hormone receptor-positive and HER2-negative breast cancer with recurence score (RS) of 25 or less. RXPONDER: a clinical trial RX for positive node, endocrine responsive breast cancer. ClinicalTrials.gov identifier: NCT01272037.

174. MINDACT (Microarray In Node-Negative and 1 to 3 positive lymph node disease may avoid chemotherapy): a prospective, randomized study comparing the 70-gene signature with the common clinical-pathological criteria in selecting patients for adjuvant chemotherapy in breast cancer with 0 to 3 positive nodes. ClinicalTrials.gov identifier: NCT00433589.

175. Albain KS, Barlow WE, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. Lancet Oncol 2010;11:55–65.

176. Hormone therapy with or without combination chemotherapy in treating women who have undergone surgery for node-negative breast cancer (The TAILORx Trial). ClinicalTrials.gov identifier: NCT00310180.

177. Swain SM, Wilson JW, Mamounas EP, et al. Estrogen receptor status of primary breast cancer is predictive of estrogen receptor status of contralateral breast cancer. J Natl Cancer Inst 2004;96:516–523.

178. Berry DA, Cirrincione C, Henderson IC, et al. Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. JAMA 2006;295:1658–1667.

179. Albain KS, Barlow WE, Ravdin PM, et al. Adjuvant chemotherapy and timing of tamoxifen in postmenopausal patients with endocrine-responsive, node-positive breast cancer: a phase 3, open-label, randomised controlled trial. Lancet 2009;374:2055–2063.

180. Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1998;351:1451–1467.

181. Arpino G, Green SJ, Allred DC, et al. HER-2 amplification, HER-1 expression, and tamoxifen response in estrogen receptor-positive metastatic breast cancer: a southwest oncology group study. Clin Cancer Res 2004;10:5670–5676.

182. Berry DA, Muss HB, Thor AD, et al. HER-2/neu and p53 expression versus tamoxifen resistance in estrogen receptor-positive, node-positive breast cancer. J Clin Oncol 2000;18:3471–3479.

183. De Laurentiis M, Arpino G, Massarelli E, et al. A meta-analysis on the interaction between HER-2 expression and response to endocrine treatment in advanced breast cancer. Clin Cancer Res 2005;11:4741–4748.

184. Eppenberger-Castori S, Kueng W, Benz C, et al. Prognostic and predictive significance of ErbB-2 breast tumor levels measured by enzyme immunoassay. J Clin Oncol 2001;19:645–656.

185. Knoop AS, Bentzen SM, Nielsen MM, et al. Value of epidermal growth factor receptor, HER2, p53, and steroid receptors in predicting the efficacy of tamoxifen in high-risk postmenopausal breast cancer patients. J Clin Oncol 2001;19:3376–3384.

186. Mass R. The role of HER-2 expression in predicting response to therapy in breast cancer. Semin Oncol 2000;27:46–52.

187. Paik S, Shak S, Tang G, et al. Expression of the 21 genes in the recurrence score assay and tamoxifen clinical benefit in the NSABP study B-14 of node negative, estrogen receptor positive breast cancer [abstract]. J Clin Oncol 2005;23(Suppl 16):Abstract 510.

188. Pegram MD, Pauletti G, Slamon DJ. HER-2/neu as a predictive marker of response to breast cancer therapy. Breast Cancer Res Treat 1998;52:65–77.

189. Dowsett M, Allred C, Knox J, et al. Relationship between quantitative estrogen and progesterone receptor expression and human epidermal growth factor receptor 2 (HER-2) status with recurrence in the Arimidex, Tamoxifen, Alone or in Combination trial. J Clin Oncol 2008;26:1059–1065.

190. Early Breast Cancer Trialists' Collaborative G, Davies C, Godwin J, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011;378:771–784.

191. Early Breast Cancer Trialists' Collaborative G. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687–1717.

192. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381:805–816.

193. Gray R, Rea D, Handley K, et al. aTTom (adjuvant Tamoxifen—To offer more?): randomized trial of 10 versus 5 years of adjuvant tamoxifen among 6,934 women with estrogen receptor-positive (ER+) or ER untested breast cancer—preliminary results [abstract]. J Clin Oncol 2008;(15 Suppl):Abstract 513.

194. Pritchard KI. Ovarian suppression/ablation in premenopausal ER-positive breast cancer patients. Issues and recommendations. Oncology (Williston Park) 2009;23:27–33.

195. Puhalla S, Brufsky A, Davidson N. Adjuvant endocrine therapy for premenopausal women with breast cancer. Breast 2009;18(Suppl 3):S122–130.

196. Tan SH, Wolff AC. The role of ovarian ablation in the adjuvant therapy of breast cancer. Curr Oncol Rep 2008;10:27–37.

197. Cuzick J, Ambroisine L, Davidson N, et al. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. Lancet 2007;369:1711–1723.

198. Davidson NE, O'Neill AM, Vukov AM, et al. Chemoendocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer: results from INT 0101 (E5188). J Clin Oncol 2005;23:5973–5982.

199. Ejlertsen B, Mouridsen HT, Jensen MB, et al. Similar efficacy for ovarian ablation compared with cyclophosphamide, methotrexate, and fluorouracil: from a randomized comparison of premenopausal patients with node-positive, hormone receptor-positive breast cancer. J Clin Oncol 2006;24:4956–4962.

200. Goel S, Sharma R, Hamilton A, Beith J. LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women. Cochrane Database Syst Rev 2009:CD004562.

201. Kaufmann M, Jonat W, Blamey R, et al. Survival analyses from the ZEBRA study. goserelin (Zoladex) versus CMF in premenopausal women with node-positive breast cancer. Eur J Cancer 2003;39:1711–1717.

202. Schmid P, Untch M, Wallwiener D, et al. Cyclophosphamide, methotrexate and fluorouracil (CMF) versus hormonal ablation with leuprorelin acetate as adjuvant treatment of node-positive, premenopausal breast cancer patients: preliminary results of the TABLE-study (Takeda Adjuvant Breast cancer study with Leuprorelin Acetate). Anticancer Res 2002;22:2325–2332.

203. Thomson CS, Twelves CJ, Mallon EA, Leake RE. Adjuvant ovarian ablation vs CMF chemotherapy in premenopausal breast cancer patients: trial update and impact of immunohistochemical assessment of ER status. Breast 2002;11:419–429.

204. von Minckwitz G, Graf E, Geberth M, et al. CMF versus goserelin as adjuvant therapy for node-negative, hormone-receptor-positive breast cancer in premenopausal patients: a randomised trial (GABG trial IV-A-93). Eur J Cancer 2006;42:1780–1788.

205. Castiglione-Gertsch M, O'Neill A, Price KN, et al. Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node-negative breast cancer: a randomized trial. J Natl Cancer Inst 2003;95:1833–1846.

206. Roche H, Fumoleau P, Spielmann M, et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 Trial. J Clin Oncol 2006;24:5664–5671.

207. Boccardo F, Rubagotti A, Amoroso D, et al. Cyclophosphamide, methotrexate, and fluorouracil versus tamoxifen plus ovarian suppression as adjuvant treatment of estrogen receptor-positive pre-/perimenopausal breast cancer patients: results of the Italian Breast Cancer Adjuvant Study Group 02 randomized trial. J Clin Oncol 2000;18:2718–2727.

208. Coombes RC, Kilburn LS, Snowdon CF, et al. Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. Lancet 2007;369:559–570.

209. Kaufmann M, Jonat W, Hilfrich J, et al. Improved overall survival in postmenopausal women with early breast cancer after anastrozole initiated after treatment with tamoxifen compared with continued tamoxifen: the ARNO 95 Study. J Clin Oncol 2007;25:2664–2670.

210. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. J Natl Cancer Inst 2005;97:1262–1271.

211. Forbes JF, Cuzick J, Buzdar A, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. Lancet Oncol 2008;9:45–53.

212. Thurlimann B, Keshaviah A, Coates AS, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med 2005;353:2747–2757.

213. Baum M, Budzar AU, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet 2002;359:2131–2139.

214. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005;365:60–62.

215. Duffy S, Jackson TL, Lansdown M, et al. The ATAC ('Arimidex', Tamoxifen, Alone or in Combination) adjuvant breast cancer trial: first results of the endometrial sub-protocol following 2 years of treatment. Hum Reprod 2006;21:545–553.

216. Fallowfield L, Cella D, Cuzick J, et al. Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer trial. J Clin Oncol 2004;22:4261–4271.

217. Eastell R, Adams JE, Coleman RE, et al. Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. J Clin Oncol 2008;26:1051–1057.

218. Dowsett M, Cuzick J, Howell A, Jackson I. Pharmacokinetics of anastrozole and tamoxifen alone, and in combination, during adjuvant endocrine therapy for early breast cancer in postmenopausal women: a sub-protocol of the 'Arimidex and tamoxifen alone or in combination' (ATAC) trial. Br J Cancer 2001;85:317–324.

219. Buzdar AU, Guastalla JP, Nabholtz JM, et al. Impact of chemotherapy regimens prior to endocrine therapy: results from the ATAC (anastrozole and tamoxifen, alone or in combination) trial. Cancer 2006;107:472–480.

220. Mouridsen H, Keshaviah A, Coates AS, et al. Cardiovascular adverse events during adjuvant endocrine therapy for early breast cancer using letrozole or tamoxifen: safety analysis of BIG 1-98 trial. J Clin Oncol 2007;25:5715–5722.

221. Rabaglio M, Sun Z, Price KN, et al. Bone fractures among postmenopausal patients with endocrine-responsive early breast cancer treated with 5 years of letrozole or tamoxifen in the BIG 1-98 trial. Ann Oncol 2009;20:1489–1498.

222. Mouridsen H, Giobbie-Hurder A, Goldhirsch A, et al. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. N Engl J Med 2009;361:766–776.

223. Boccardo F, Rubagotti A, Puntoni M, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary results of the Italian Tamoxifen Anastrozole Trial. J Clin Oncol 2005;23:5138–5147.

224. Boccardo F, Rubagotti A, Guglielmini P, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer. Updated results of the Italian tamoxifen anastrozole (ITA) trial. Ann Oncol 2006;17(Suppl 7):10–14.

225. Coombes RC, Hall E, Gibson LJ, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004;350:1081–1092.

226. Jakesz R, Jonat W, Gnant M, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. Lancet 2005;366:455–462.

227. Jonat W, Gnant M, Boccardo F, et al. Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis. Lancet Oncol 2006;7:991–996.

228. van de Velde CJ, Rea D, Seynaeve C, et al. Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. Lancet 2011;377:321–331.

229. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003;349:1793–1802.

230. Goss PE, Ingle JN, Pater JL, et al. Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen. J Clin Oncol 2008;26:1948–1955.

231. Ingle JN, Tu D, Pater JL, et al. Intent-to-treat analysis of the placebo-controlled trial of letrozole for extended adjuvant therapy in early breast cancer: NCIC CTG MA.17. Ann Oncol 2008;19:877–882.

232. Perez EA, Josse RG, Pritchard KI, et al. Effect of letrozole versus placebo on bone mineral density in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen: a companion study to NCIC CTG MA.17. J Clin Oncol 2006;24:3629–3635.

233. Whelan TJ, Goss PE, Ingle JN, et al. Assessment of quality of life in MA.17: a randomized, placebo-controlled trial of letrozole after 5 years of tamoxifen in postmenopausal women. J Clin Oncol 2005;23:6931–6940.

234. Jakesz R, Greil R, Gnant M, et al. Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a. J Natl Cancer Inst 2007;99:1845–1853.

235. Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. J Clin Oncol 2010;28:509–518.

236. Smith IE, Dowsett M, Yap YS, et al. Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines. J Clin Oncol 2006;24:2444–2447.

237. Yu B, Douglas N, Ferin MJ, et al. Changes in markers of ovarian reserve and endocrine function in young women with breast cancer undergoing adjuvant chemotherapy. Cancer 2010;116:2099–2105.

238. Dowsett M, Nielsen TO, A'Hern R, et al. Assessment of Ki67 in Breast Cancer: Recommendations from the International Ki67 in Breast Cancer Working Group. J Natl Cancer Inst 2011;103:1656–1664.

239. Dowsett M, Smith IE, Ebbs SR, et al. Prognostic value of Ki67 expression after short-term presurgical endocrine therapy for primary breast cancer. J Natl Cancer Inst 2007;99:167–170.

240. The Human Cytochrome P450 (CYP) Allele Nomenclature Database. Available at: http://www.cypalleles.ki.se/. Accessed March 7, 2014.

241. Schroth W, Goetz MP, Hamann U, et al. Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. JAMA 2009;302:1429–1436.

242. Leyland-Jones B, Regan M, Bouzyk M, et al. Outcome according to CYP2D6 genotype among postmenopausal women with endocrine-responsive early invasive breast cancer randomized in the BIG 1-98 trial [abstract]. Cancer Res 2010;70(24 Suppl):Abstract S1-8.

243. Rae J, Drury S, Hayes D, et al. Lack of correlation between gene variants in tamoxifen metabolizing enymes with primary endpoints in the ATAC trial [abstract]. Cancer Res 2010;70(24 Suppl):Abstract S1-7.

244. Higgins MJ, Stearns V. Pharmacogenetics of endocrine therapy for breast cancer. Annu Rev Med 2011;62:281–293.

245. Visvanathan K, Chlebowski RT, Hurley P, et al. American society of clinical oncology clinical practice guideline update on the use of pharmacologic interventions including tamoxifen, raloxifene, and aromatase inhibition for breast cancer risk reduction. J Clin Oncol 2009;27:3235–3258.

246. Erban JK, Lau J. On the toxicity of chemotherapy for breast cancer—the need for vigilance. J Natl Cancer Inst 2006;98:1096–1097.

247. Henderson I, Berry D, Demetri G, et al. Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol 2003;21:976–983.

248. Mamounas E, Bryant J, Lembersky B, et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. J Clin Oncol 2005;23:3686–3696.

249. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003;21:1431–1439.

250. Sparano JA, Wang M, Martino S, et al. Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node positive or high risk node negative breast cancer [abstract]. Presented at the 28th Annual San Antonio Breast Cancer Symposium; December 8–11, 2005; San Antonio, Texas. Abstract 48.

251. Sparano JA, Wang M, Martino S, et al. Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in operable breast cancer: results of Intergroup trial E1199 [abstract]. J Clin Oncol 2007;25(Suppl 18):Abstract 516.

252. Sparano J, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med 2008;358:1663–1671.

253. Jones S, Holmes FA, O'Shaughnessy J, et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research trial 9735. J Clin Oncol 2009;27:1177–1183.

254. Bang SM, Heo DS, Lee KH, et al. Adjuvant doxorubicin and cyclophosphamide versus cyclophosphamide, methotrexate, and 5-fluorouracil chemotherapy in premenopausal women with axillary lymph node positive breast carcinoma. Cancer 2000;89:2521–2526.

255. Fisher B, Anderson S, Tan-Chiu E, et al. Tamoxifen and chemotherapy for axillary node-negative, estrogen receptor-negative breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-23. J Clin Oncol 2001;19:931–942.

256. Fisher B, Brown AM, Dimitrov NV, et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. J Clin Oncol 1990;8:1483–1496.

257. Fisher B, Anderson S, Wickerham DL, et al. Increased intensification and total dose of cyclophosphamide in a

doxorubicin-cyclophosphamide regimen for the treatment of primary breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-22. J Clin Oncol 1997;15:1858–1869.

258. Polychemotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1998;352:930–942.

259. Wood WC, Budman DR, Korzun AH, et al. Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast carcinoma. N Engl J Med 1994;330:1253–1259.

260. Menard S, Valagussa P, Pilotti S, et al. Response to cyclophosphamide, methotrexate, and fluorouracil in lymph node-positive breast cancer according to HER2 overexpression and other tumor biologic variables. J Clin Oncol 2001;19:329–335.

261. Muss HB, Thor AD, Berry DA, et al. c-erbB-2 expression and response to adjuvant therapy in women with node-positive early breast cancer. N Engl J Med 1994;330:1260–1266.

262. Watanabe T, Kuranami M, Inoue K, et al. Phase III trial comparing 4-cycle doxorubicin plus cyclophosphamide followed by 4-cycle taxan with 8-cycle taxan as adjuvant therapy for node-positive breast cancer: results of N-SAS-BC02 trial [abstract]. J Clin Oncol 2009;27(Suppl 15):Abstract 516.

263. Levine M, Pritchard K, Bramwell V, et al. Randomized trial comparing cyclophosphamide, epirubicin, and fluorouracil with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer: update of National Cancer Institute of Canada Clinical Trials Group Trial MA5. J Clin Oncol 2005;23:5166–5170.

264. Benefit of a high-dose epirubicin regimen in adjuvant chemotherapy for node-positive breast cancer patients with poor prognostic factors: 5-year follow-up results of French Adjuvant Study Group 05 Randomized Trial. J Clin Oncol 2001;19:602–611.

265. Piccart MJ, Di Leo A, Beauduin M, et al. Phase III trial comparing two dose levels of epirubicin combined with cyclophosphamide with cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer. J Clin Oncol 2001;19:3103–3110.

266. Ellis P, Barrett-Lee P, Johnson L, et al. Sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACT): an open-label, phase III, randomised controlled trial. Lancet 2009;373:1681–1692.

267. Martin M, Rodriguez-Lescure A, Ruiz A, et al. Randomized phase 3 trial of fluorouracil, epirubicin, and cyclophosphamide alone or followed by Paclitaxel for early breast cancer. J Natl Cancer Inst 2008;100:805–814.

268. Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med 2005;352:2302–2313.

269. Swain SM, Jeong JH, Geyer CE, et al. NSABP B-30: definitive analysis of patient outcome from a randomized trial evaluating different schedules and combinations of adjuvant therapy containing doxorubicin, docetaxel and cyclophosphamide in women with operable, node-positive breast cancer [abstract]. Cancer Res 2009;69(Suppl 1):Abstract 75.

270. Burstein HJ. The distinctive nature of HER2-positive breast cancers. N Engl J Med 2005;353:1652–1654.

271. Joensuu H, Bono P, Kataja V, et al. Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer Trial. J Clin Oncol 2009;27:5685–5692.

272. Perez EA, Romond EH, Suman VJ, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. J Clin Oncol 2011;29:3366–3373.

273. Gianni L, Dafni U, Gelber RD, et al. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. Lancet Oncol 2011;12:236–244.

274. Perez EA, Suman VJ, Davidson NE, et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol 2008;26:1231–1238.

275. Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol 2005;23:7811–7819.

276. Geyer CE Jr, Bryant JL, Romond EH, et al. Update of cardiac dysfunction on NSABP B-31, a randomized trial of sequential doxorubicin/cyclophosphamide (AC)->paclitaxel (T) vs. AC->T with trastuzumab (H) [abstract]. J Clin Oncol 2006;24(Suppl 18):Abstract 581.

277. Telli ML, Hunt SA, Carlson RW, Guardino AE. Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility. J Clin Oncol 2007;25:3525–3533.

278. Smith I, Procter M, Gelber RD, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet 2007;369:29–36.

279. Spielmann M, Roché H, Delozier T, et al. Trastuzumab for patients with axillary-node-positive breast cancer: results of the FNCLCC-PACS 04 trial. J Clin Oncol 2009;27:6129–6134.

280. Chia S, Norris B, Speers C, et al. Human epidermal growth factor receptor 2 overexpression as a prognostic factor in a large tissue microarray series of node-negative breast cancers. J Clin Oncol 2008;26:5697–5704.

281. Gonzalez-Angulo AM, Litton JK, Broglio KR, et al. High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. J Clin Oncol 2009;27:5700–5706.

282. O'Sullivan C, Holmes E, Spielmann M, et al. The prognosis of small HER2+ breast cancers: a meta-analysis of the randomized trastuzumab trials [abstract]. Presented at the 2013 San Antonio Breast Cancer Symposium; December 10–14, 2013; San Antonio, Texas. Abstract S6-03

283. Zhou Q, Yin W, Du Y, Lu J. For or against adjuvant trastuzumab for pT1a-bN0M0 breast cancer patients with HER2-positive tumors: a meta-analysis of published literatures. PLoS One 2014;9:e83646.

284. Tolaney S, Barry W, Dang C, et al. A phase II study of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC) [abstract]. Presented at the 2013 San Antonio Breast Cancer Symposium; December 10–14, 2013; San Antonio, Texas. Abstract S1-04.

285. Norris B, Chia S, Cheang M, et al. Poor 10 yr breast cancer specific survival and relapse free survival for HER2 positive T1N0 tumors [abstract]. Presented at the 29th San Antonio Breast Cancer Symposium; December 14–17, 2006; San Antonio, Texas. Abstract 2031.

286. Curigliano G, Viale G, Bagnardi V, et al. Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node-negative breast cancer. J Clin Oncol 2009;27:5693–5699.

287. Perez EA, Romond EH, Suman VJ, et al. Updated results of the combined analysis of NCCTG N9831 and NSABP B-31 adjuvant chemotherapy with/without trastuzumab in patients with HER2-positive breast cancer [abstract]. J Clin Oncol 2007;25(Suppl 18):Abstract 512.

288. Untch M, Gelber RD, Jackisch C, et al. Estimating the magnitude of trastuzumab effects within patient subgroups in the HERA trial. Ann Oncol 2008;19:1090–1096.

289. von MG, Baselga J, Bradbury I, et al. Adjuvant Pertuzumab and Herceptin IN IniTial TherapY of Breast Cancer: APHINITY (BIG 4–11/BO25126/TOC4939g) [abstract]. Cancer Res 2011;71(Suppl 24):Abstract OT1-02-04.

290. A randomized multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast ClinicalTrials.gov identifier: NCT01358877.

291. Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. A multicenter randomized controlled trial. The GIVIO Investigators. JAMA 1994;271:1587–1592.

292. Rosselli Del Turco M, Palli D, Cariddi A, et al. Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. National Research Council Project on Breast Cancer follow-up. JAMA 1994;271:1593–1597.

293. Smith TJ, Davidson NE, Schapira DV, et al. American Society of Clinical Oncology 1998 update of recommended breast cancer surveillance guidelines. J Clin Oncol 1999;17:1080–1082.

294. Bast RC, Ravdin P, Hayes DF, et al. 2000 update of recommendations for the use of tumor markers in breast and colorectal cancer: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001;19:1865–1878.

295. Kirova YM, Stoppa-Lyonnet D, Savignoni A, et al. Risk of breast cancer recurrence and contralateral breast cancer in relation to BRCA1 and BRCA2 mutation status following breast-conserving surgery and radiotherapy. Eur J Cancer 2005;41:2304–2311.

296. Metcalfe K, Lynch HT, Ghadirian P, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. J Clin Oncol 2004;22:2328–2335.

297. Pierce LJ, Levin AM, Rebbeck TR, et al. Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer. J Clin Oncol 2006;24:2437–2443.

298. ACOG committee opinion. No. 336: Tamoxifen and uterine cancer. Obstet Gynecol 2006;107:1475–1478.

299. Loprinzi CL, Kugler JW, Sloan JA, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet 2000;356:2059–2063.

300. Boekhout AH, Vincent AD, Dalesio OB, et al. Management of hot flashes in patients who have breast cancer with venlafaxine and clonidine: a randomized, double-blind, placebo-controlled trial. J Clin Oncol 2011;29:3862–3868.

301. Kaplan M, Mahon S, Cope D, et al. Putting evidence into practice: evidence-based interventions for hot flashes resulting from cancer therapies. Clin J Oncol Nurs 2011;15:149–157.

302. Bordeleau L, Pritchard KI, Loprinzi CL, et al. Multicenter, randomized, cross-over clinical trial of venlafaxine versus gabapentin for the management of hot flashes in breast cancer survivors. J Clin Oncol 2010;28:5147–5152.

303. Garber K. Tamoxifen pharmacogenetics moves closer to reality. J Natl Cancer Inst 2005;97:412–413.

304. Jin Y, Desta Z, Stearns V, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. J Natl Cancer Inst 2005;97:30–39.

305. Henry NL, Stearns V, Flockhart DA, et al. Drug interactions and pharmacogenomics in the treatment of breast cancer and depression. Am J Psychiatry 2008;165:1251–1255.

306. Ahern TP, Pedersen L, Cronin-Fenton DP, et al. No increase in breast cancer recurrence with concurrent use of tamoxifen and some CYP2D6-inhibiting medications. Cancer Epidemiol Biomarkers Prev 2009;18:2562–2564.

307. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487–497.

308. Li CI, Daling JR, Porter PL, et al. Relationship between potentially modifiable lifestyle factors and risk of second primary contralateral breast cancer among women diagnosed with estrogen receptor-positive invasive breast cancer. J Clin Oncol 2009;27:5312–5318.

309. Pierce JP, Stefanick ML, Flatt SW, et al. Greater survival after breast cancer in physically active women with high vegetable-fruit intake regardless of obesity. J Clin Oncol 2007;25:2345–2351.

310. Hickey M, Peate M, Saunders CM, Friedlander M. Breast cancer in young women and its impact on reproductive function. Human Reprod Update 2009;15:323–339.

311. Moran MS, Colasanto JM, Haffty BG, et al. Effects of breast-conserving therapy on lactation after pregnancy. Cancer J 2005;11:399–403.

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The NCCN guidelines staff have no conflicts to disclose.